Aging, Comorbidities, & HIV: CROI Update 2022

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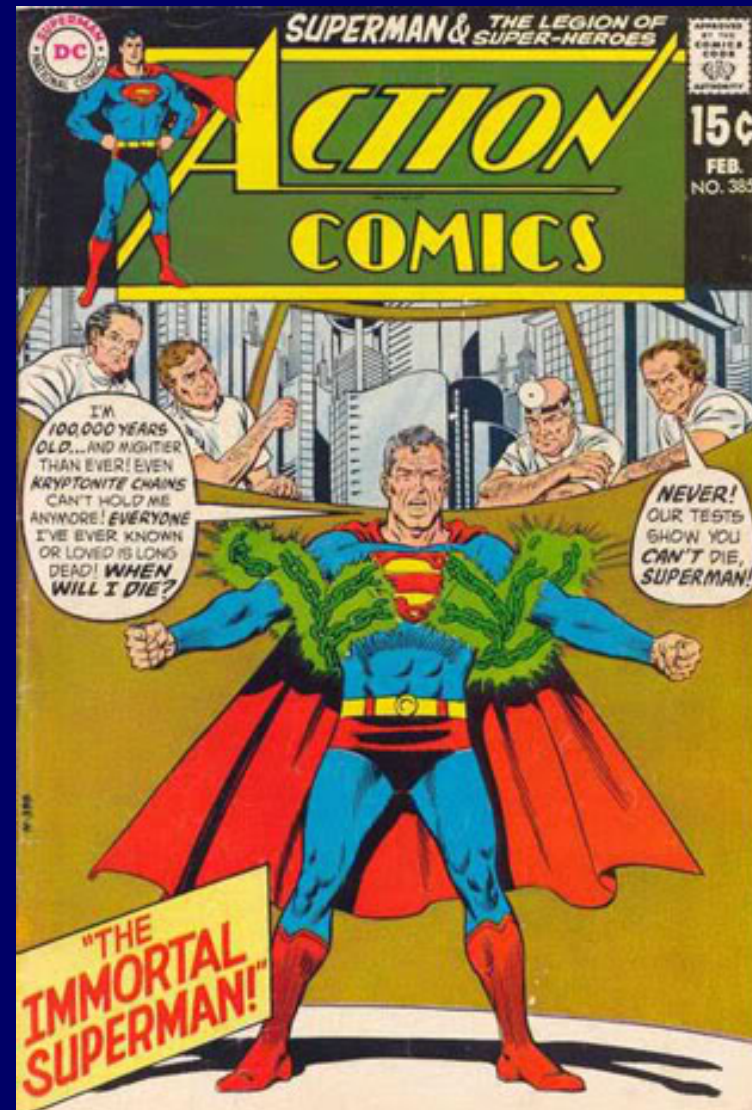
Johns Hopkins University

Disclosures

- Dr Brown has served as a consultant to Gilead, ViiV Healthcare, Merck, Janssen, Theratechnologies, and EMD-Serono.
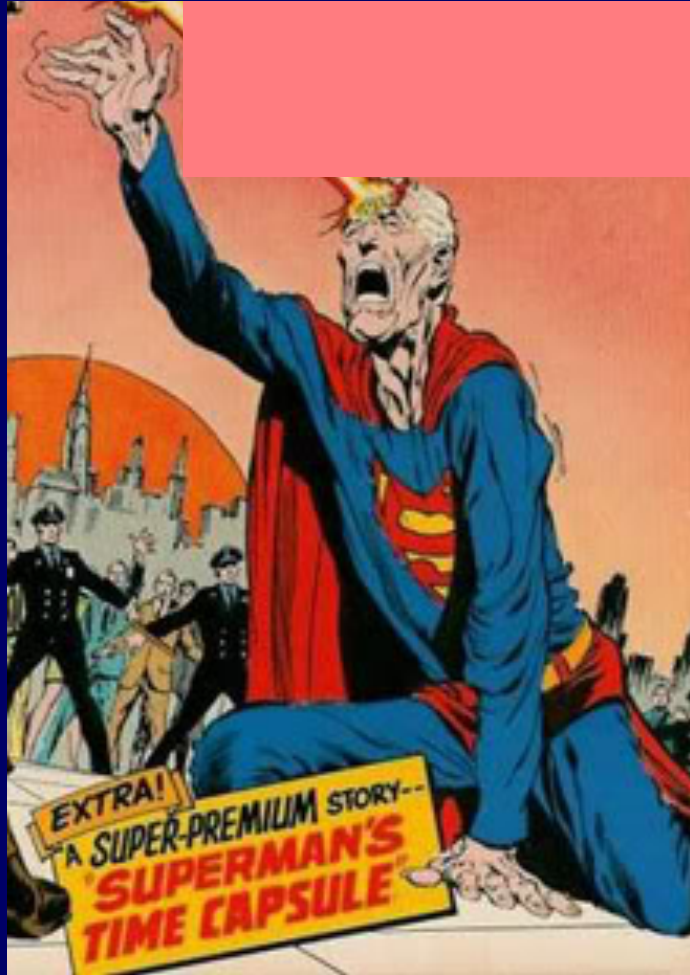
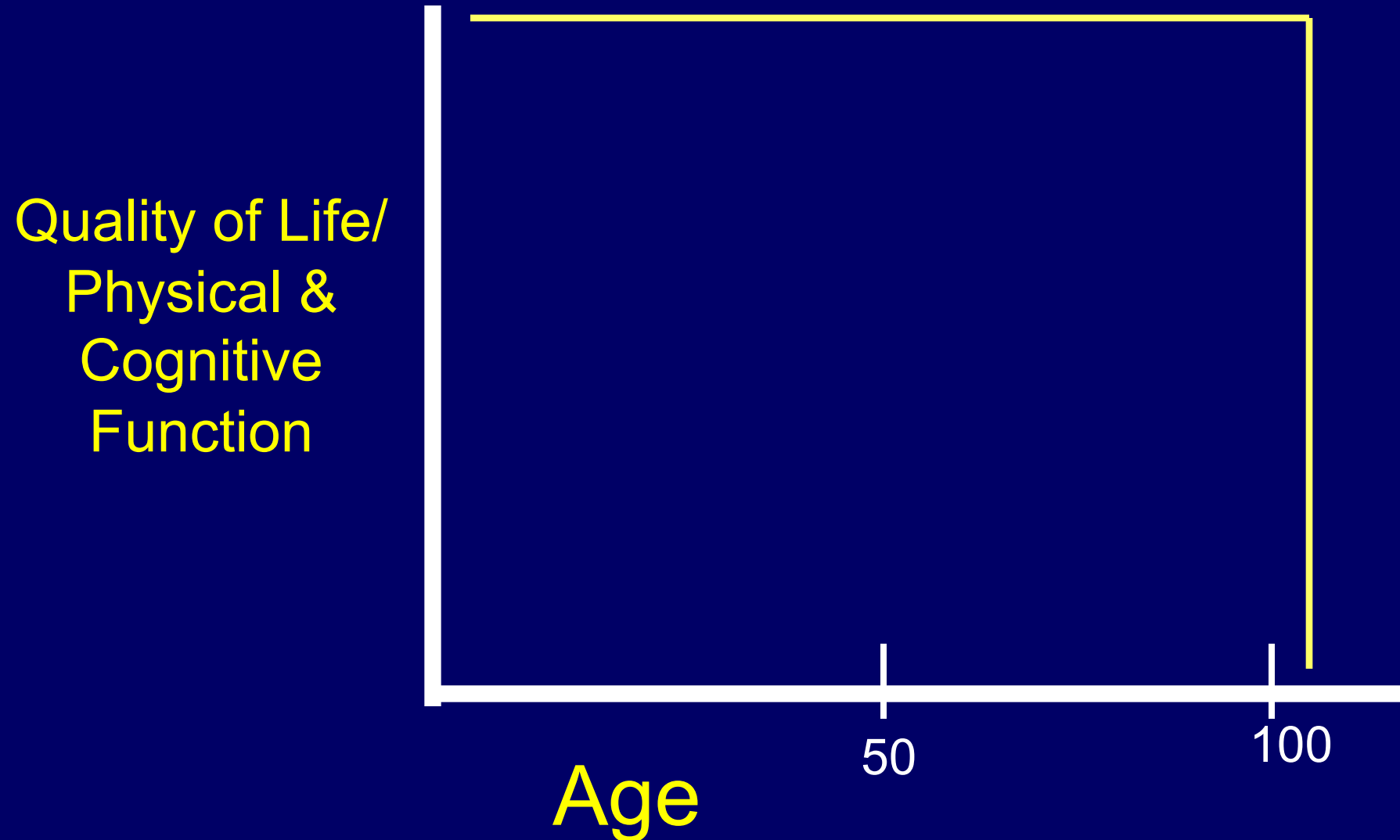# Why do we age?

Chronological Age ≠ Biological Age

Unfortunately, We are Not Immortal…

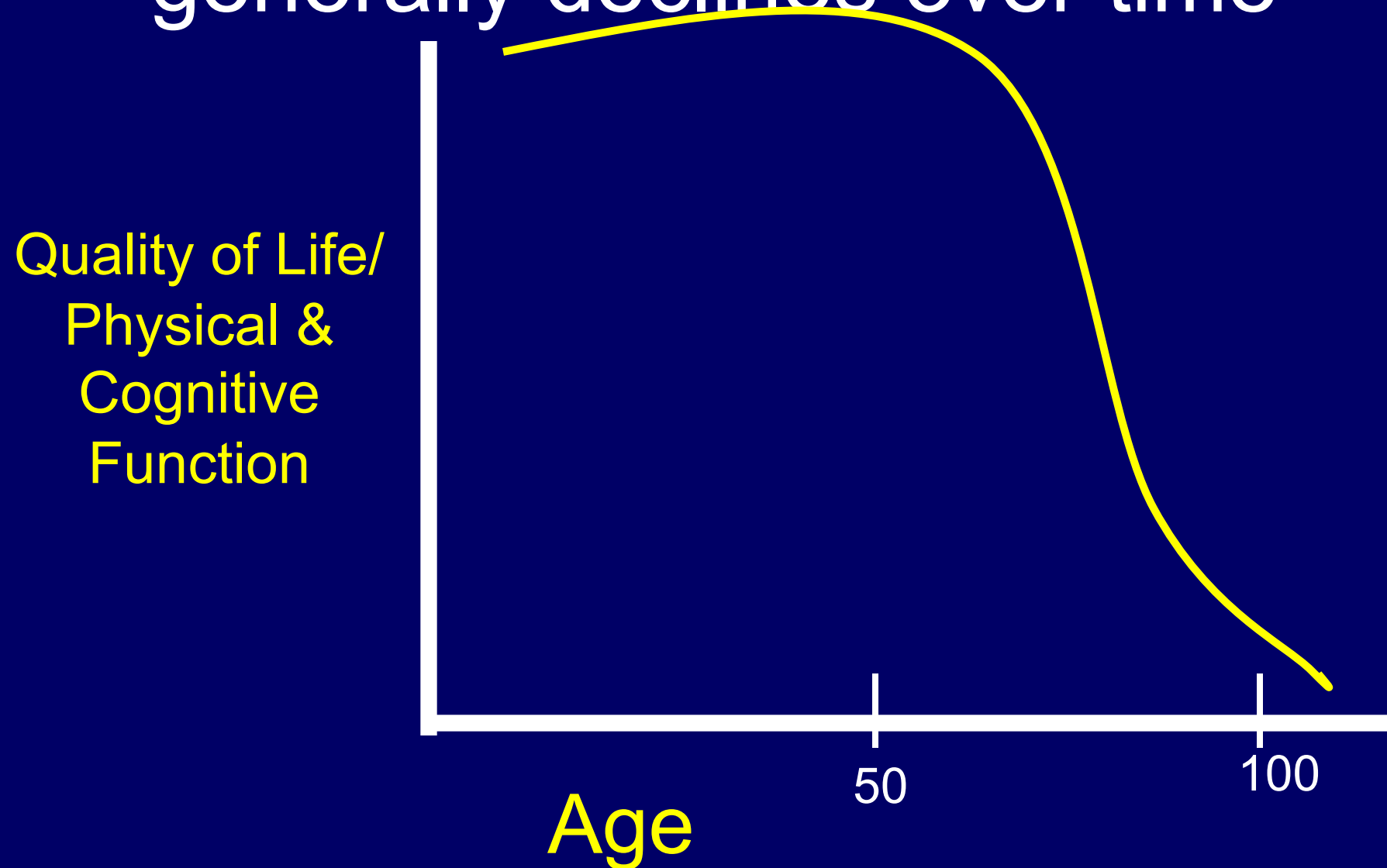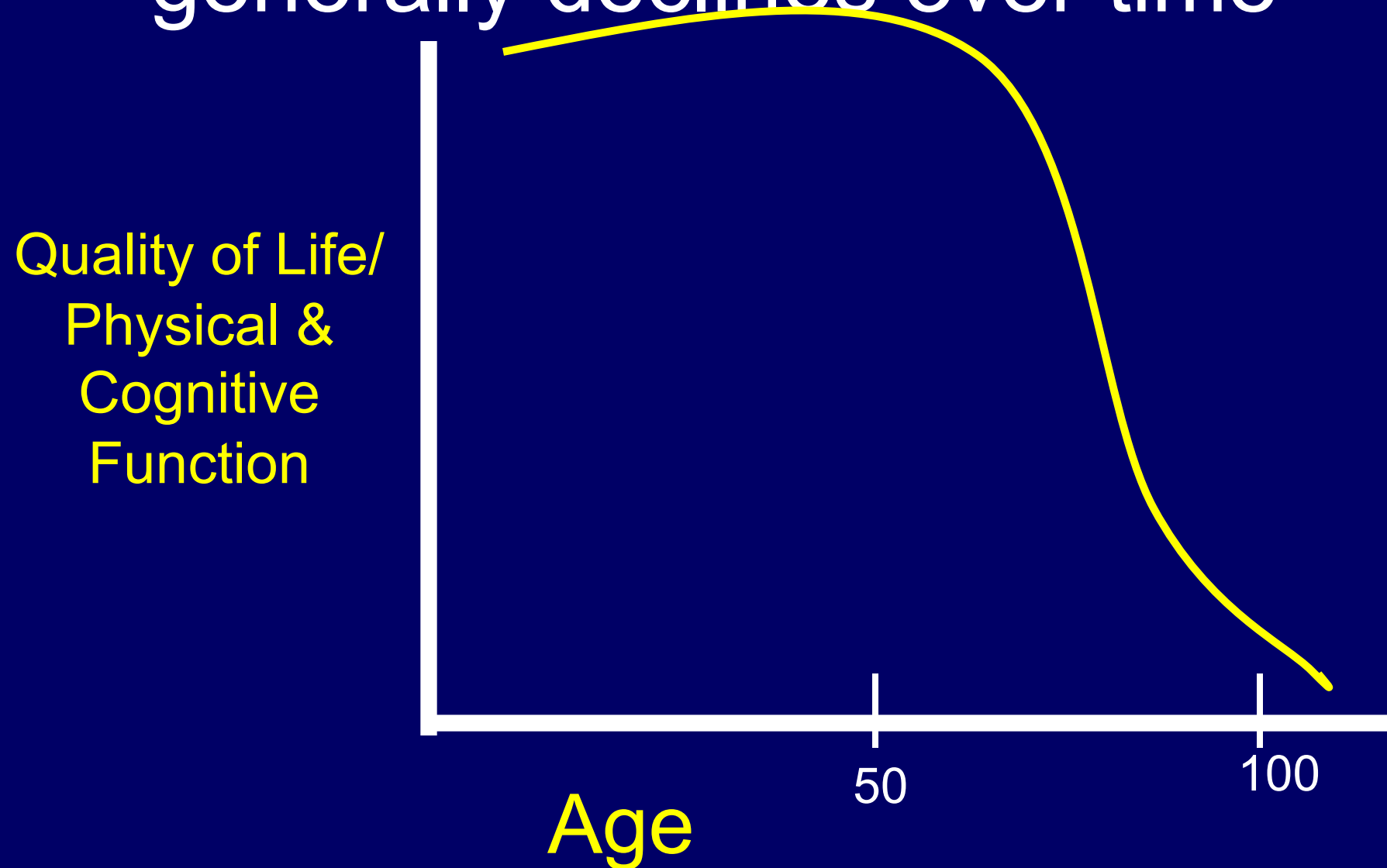# But How Do We Want to Age?

The Ideal Life: Quality x Time

Quality of Life/ Physical & Cognitive Function

50 100

Age

Physical & cognitive function generally declines over time

Quality of Life/ Physical & Cognitive Function

Age

50

100
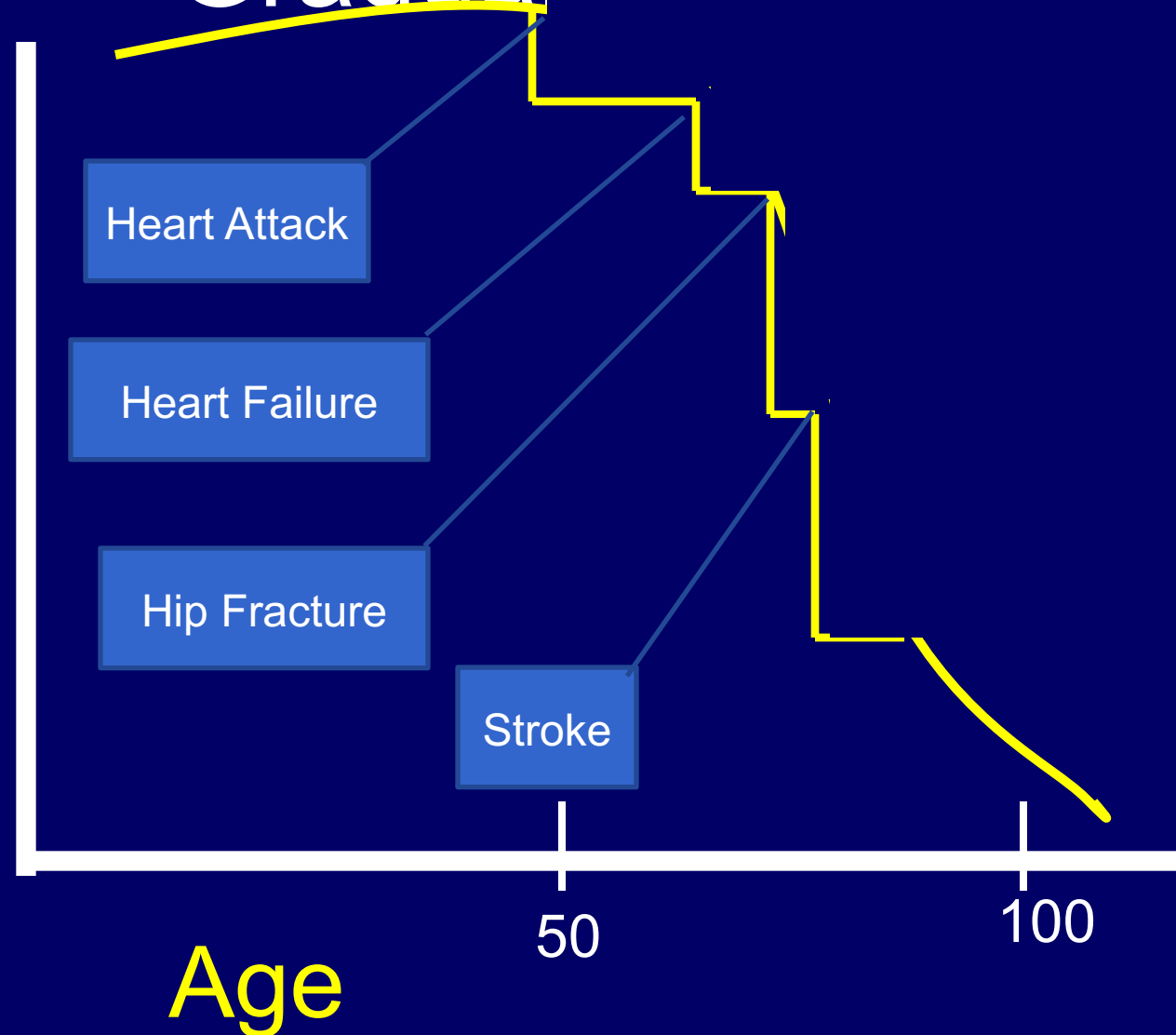
Prevention of Comorbid Events is Essential and Achievable

- Good screening tests are available for comorbid conditions
- Many behavioral factors contribute to comorbid conditions and can be modified
- Early treatment is important
- Good treatments exist that can decrease the risk of events (cardiovascular disease, fracture)
- Preventing complications can alter the aging process

A look in the future: Projected Ages of Persons with HIV in the Netherlands

Smit, Lancet Inf Diseases, 2015
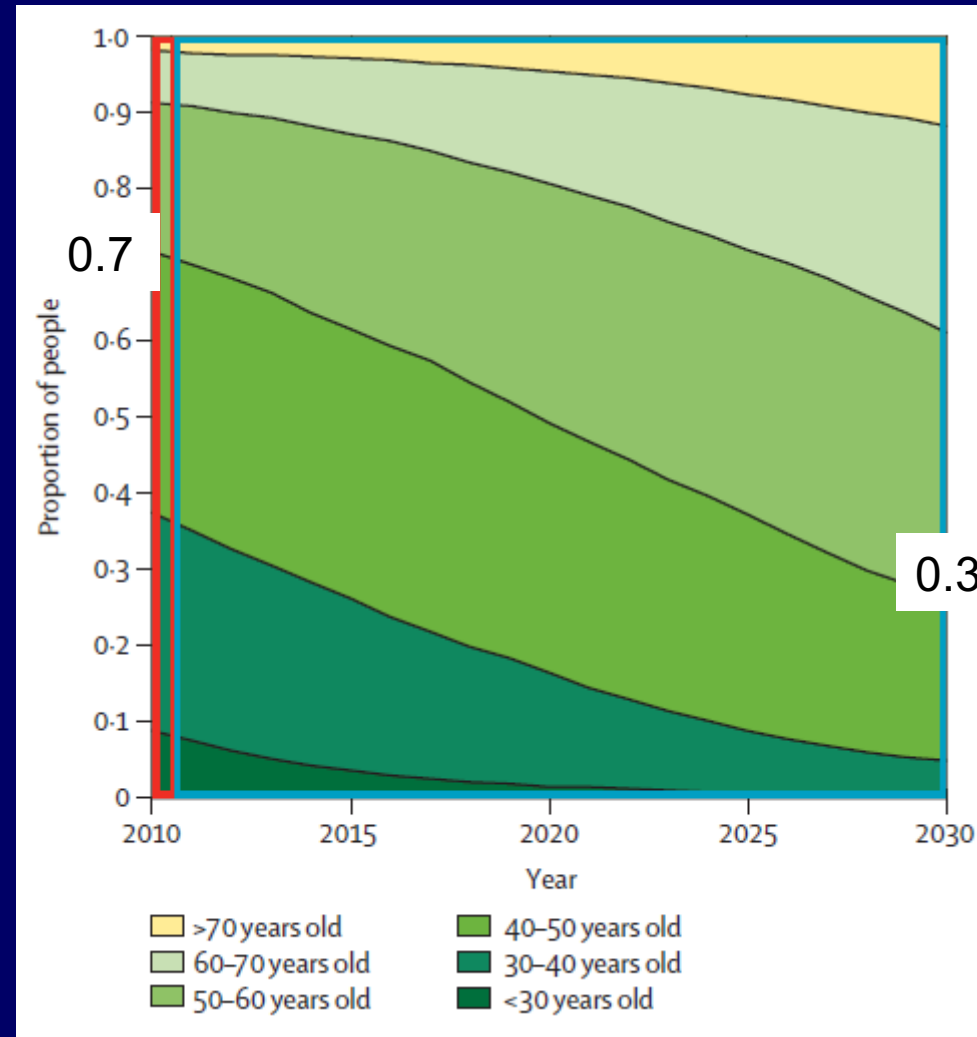
Comorbidity distribution
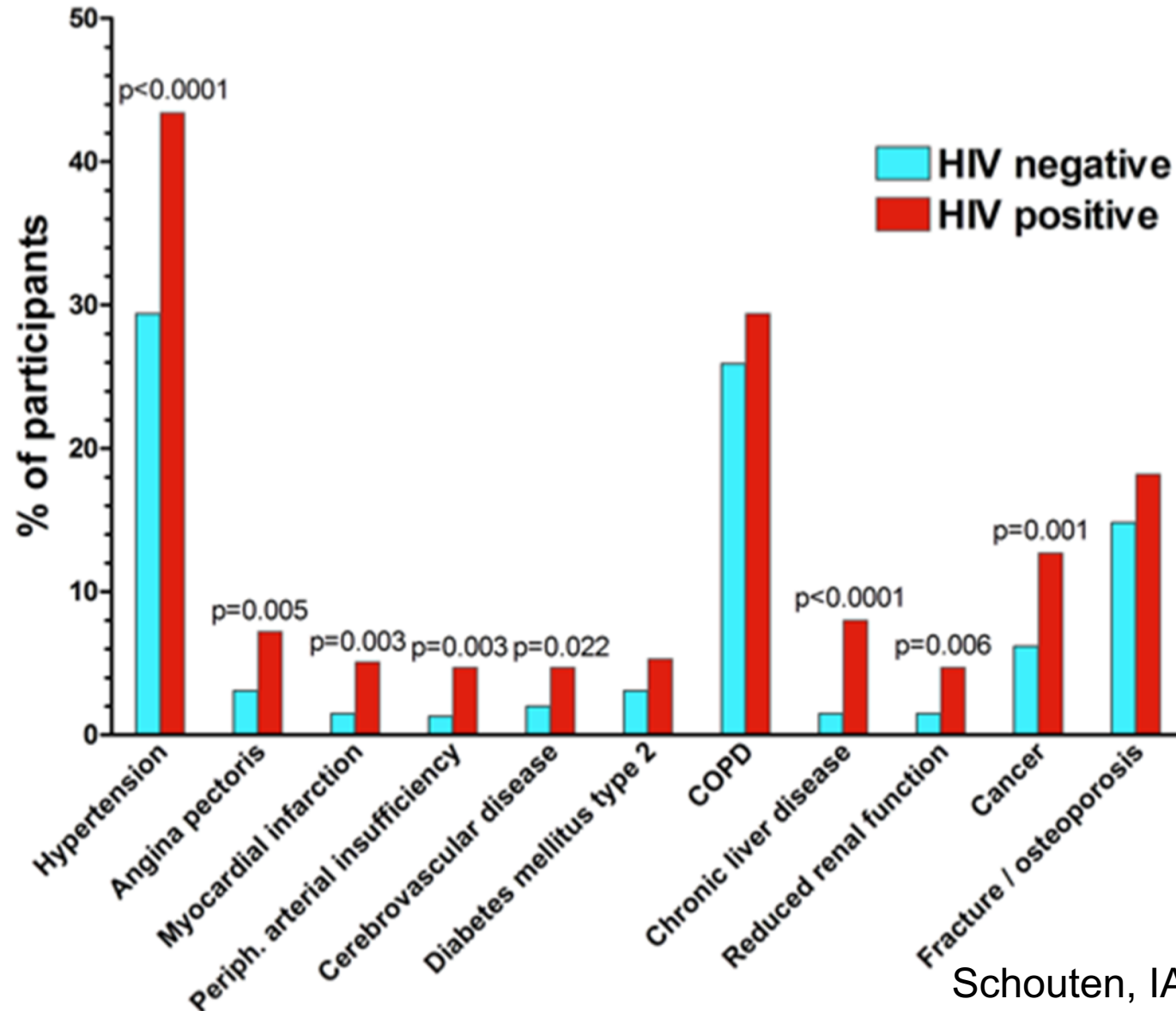
Schouten, IAS, 2012
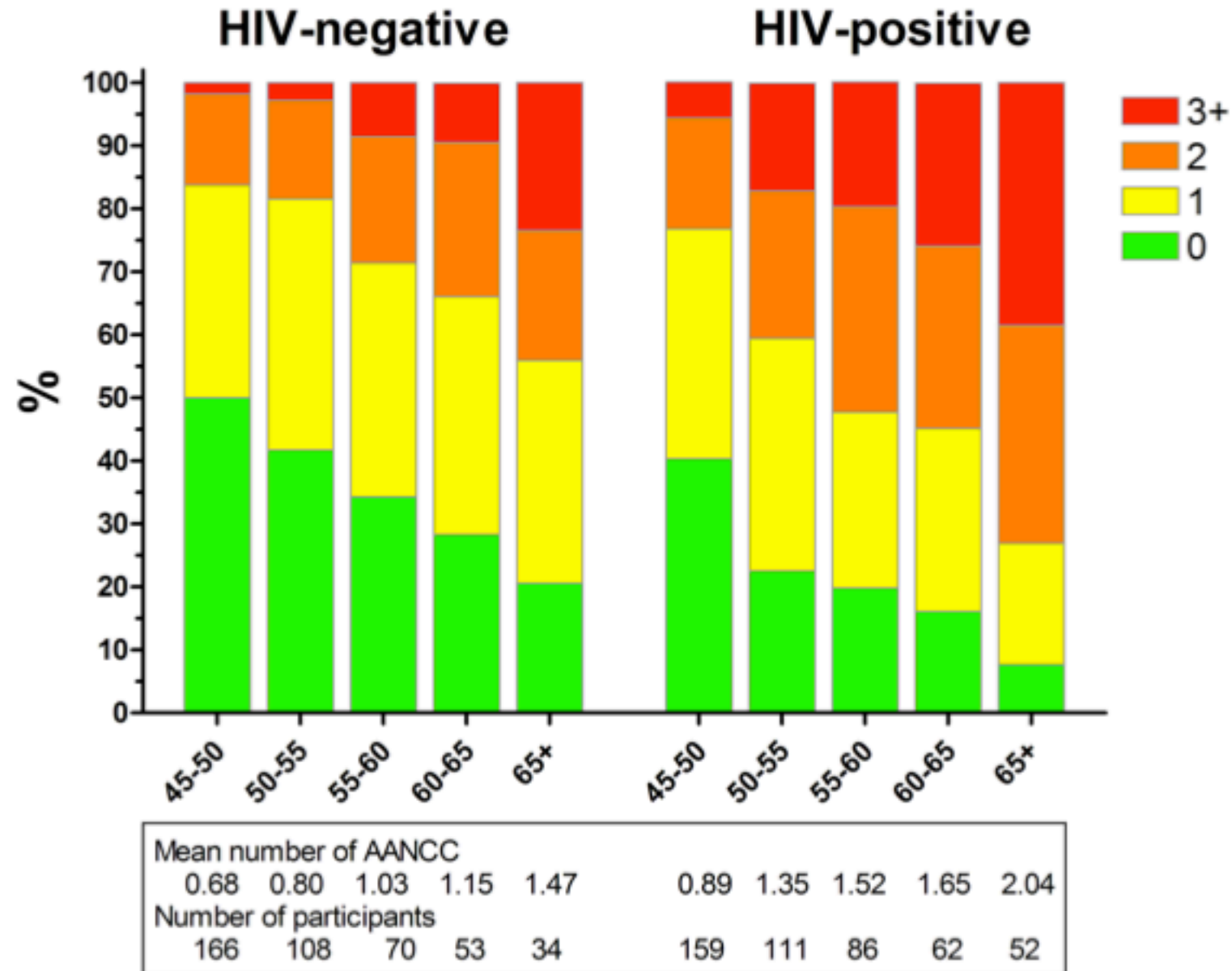
Multimorbidity will increase markedly in PLWH over the next 10 years

- Older age-groups experience an **increase** in **population size** and **prevalence of multimorbidity**

- Among those ≥ 70yrs, the projected prevalence of multimorbidity increases from 58% (in 2020) to 69% (in 2030), corresponding to an additional 71,000 individuals living with 2+ physical comorbidities beside HIV by 2030

Kasaie , CROI 2021, Abstract 102
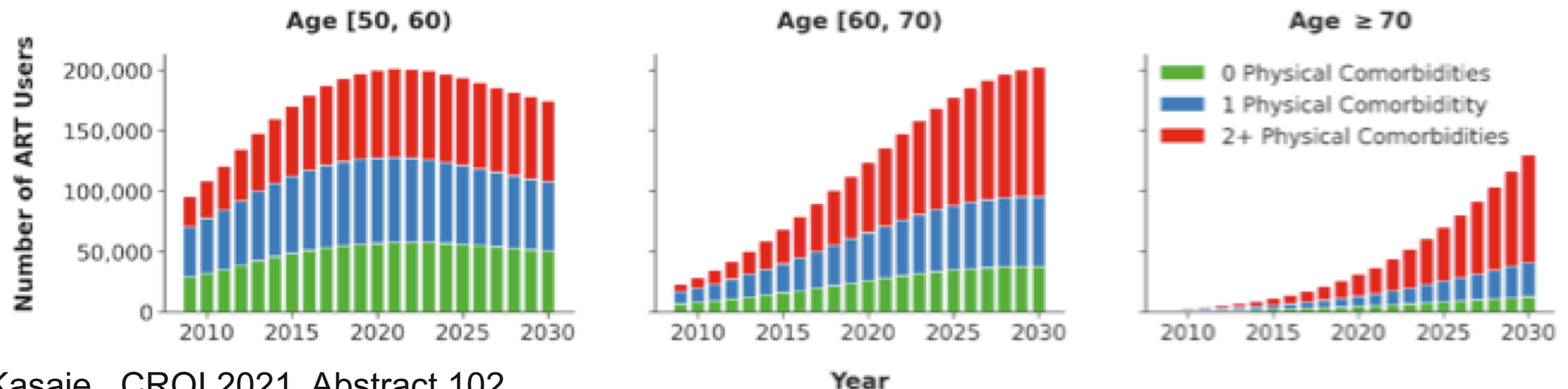
Myocardial Infarction in People with and Without HIV: MGH Study

Overall RR 1.8 (1.5-2.0), p<0.001*

HIV-infected
HIV-negative
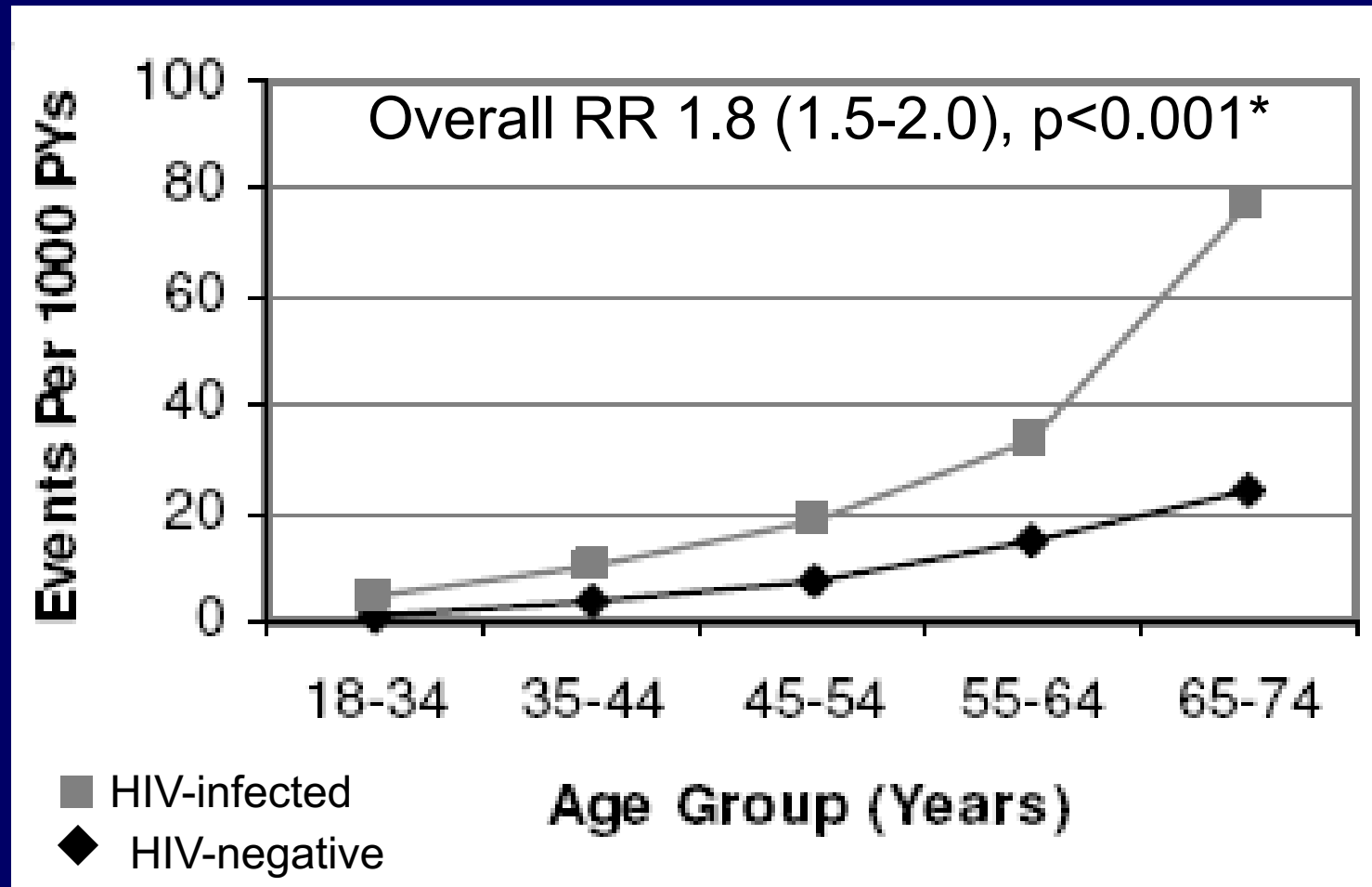
*adjusted for age, gender, race, HTN, DM, dyslipidemia

Triant, JCEM, 2007

Cardiovascular Disease at CROI 2022

Myocardial Infarction in People With and Without HIV

Baseline Characteristics by HIV and Calendar Era
reflects matching by HIV status

	PWH		PWoH		
Baseline Calendar Era	2005-2009	2010-2017	2005-2009	2010-2017	
N	4,280	5,121	14,059	15,359	
Mean age, years	44.5	43.7	44.2	43.3	
Men, %	87	89	85	90	
White / Black / Other, %	53 / 17 / 30	49 / 18 / 34	51 / 19 / 30	49 /17 / 34	
Mean total cholesterol, mg/dL	182.6	177.2	182.9	178.4	⬇
Mean HDL cholesterol, mg/dL	42.6	45.8	43.7	45.4	⬆
Mean systolic blood pressure, mmHg	123.0	123.6	123.8	123.0	
Current smoker, %	27	22	28	23	⬇
Hypertension medications, %	26	25	28	23	⬇
Diabetes, %	7	5	6	6	

- Kaiser Permanente/Partners
- 3:1 matching KP; 4;1 Partners
- Two Periods: 2005-9; 2010-17
- Validated/Adjudicated Events

Silverberg, CROI, 2022

Myocardial Infarction in People With and Without HIV

HIV-specific Baseline Characteristics

Baseline Calendar Era	PWH		
	2005-2009	2010-2017	
N	4,280	5,121	
HIV RNA>400 copies/mL, %	39	23	↓
Mean CD4, cells/µL	470	587	↑
ART use, %	76	88	↑
Mean years HIV	7.8	9.1	↑
Prior ART Class experience (among ART users), %			
NNRTI	52	46	↓
PI	54	27	↓
INSTI	3	40	↑↑

Silverberg, CROI, 2022

Cumulative incidence of MI similar by HIV status in 2005-2009 but higher for PWH compared with PWoH in 2010-2017
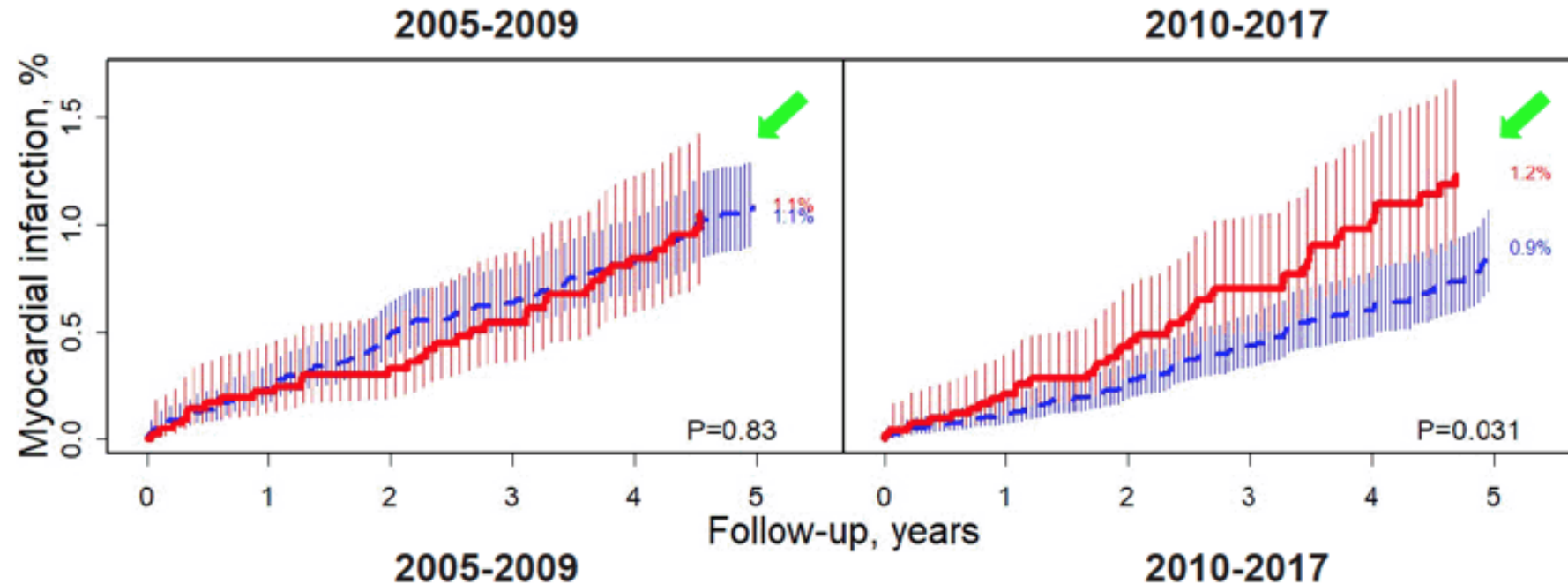
Era	KPNC		Partners		Overall	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
2005-2009	1.0 (0.7, 1.5)	0.90	1.2 (0.3, 5.8)	0.82	1.1 (0.8, 1.5)	0.61
2010-2017	1.6 (1.1, 2.4)	0.02	2.1 (0.6, 7.5)	0.28	1.6 (1.1, 2.4)	0.007

*Stepwise adjusted models considering demographics and Framingham risk score components.

P-interaction (Era*HIV)=0.12

Silverberg

Inflammation and Immune Dysfunction: A Central Mechanism for Aging

Aging → Inflammation →

- Diabetes Mellitus
- Heart Disease
- Cancer
- Cognitive Problems
- Osteoporosis
- Frailty
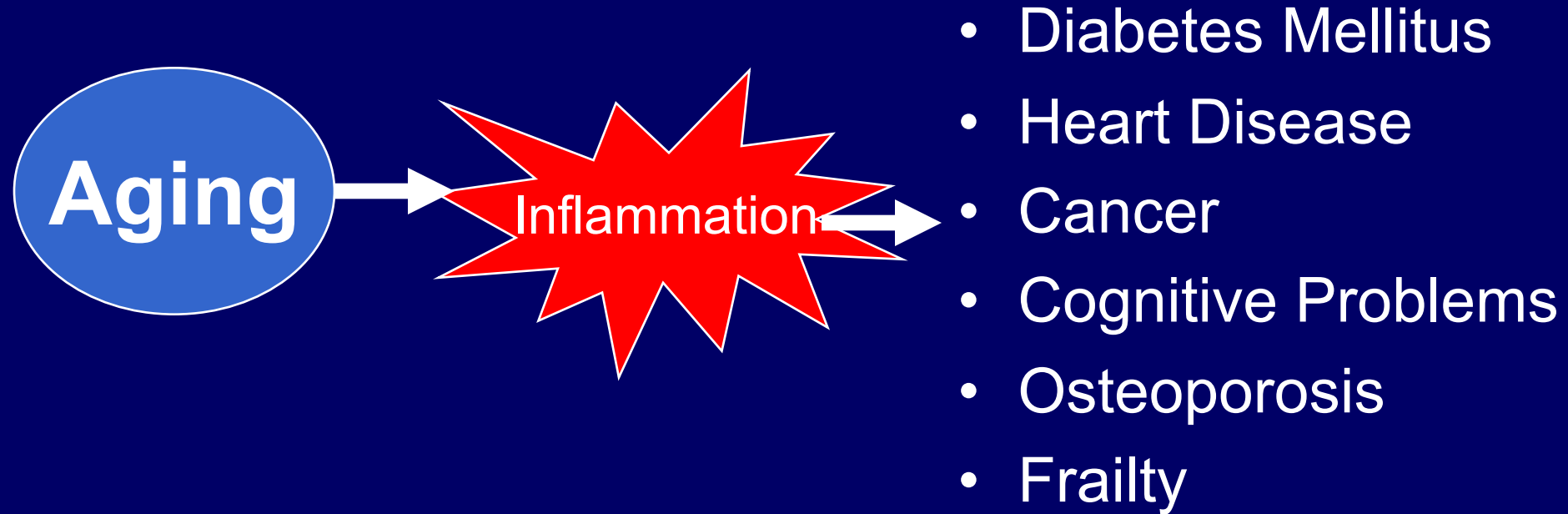
Aging & HIV: The Inflammation Double Whammy

Aging

HIV

Inflammation

- Diabetes Mellitus
- Heart Disease
- Cancer
- Cognitive Problems
- Osteoporosis
- Frailty
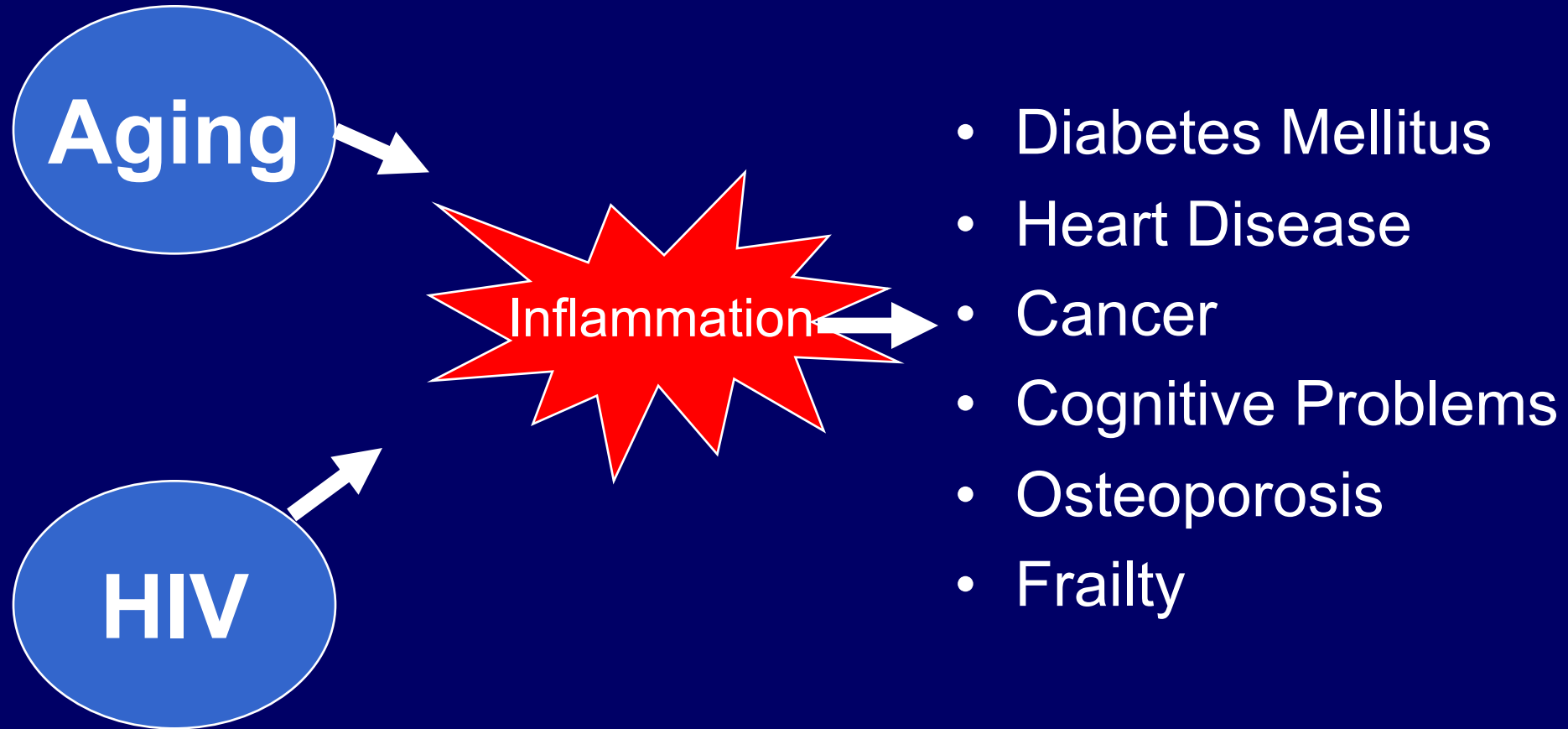
Microbial translocation, HIV persistence and coinfections cause persistent innate immune activation

HIV persistence

Co-Infections
Poor pathogen control

Microbial Translocation

Inflammation

Immune Senescence

Immune Activation

Metabolic Dysregulation

Courtesy of Suzanne Crowe

Hui Ling Yeoh, Burnet, 2016
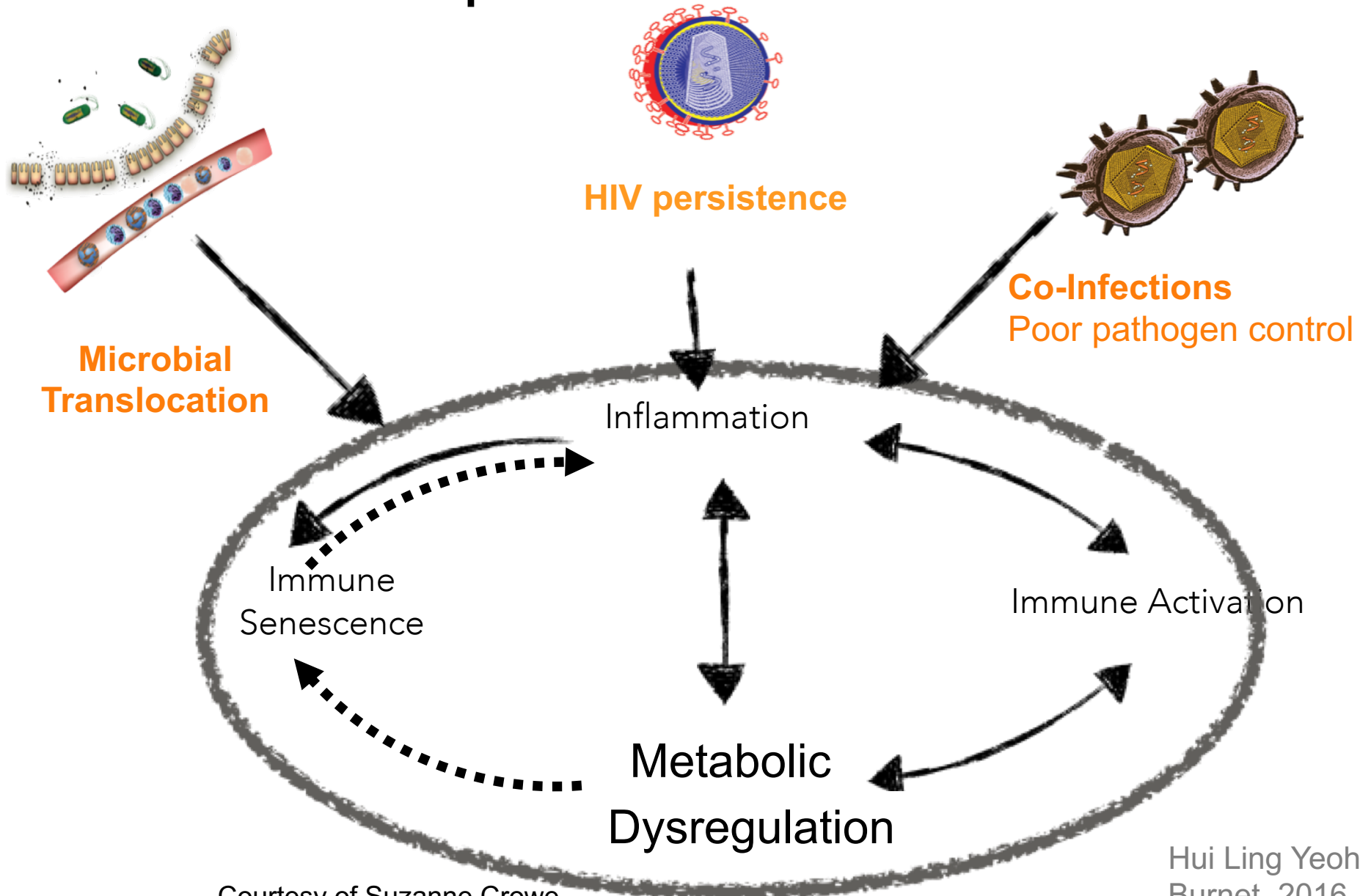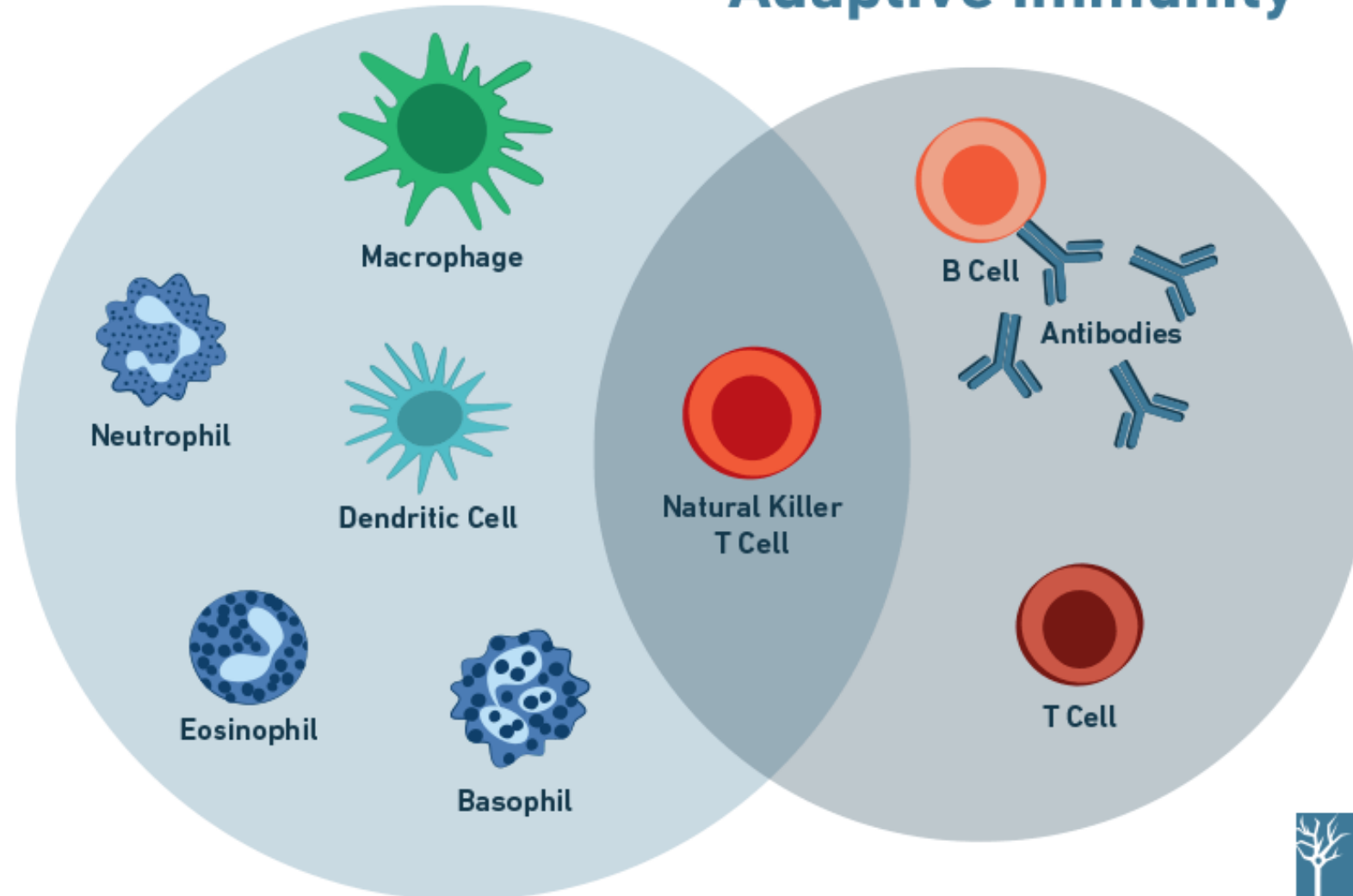
Vascular Inflammation in HIV

99m Tc-tilmanocept SPECT/CT is a novel imaging modality that allows quantification of macrophage-specific arterial inflammation/ vascular inflammation

Aortic 99mTc-tilmanocept uptake was quantified using a signal to background ratio (SBR): aortic 99mTc-tilmanocept activity to background muscle activity

SBR   HU

7   215

2   -35

Toribio, CROI, 2022

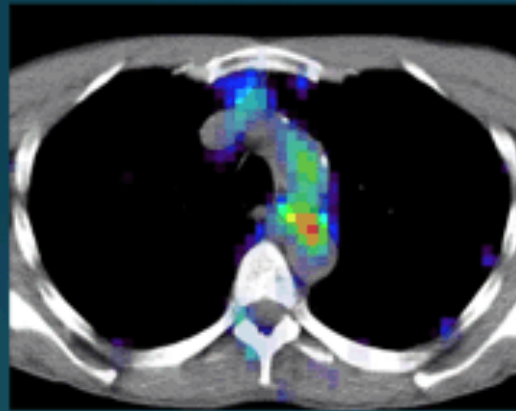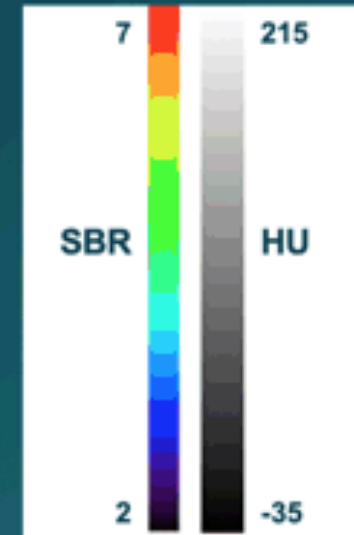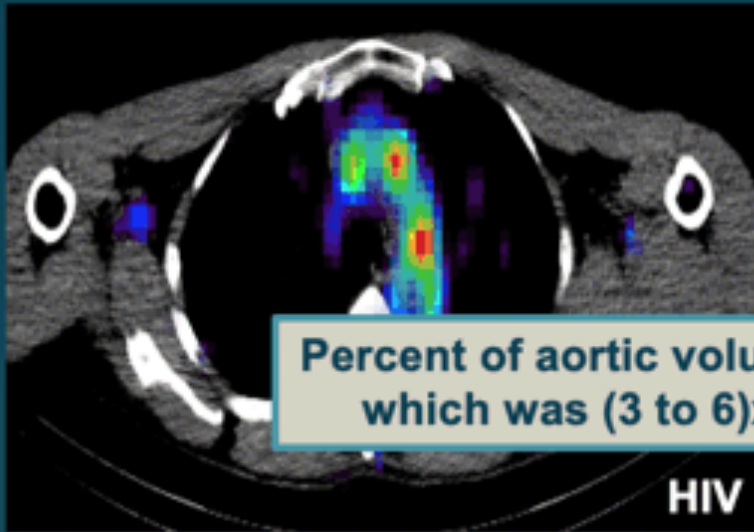# Macrophage-specific arterial inflammation was higher among PWH on ART compared to matched participants of similar ASCVD risk without HIV

Percent of aortic volume with ^{99m}Tc-tilmanocept uptake which was (3 to 6)x's background muscle activity

HIV

Non-HIV

Participants with HIV
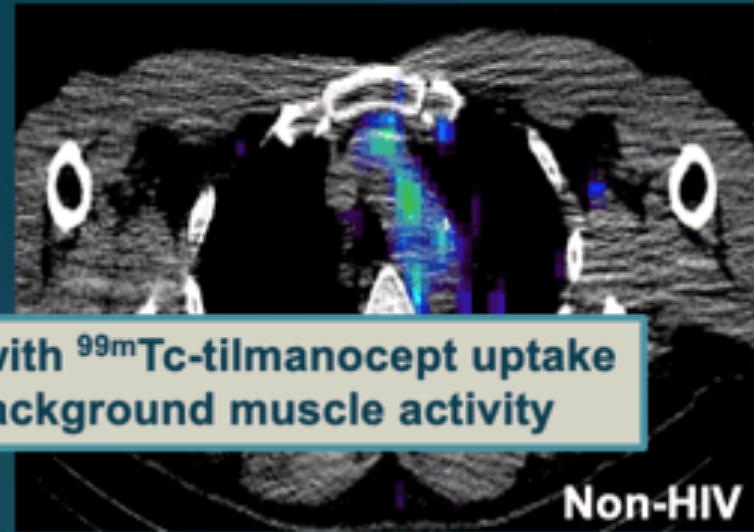
Participants without HIV
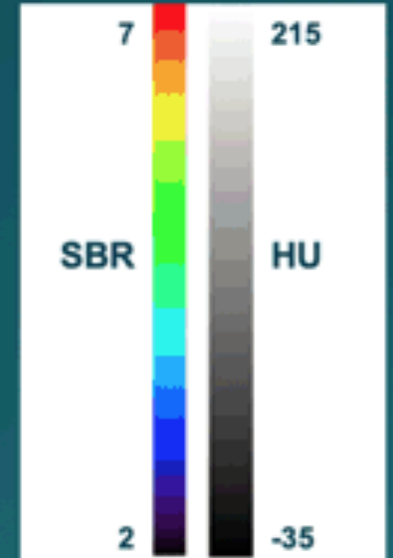
Arterial Inflammation was related to:
- **Non-calcified aortic plaque volume**
- **Markers of Systemic Inflammation**
- **Activated Monocytes**
- **Lower CD4/CD8 ratio**
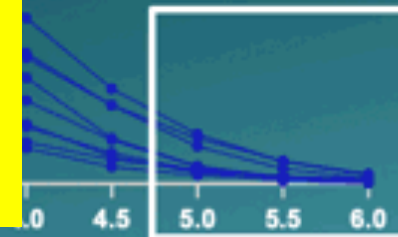
In a repeated measures ANOVA controlling for sex, aortic ^{99m}Tc-tilmanocept uptake was higher among PWH than in participants without HIV (P=0.02)

Threshold above muscle activity

Threshold above muscle activity

Inflammatory clusters are associated with CVD in People with HIV on effective treatment

- 277 PWH
- 27 markers measured
- -Used Principal Components Analysis to split sample into 3 clusters

McGettrick, CROI, 2022

Figure 2: Characterisation of biomarker derived clusters

Clus I   Clus II   Clus III

sCD163
IL-18
Lp-PLA2
sICAM-1
MCP-1
sCD40L
E-Selectin
P-Selectin
vWF
VCAM-1
TNFR-II
TNFR-I
sCD14
LBP
D-dimer
IL-1RA
hs-CRP
I-FABP
IL-6
IFN-gamma
IL-2
IL-12
IL-1b
IL-4
IL-10
TNF-alpha
CD8+ Senes 57+ 28-
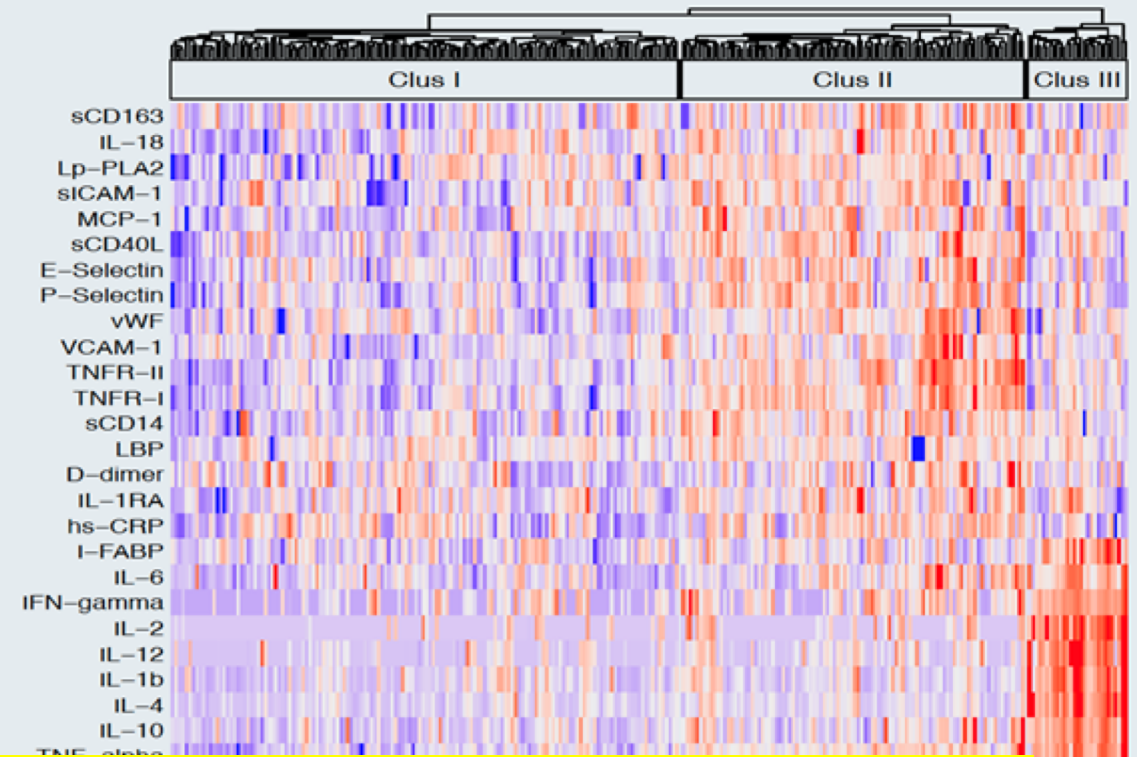
Cluster 2: Higher vascular and innate inflammation
Cluster 3: Higher T-cell activation/proliferation, Microbial Translocation

Inflammatory clusters are associated with CVD in People with HIV on effective treatment

- Multimorbidity: 2 or More of 10 conditions
- CVD: MI, Angina, Stroke, PVD

McGettrick, CROI, 2022

Figure 3: Aassociations between variables and (a) multimorbidity and (b) CVD
Adjusted for (a): Age ethnicity, IVDU, Smoking, Treatment duration and (b) age, gender, IVDU, smoking, total and LDL cholesterol
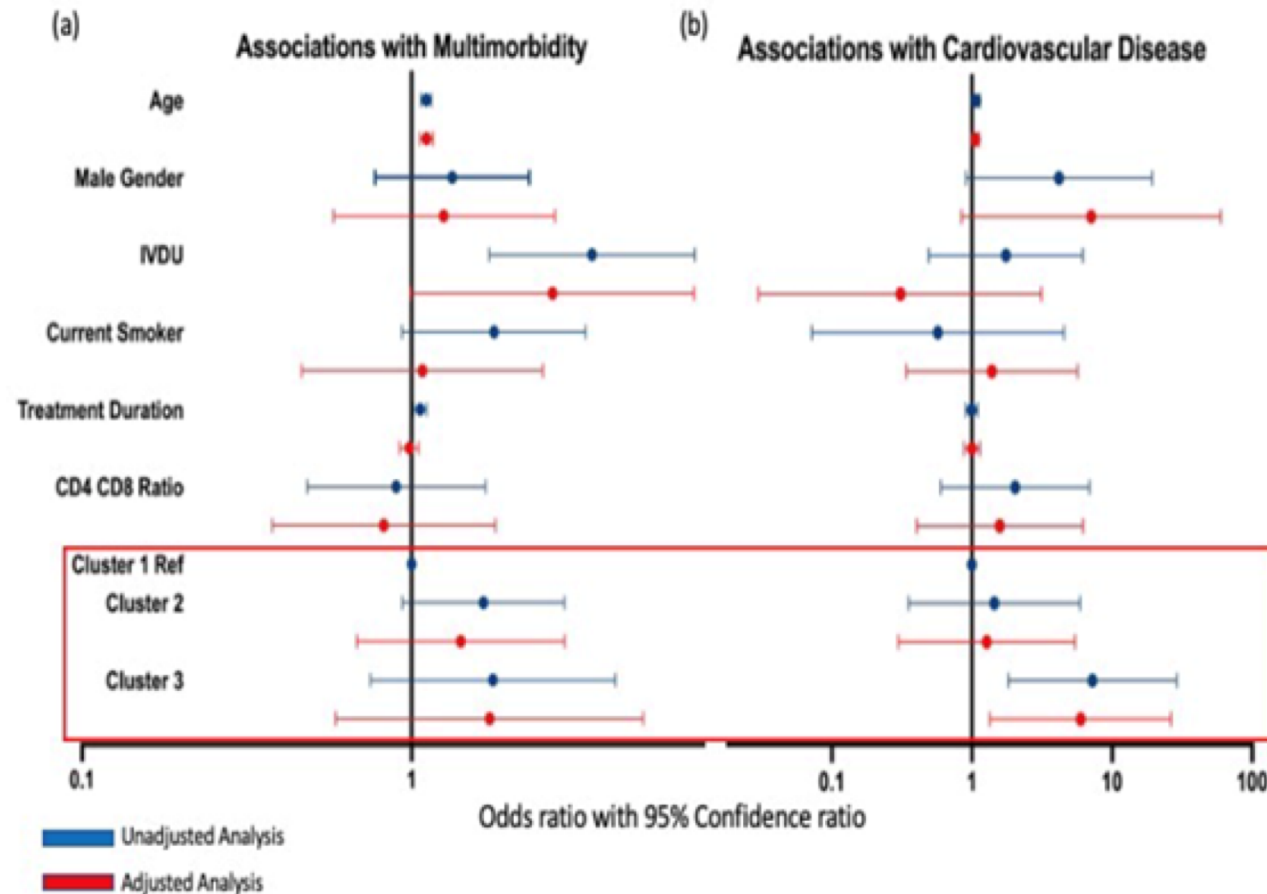
Intestinal Barrier in Health and with HIV

In health
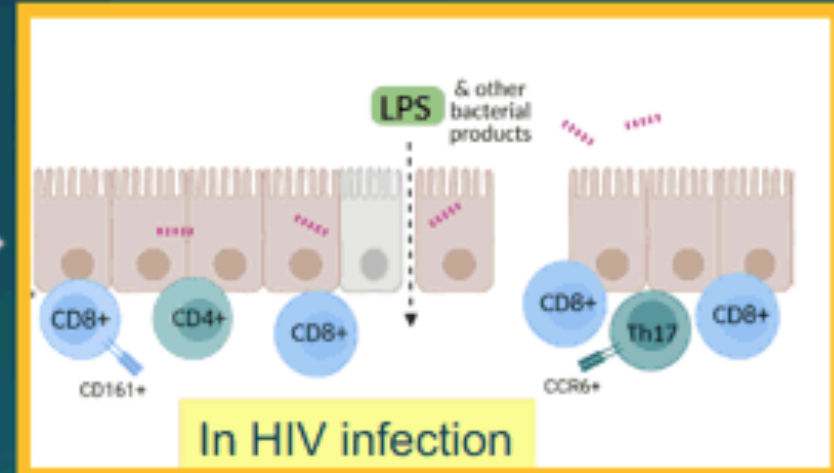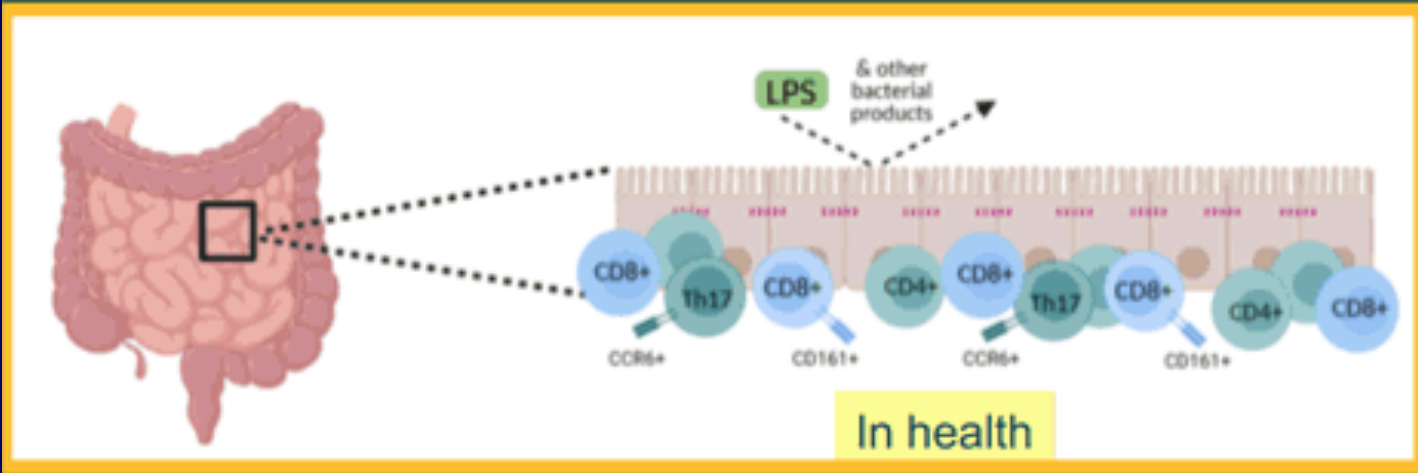
In HIV infection

Intestinal damage with HIV infection

Immune changes including:

- CD4+ T cells in the GI tract are depleted during HIV infection, especially Th17 cells
- Loss of IL-17 producing CD161+CD8+ mucosal associated invariant T cells

Structural damage:

- Enterocyte apoptosis
- Decreased tight junction and adherens junction protein expression
- Increased intestinal permeability
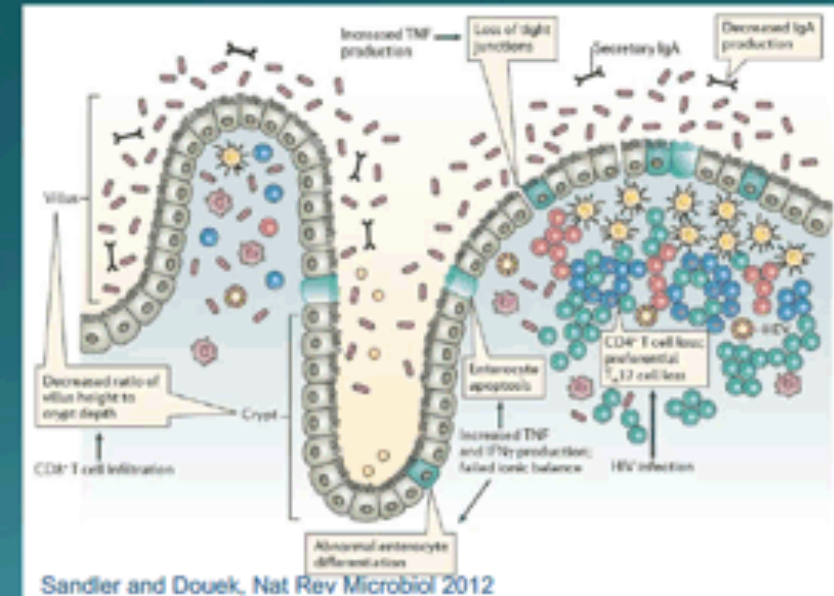
Brenchley et al. Nature Medicine 2006; Guadalupe et al. J of Virology 2006'; Estes et al. PLoS Pathog 2010; Nazli et al. PLoS Pathog 2010; Klatt et al. Mucosal Immunol 2012; Cosgrove et al. Blood 2013

Sandler and Douek, Nat Rev Microbiol 2012

Lo, CROI, 2022

Intervention: Glucagon-like peptide-2

- GLP-2 is a gastrointestinal hormone released by intestinal L-cells that regulates intestinal epithelial cell growth and functions related to absorption of nutrients

- GLP-2 restores intestinal epithelium and promotes mucosal healing

- In animal models of intestinal injury, GLP-2 reduces intestinal permeability, microbial translocation and intestinal inflammation

- A GLP-2 analog, teduglutide, is FDA approved for short bowel syndrome

Figure modified from Drucker et al. JCI 2017

Drucker et al. AJP 1999
Cani et al. Gut 2009
Drucker et al. JCI 2017

Hypothesis

Lo, CROI, 2022
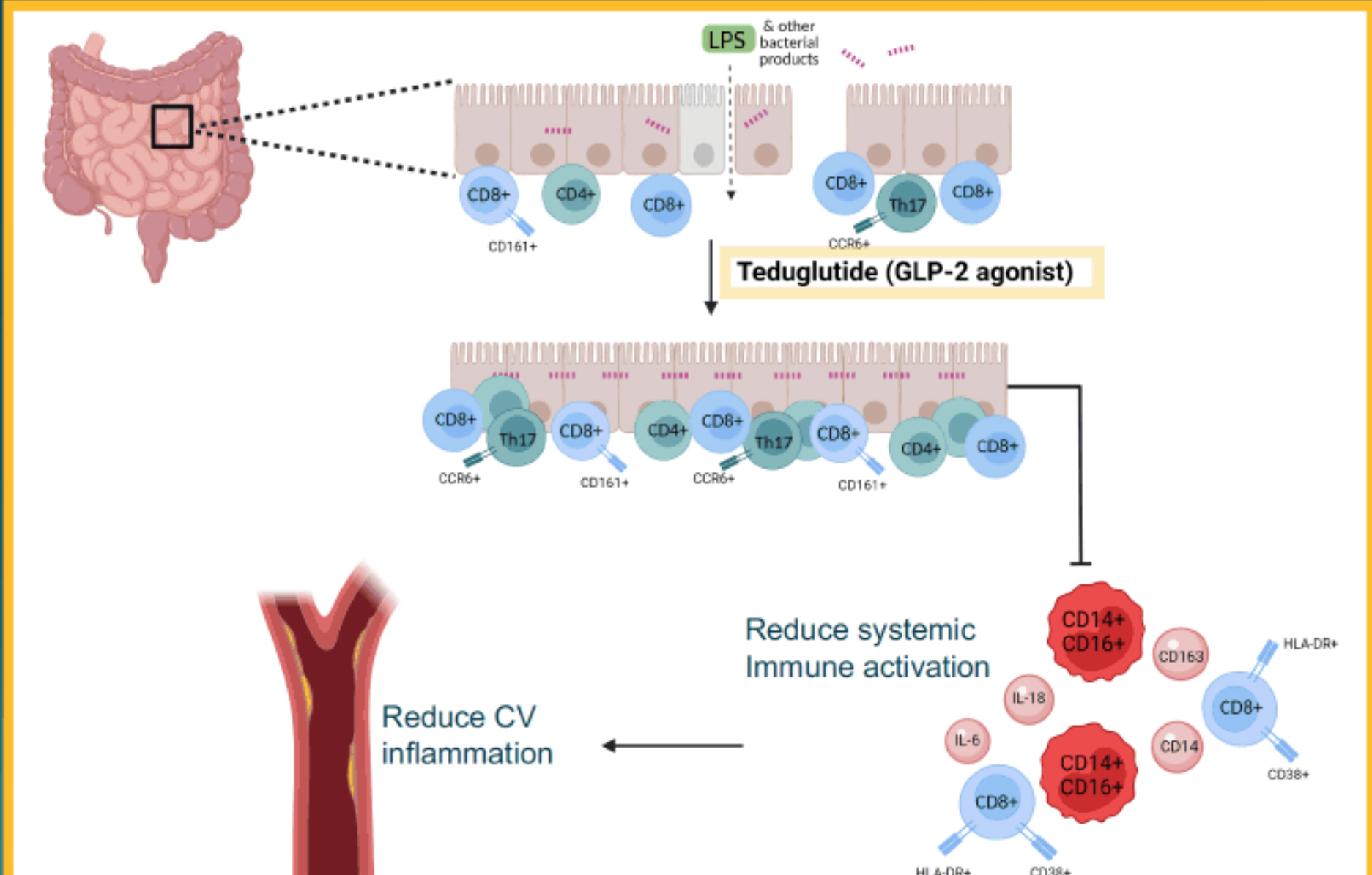
Baseline Characteristics

9/17 in teduglutide arm were analyzed.
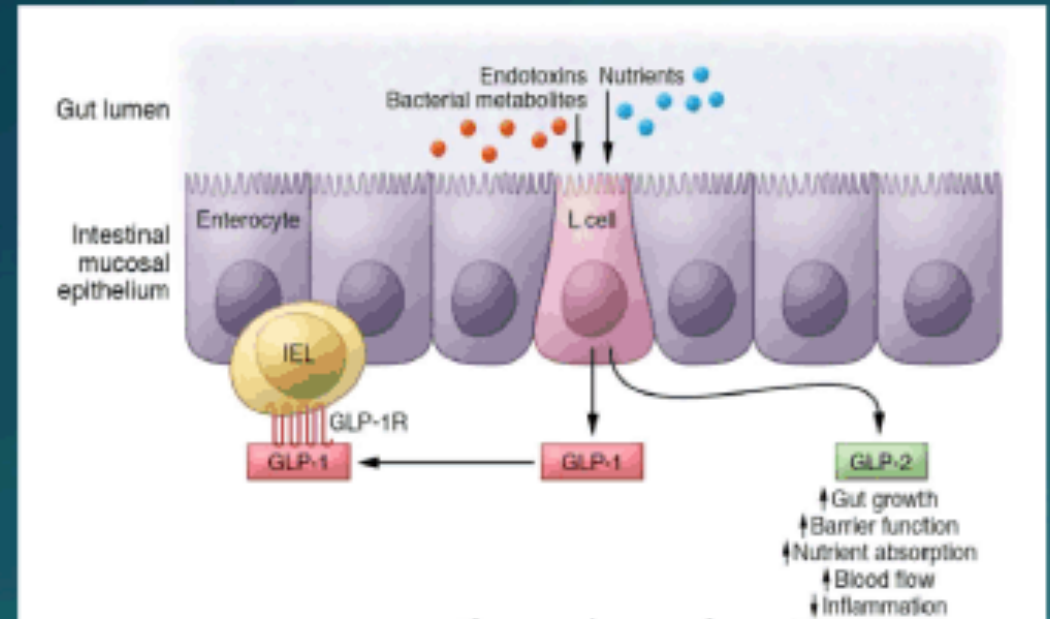4 discontinued intervention because of adverse effects

	Teduglutide (N = 17)	Placebo (N = 15)	p-value
Age, years	58.3 [50.1-59.8]	54.6 [49.5-59.2]	0.62
Sex (male), %	76.5	80.0	0.81
Race, %			0.32
White	64.7	40.0	
Black/African American	23.5	46.7	
More than one race	11.8	6.7	
Other	0.00	6.7	
Active smoker, %	29.4	40.0	0.53
Viral load < 200 cp/mL, %	100.0	100.0	
Current ART use, %	100.0	100.0	
NNRTI, %	17.7	33.3	0.31
PI, %	23.5	26.7	0.84
INSTI, %	76.5	60.0	0.32
CD4+ T-cell Count	639 ± 165	685 ± 225	0.51
Nadir CD4 Count (reported)	199 [20.5-382.5]	200 [50-350]	0.98
BMI (kg/m²)	27.1 ± 5.0	28.6 ± 4.4	0.36
Current statin use, %	41.2	26.7	0.39
HbA1c, %	5.5 ± 0.4	5.6 ± 0.3	0.54
Total Cholesterol, mg/dL	180.82 ± 32.78	186.33 ± 35.04	0.65
LDL Cholesterol, mg/dL	102.53 ± 27.93	113.93 ± 33.28	0.30
HDL Cholesterol, mg/dL	50.94 ± 16.54	48.33 ± 17.54	0.67
Triglycerides, mg/dL	129 [83.5-174.5]	105 [95-141]	0.43

Results: Primary Endpoint
Change in Arterial Inflammation

Treatment effect= -21%
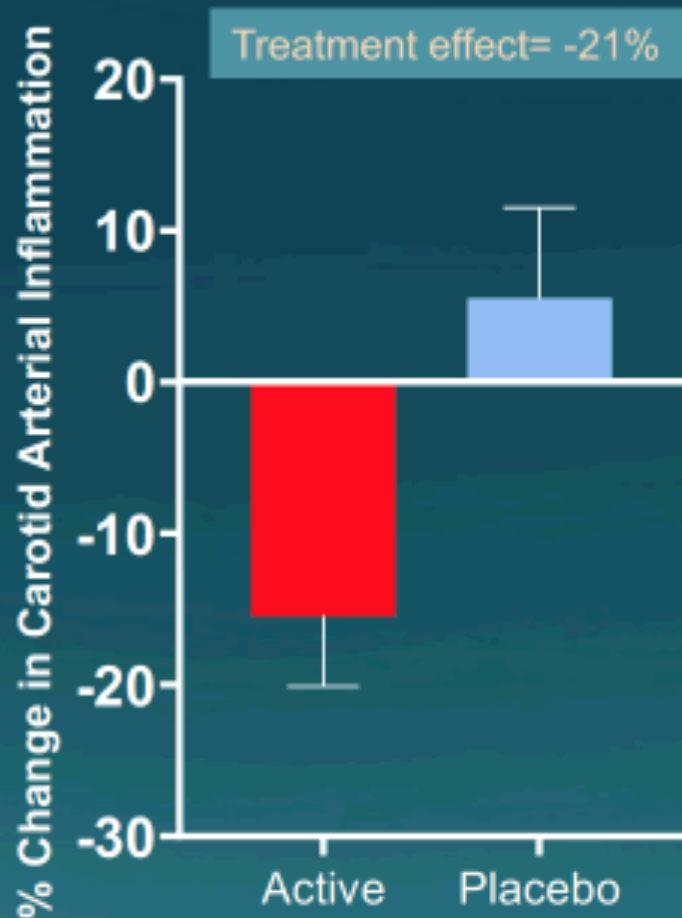
Primary analysis
Carotid arterial inflammation:
Target-to-background ratio of most diseased segment of index carotid vessel,
ANCOVA p=0.01

ITT (including participant in placebo group who stopped ART)
ANCOVA p=0.03

Also:
Decrease in activated monocytes
Decrease in activated CD8+ cells
Trends towards increase in intestinal TH17 cells

Adipose tissue fibrosis is linked to metabolic dysfunction

Hydroxyproline Assay

Hydroxyproline

Hydroxyproline is a direct measurement of collagen
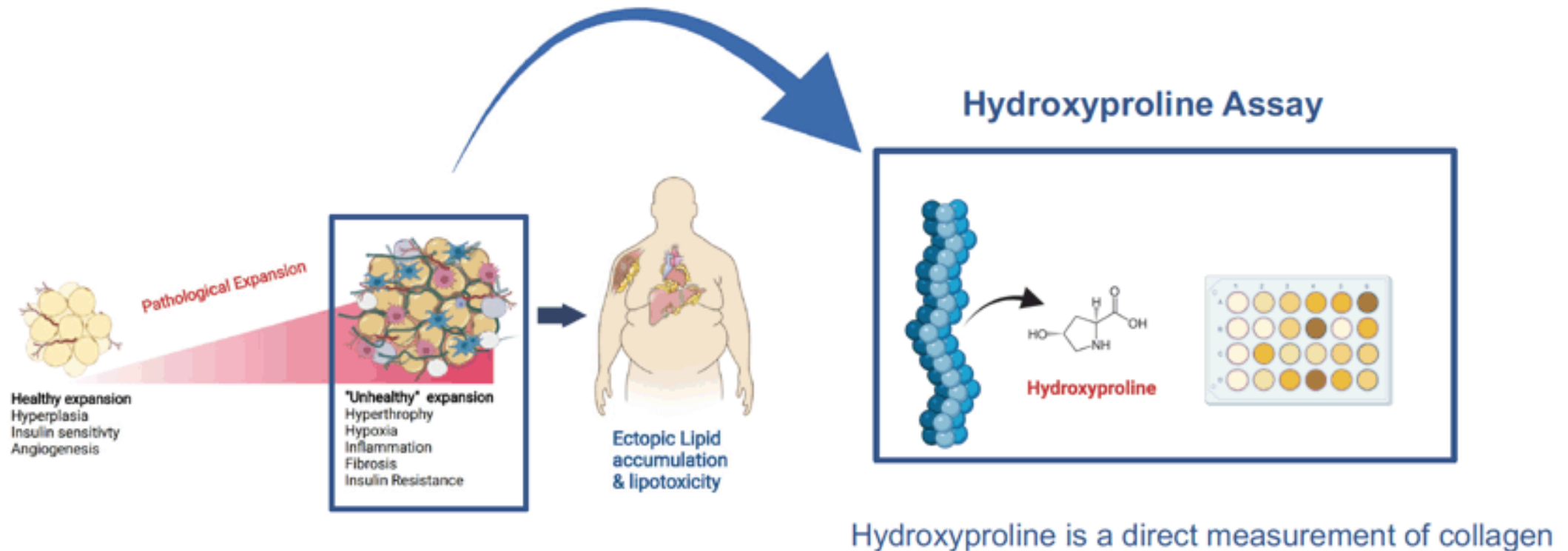
Kliment C. et al. *Int. J Clin Pathol* 2011; Alba, DL. et al. *J. Clin. Endocrinol. Metab.* 2018

Alba, CROI, 2022

People with treated HIV have higher levels of adipose tissue fibrosis
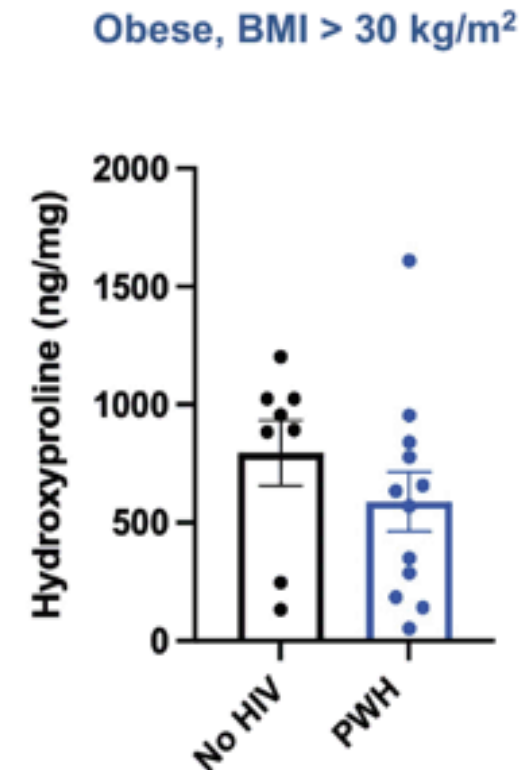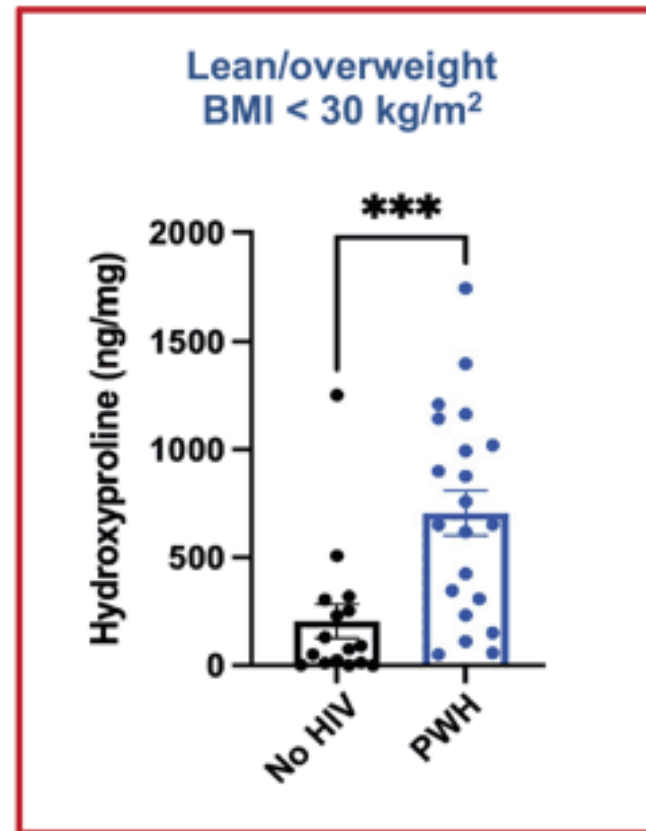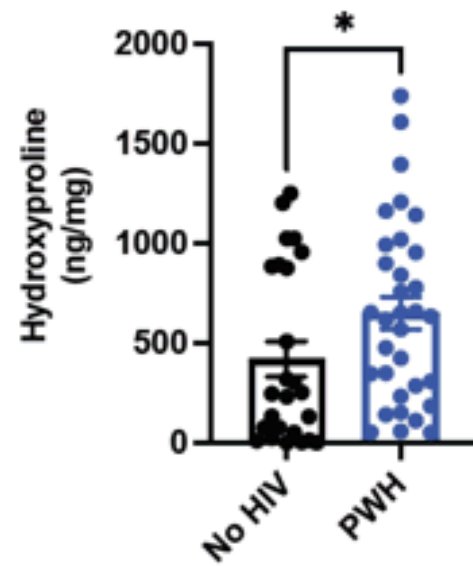
*p < 0.05, *** p<0.01, *** p<0.001

IR and visceral adiposity are strongly correlated to various inflammatory pathways
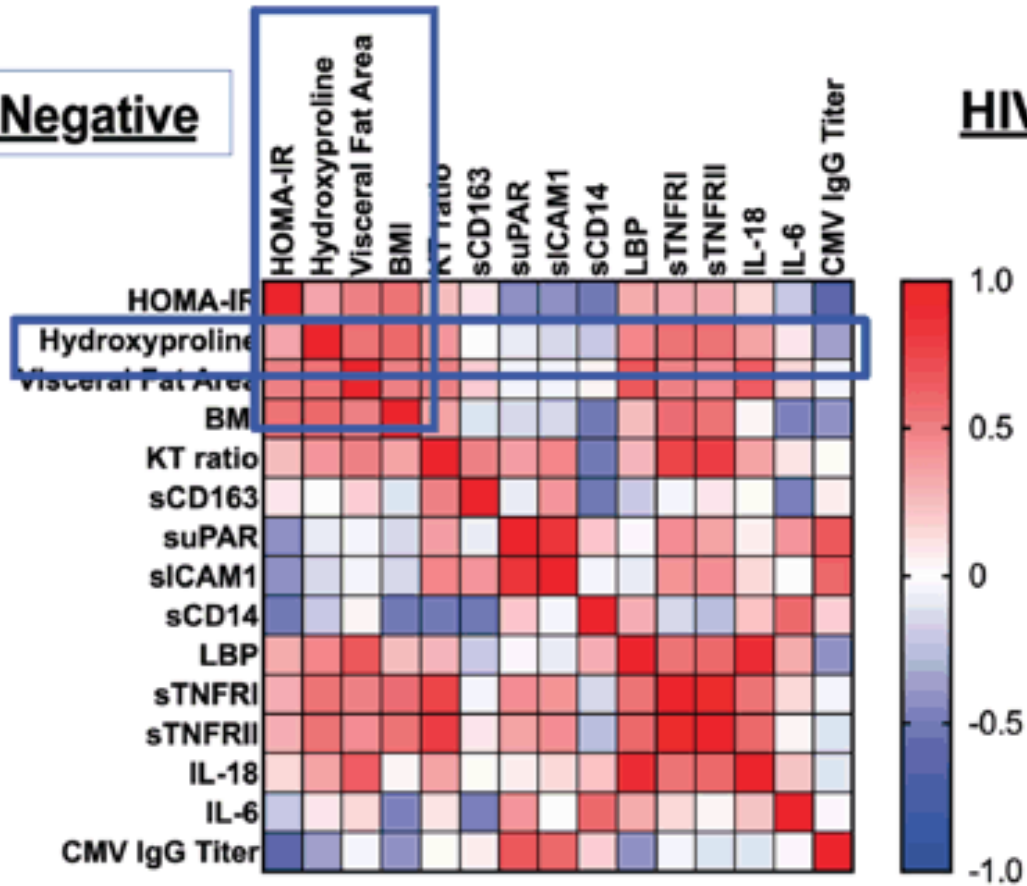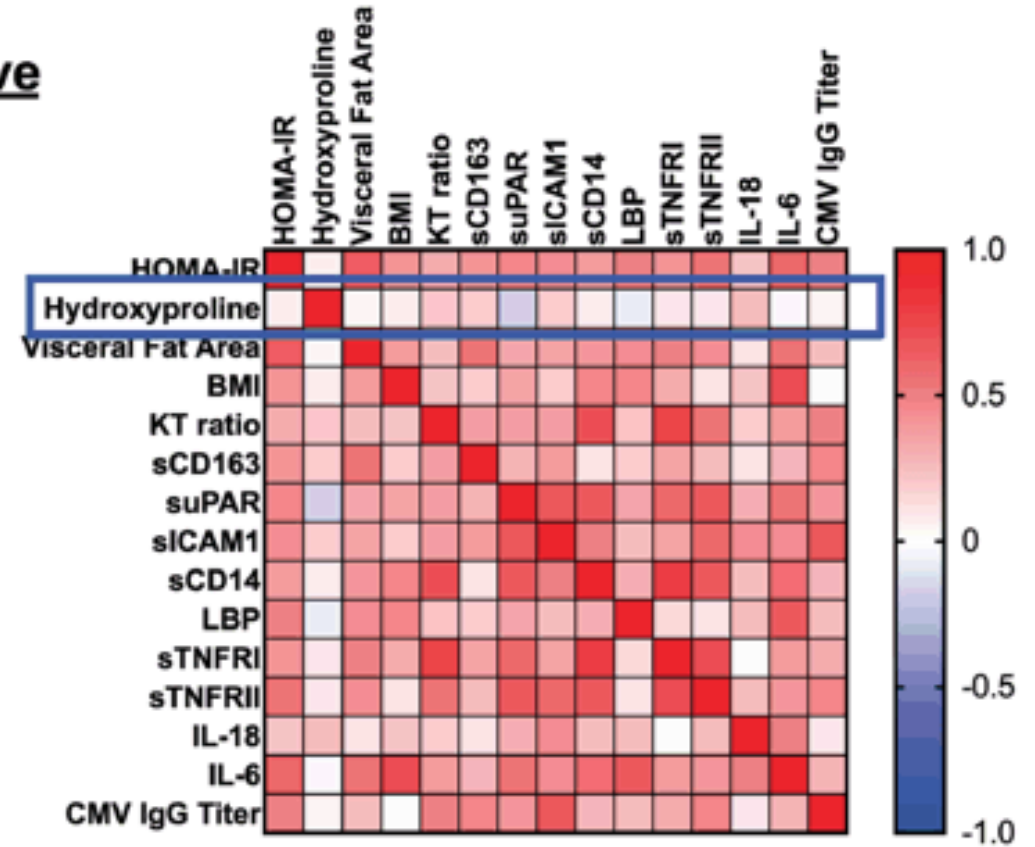
*Spearman's correlation coefficient are denoted by the color scale

Physical function generally declines over time

Quality of Life/ Physical & Cognitive Function

Age

50

100
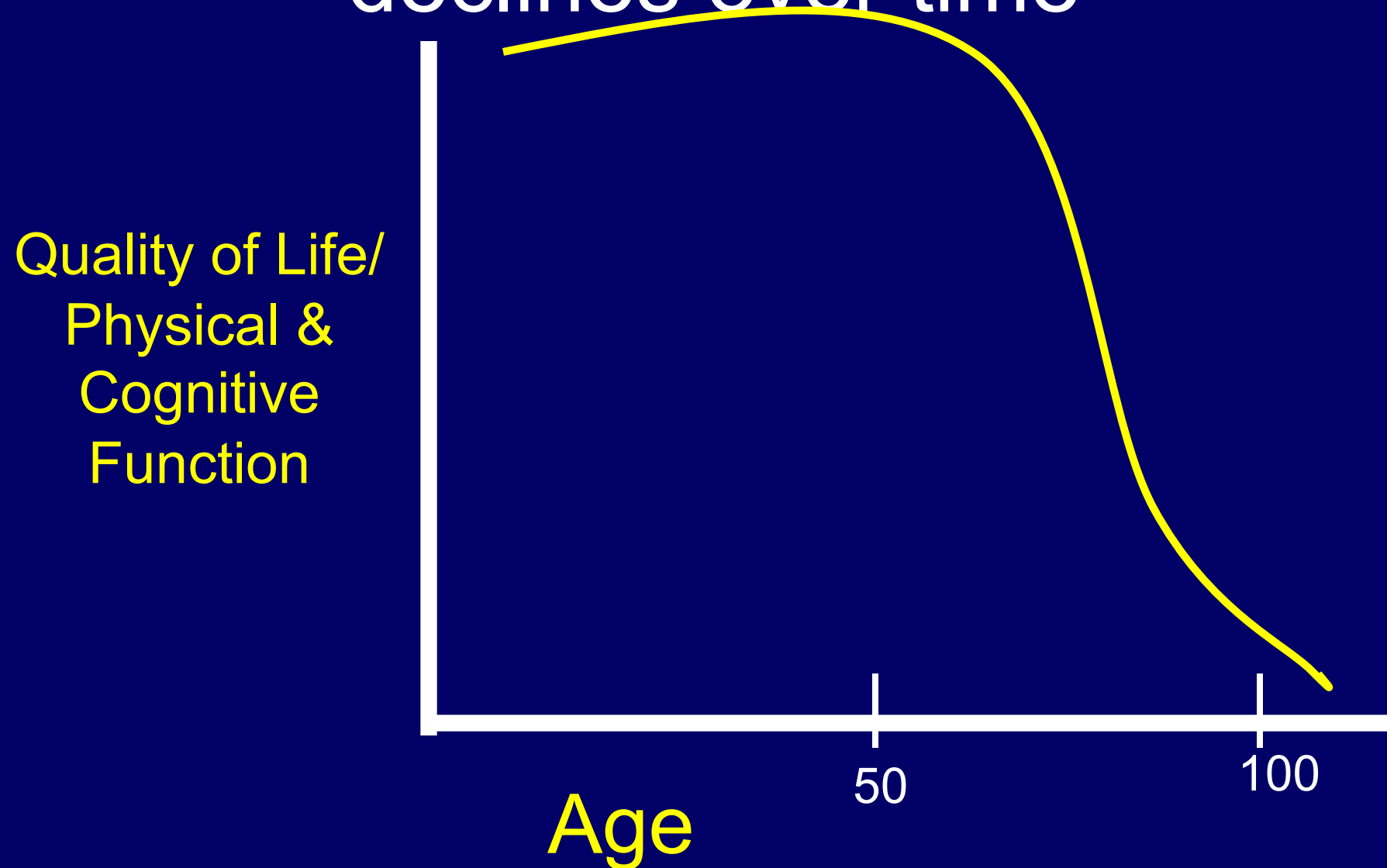
Physical function impairment is common among PLWH around the globe: REPRIEVE Study

Erlandson, CROI, 2022
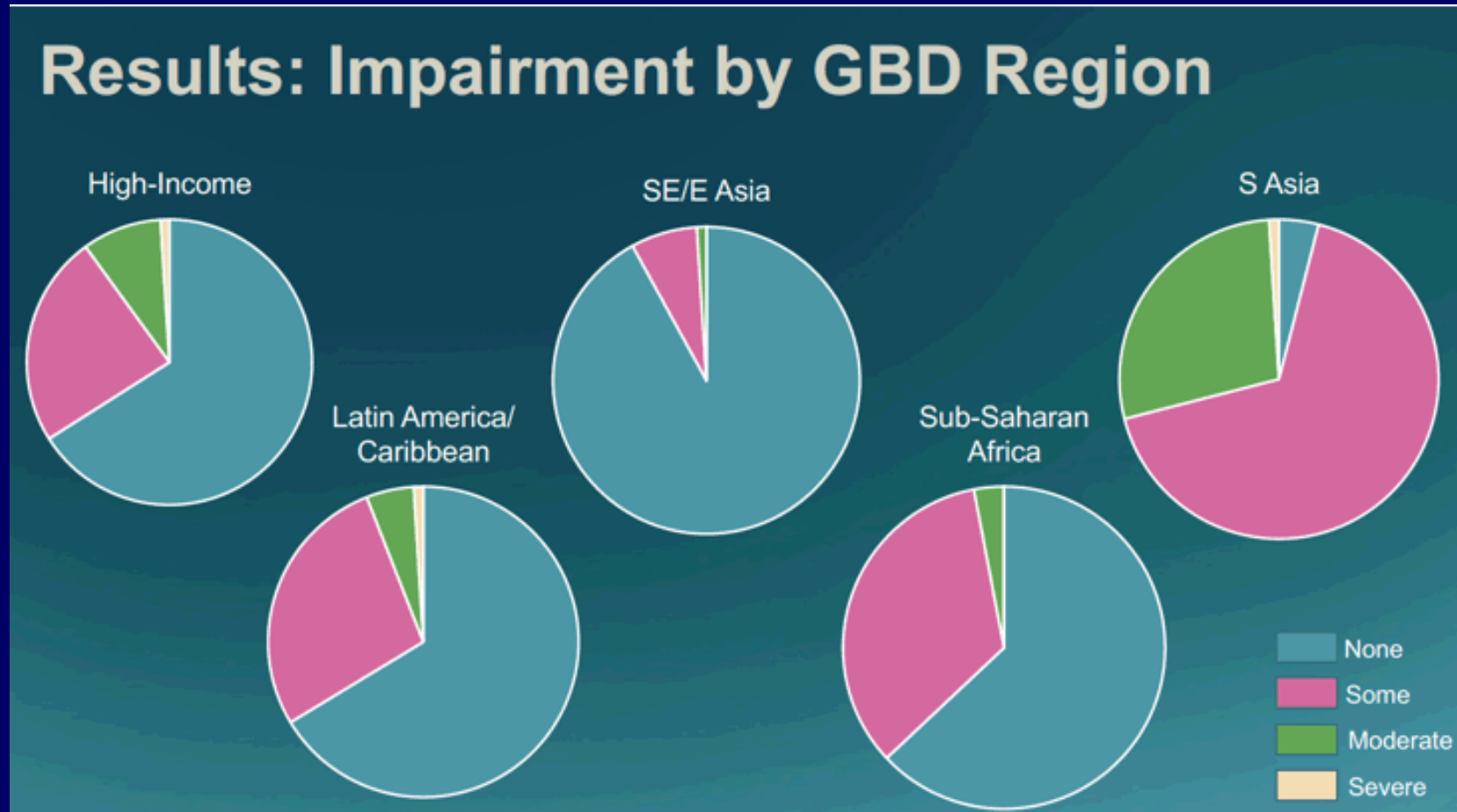
Functional Impairment and Cardiometabolic Risk

	N		Est.	95% CI	P-value
Impairment:		**Difference in ASCVD Risk Score by Functional Status**			
No impairment	4940		ref.		<0.001
Some impairment	2139		0.3	(0.1, 0.4)	
Moderate-Severe impairment	657		0.5	(0.2, 0.8)	
		Difference in Waist Circumference by Functional Status			
No impairment	4876		ref.		<0.001
Some impairment	2111		3.0	(2.3, 3.7)	
Moderate-Severe impairment	646		6.0	(4.9, 7.2)	

Adjusted for GBD Region

Difference in Outcome (>> Higher outcome >>)

- Moderate to severe impairment was associated with 0.5 point greater ASCVD risk score, 6 cm greater waist circumference, and a 1.45 greater odds of metabolic syndrome

Frailty: A Brief Overview

- **Weight loss**

- **Weakness**

- **Exhaustion**

- **Slowness**

- **↓ Physical Activity**

Fried LP, *et al.* 2005
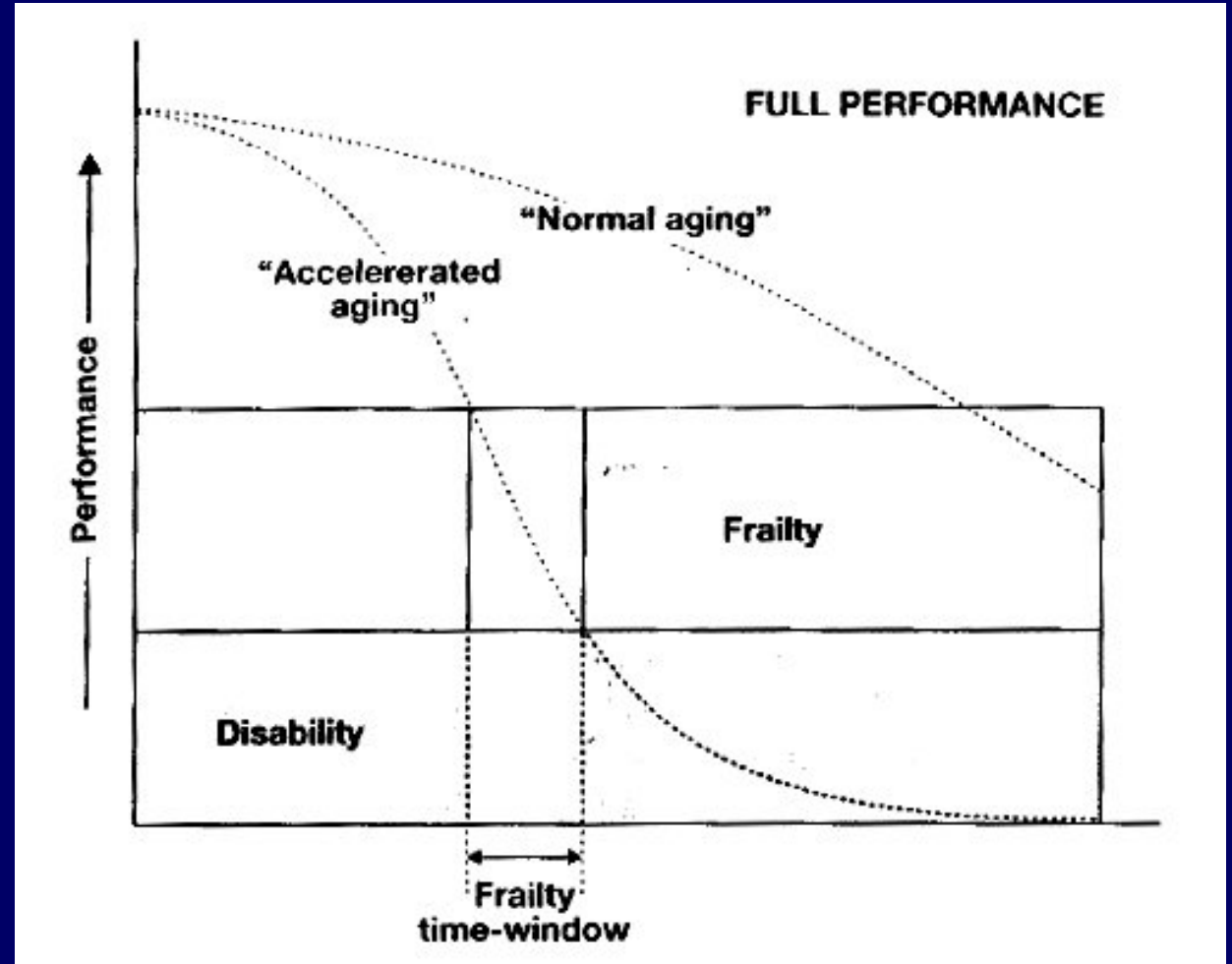
HIV+ Men Are More Frail At a Younger Age vs HIV- Men: MACS
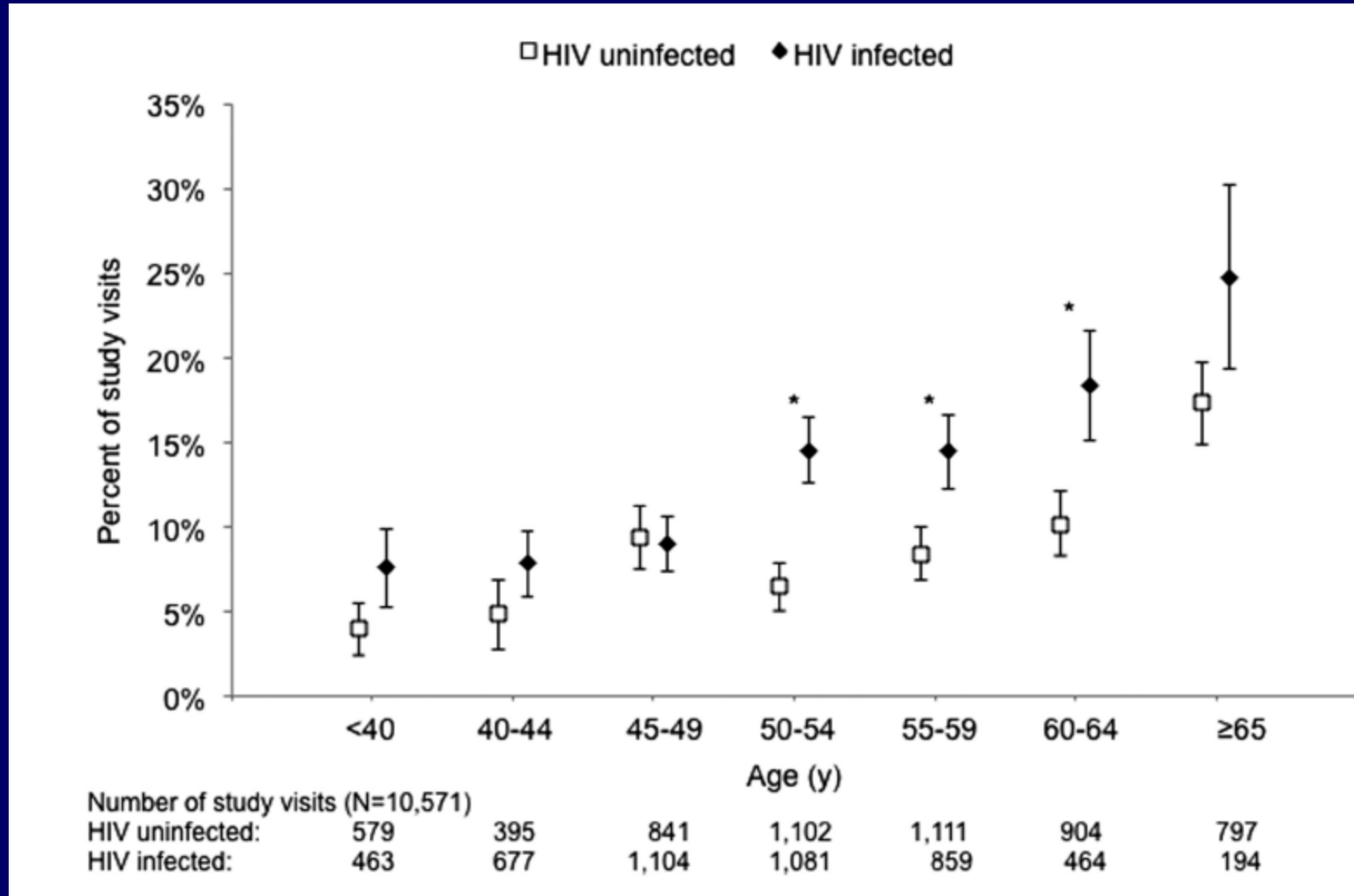
Althoff, J of Gerontology, 2013

The FUNCFRAIL Score to discriminate Frailty in Older Adults with HIV

THE FUNCFRAIL SCORE

SCORE

- Age 65 or over [+2 p]
- Polypharmacy [+2 p]
- Diabetes [+1 p]
- Albumin < 4 g/L [+2 p]
- Falls [+1p]
- Not being satisfied with his/her life [+1 p]
- Not living alone or with a partner [2+ p]
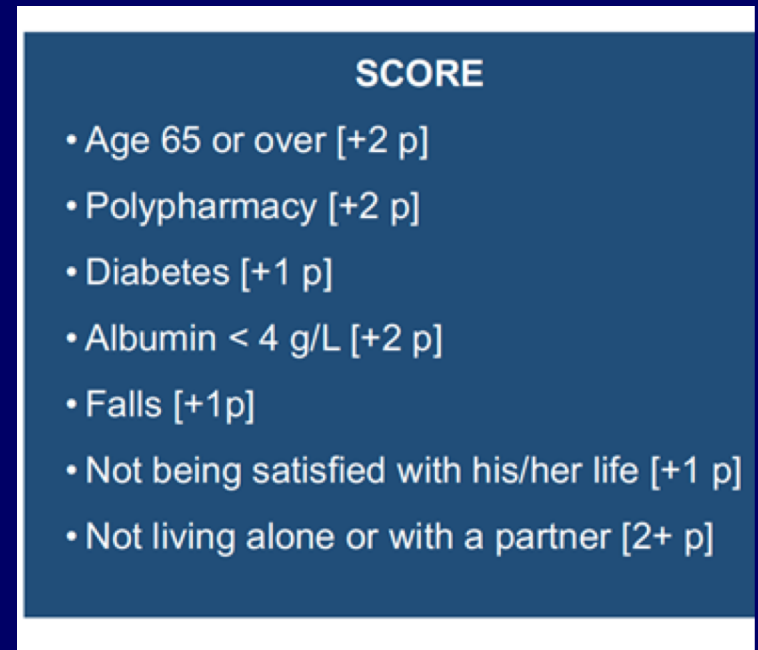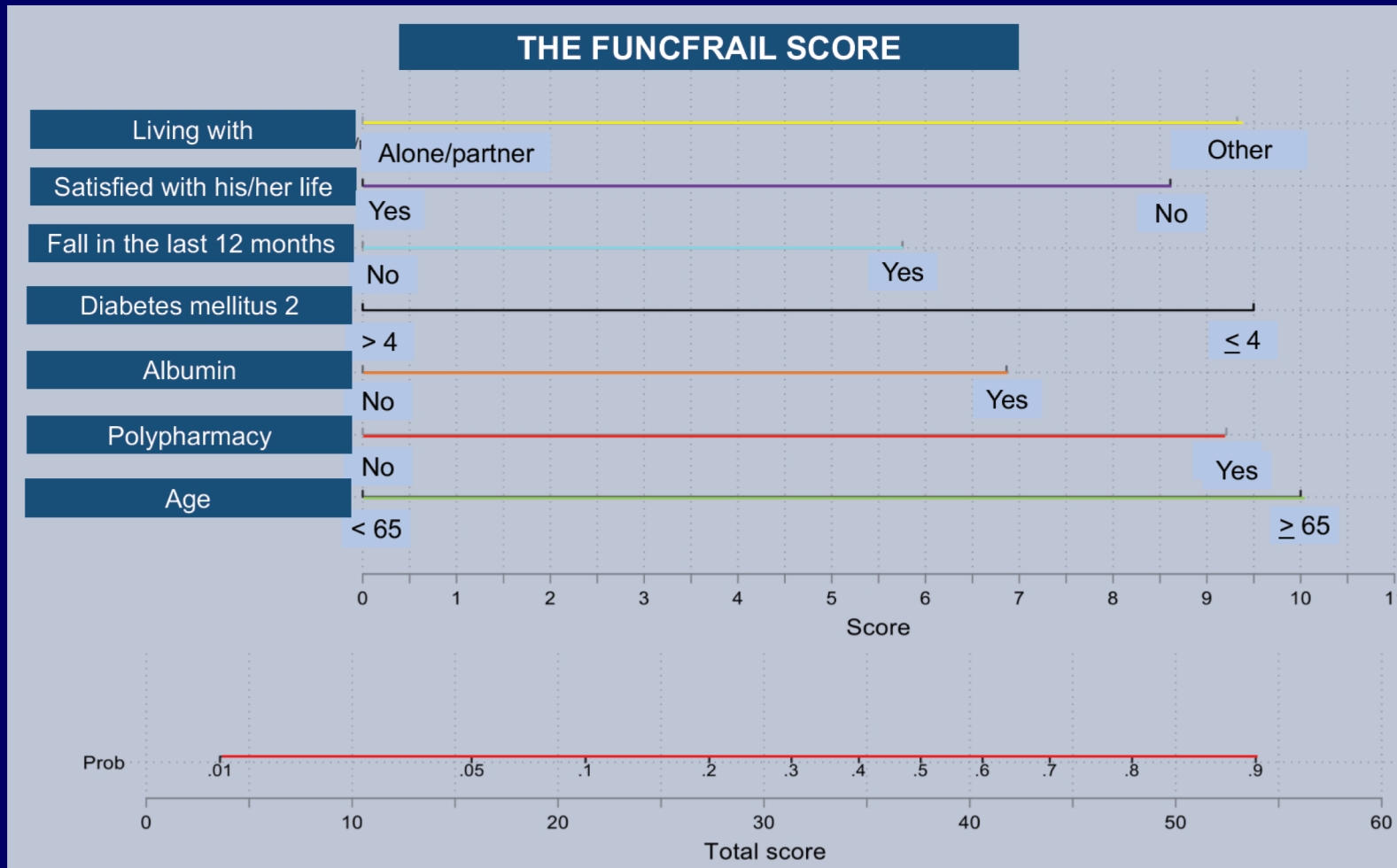
Range: 0-11
AUC 0.78 (0.71-0.85)

Sanchez-Conde, CROI, 2022

Anticholinergic Medications Associated with Falls and Frailty in PLWH:POPPY

Results

Demographics of PWH ≥ 50

Variable	N=699
Age (median (IQR)), years	57 (53-62)
Male, n (%)	612 (88)
White, n (%)	603 (86)
Unemployed, n (%)	99 (14)
High education, n (%)	479 (69)
Rec drugs last 6 months, n (%)	177 (25)

Prevalence of outcome

9% (63/673) reported recurrent falls

32% (126/609) met frailty criteria

Number of ACM prescribed

ACM number	Frequency n (%)
0	507 (73)
1	129 (18)
≥2 (maximum 9)	63 (9)

ACM1

ACM2

ACM3

Commonest ACM prescribed

ACM	Frequency n (%)
Codeine	36 (12)
Citalopram	34 (12)
Loperamide	25 (9)
Amitriptyline	21 (7)
Diazepam	17 (6)
Cetirizine	16 (5)

Doctor, CROI, 2022

Association between any ACM use and outcomes

Percentage of PWH reporting recurrent falls

p<0.001

■ No ACM ■ Using ACM

Percentage of PWH meeting frailty criteria

p<0.001

■ No ACM ■ Using ACM
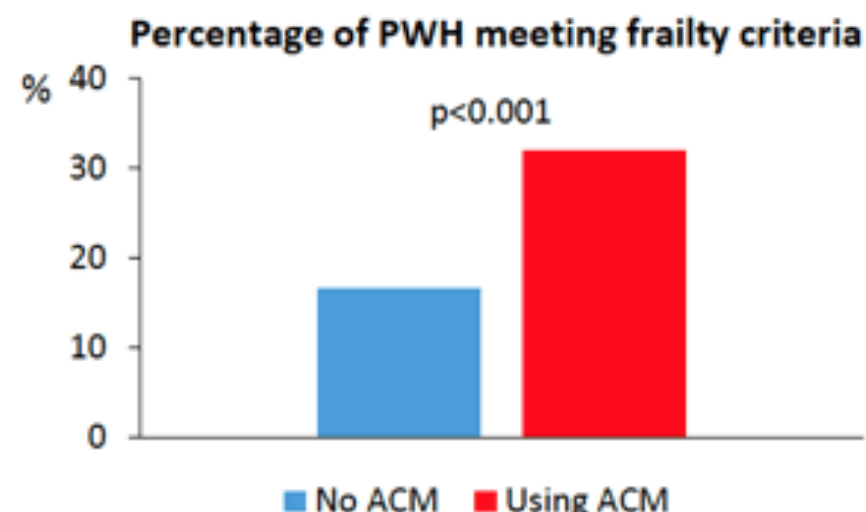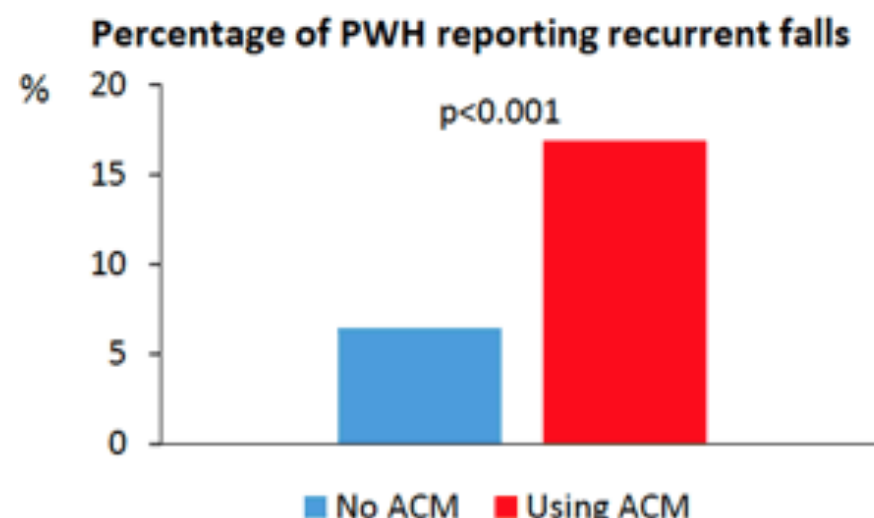
Final regression model of the association of using any ACM with recurrent falls and frailty

Adjustment	ACM	Recurrent falls			Frailty		
		OR	CI	P value	OR	CI	P value
Unadjusted	none	1	n/a		1	n/a	
	Any	3.3	1.9 - 5.9	<0.001	2.3	1.5 - 3.6	<0.001
Demographic/lifestyle	Any	2.5	1.3 - 4.6	0.004	1.8	1.1 – 3.0	0.02
Demographic/lifestyle and clinical factors	Any	1.9	0.9 - 4.0	0.08	1.7	0.9 – 3.0	0.08

Is there a dose relationship?

Association between <u>number</u> of ACM and recurrent falls

Number of ACMs	Adjustment		OR (95% CI)	p-value
0 (reference)			1 (1 - 1)	
1	Unadjusted		2.1 (1 - 4.2)	0.04
	Demographic/lifestyle factors only [1]		1.7 (0.8 - 3.5)	0.18
	Demographic/lifestyle factors plus clinical factors [2]		1.4 (0.6 - 3.2)	0.40
2 or more	Unadjusted		6.8 (3.3 - 14.1)	<0.001
	Demographic/lifestyle factors only [1]		4.5 (2.1 - 10)	<0.001
	Demographic/lifestyle factors plus clinical factors [2]		3.6 (1.4 - 9.4)	0.009

Odds ratio: 0.50 1.0 2.0 4.0 8.0 16.0

[1] age, work, marital status and recent recreational drug use
[2] additionally adjusted for number of non ACM co-medications, number of comorbidities and PHQ-9 score

Sleep and Frailty Among Men with and Without HIV

Table. Participant Characteristics by HIV Serostatus

| Characteristic	Men without HIV (N = 356)	Men living with HIV (N = 446)
Frailty phenotype	30 (8%)	49 (11%)
Age in years, median (IQR)	63.0 (56.5-68.7)	56.3 (49.2-63.6)
BMI (kg/m^2), median (IQR)	27.0 (24.1-30.7)	26.5 (23.4-30.2)
Type 2 diabetes	130 (38%)	187 (44%)
Suppressed HIV viral load		423 (96%)
Current CD4 cell count, median (IQR)		704.5 (526.0-912.0)
Total sleep time	162 (46%)	236 (53%)
< Median, 382 minutes		
Sleep efficiency	163 (46%)	224 (50%)
< Median, 93%		
Wake after sleep onset	179 (50%)	224 (50%)
≥ Median, 33 minutes		

Figure. Probability ratio of frailty by sleep parameter and by HIV serostatus

Masters, CROI, 2022
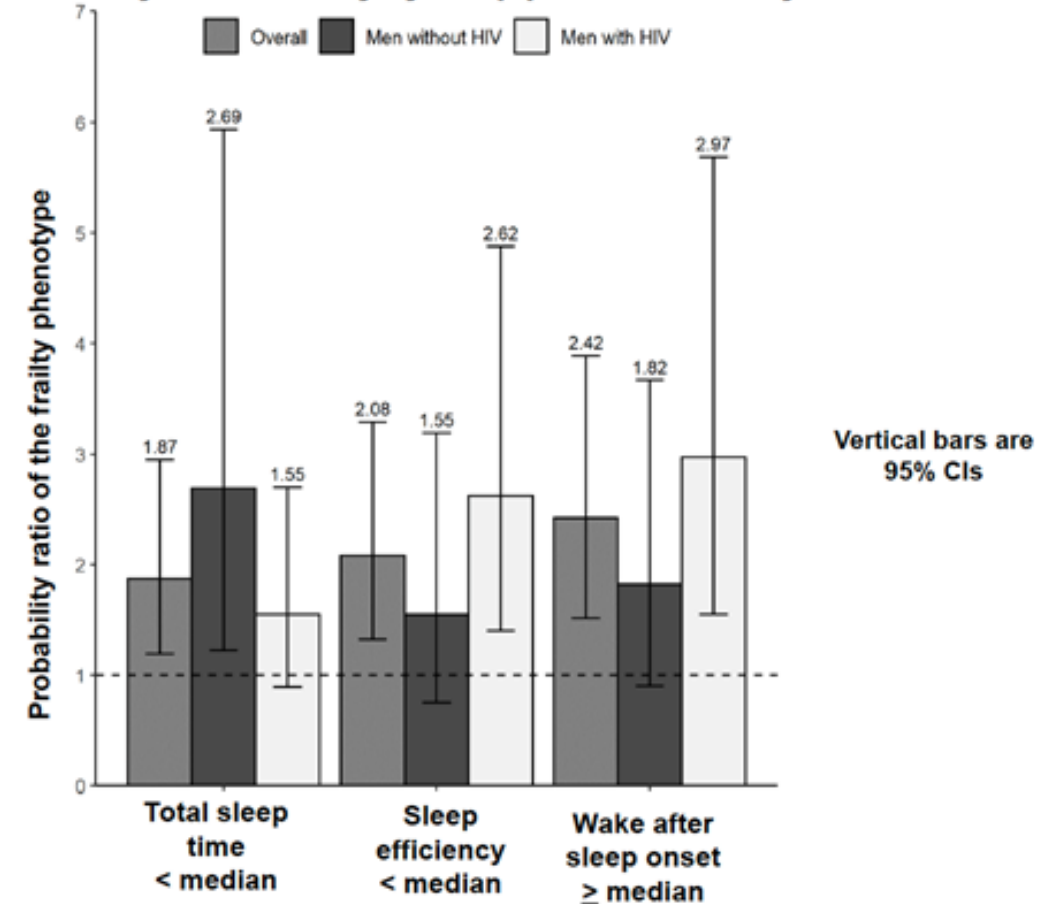
Poor sleep in women with HIV association with activation of key inflammatory pathway

	HIV-uninfected N=139			WLWH N=141			
	Effect estimate	95% CI	P-value	Effect estimate	95% CI	P-value	P for interaction
Kynurenine-to-tryptophan ratio							
Mean sleep start time (hr)	0.98	0.94, 1.02	0.401	0.94	0.90, 0.98	0.007	0.135
Mean sleep end time (hr)	1.03	0.98, 1.07	0.297	0.98	0.93, 1.03	0.354	0.165
Mean % sleep	1.03	0.91, 1.16	0.682	0.87	0.78, 0.97	0.013	0.049
Mean sleep fragmentation	1.00	0.93, 1.09	0.921	1.13	1.05, 1.22	0.001	0.032
Mean number of wake bouts	0.96	0.90, 1.02	0.199	1.10	1.04, 1.17	0.001	0.002

Rogando, CROI, 2022

FRAILTY

A Circulation
1 Increased inflammatory cytokines
TNFα
IFNγ
IL-6
2 Enzymes
IDO
KMO
3HK
Blood
Immune cell KYN
TRP
3 Increased KYN in blood and tissue

Liver:
Dispersion of TRP, KYN & NAD+ production

Kidney:
Decreased KYN excretion

B Muscle
KYN
KAT
KYN KA
Healthy
Normal
Atrophy
Muscle wasting
KYN
KYN KAT KA
Denervation
Sedentary lifestyle

Westbrook, JCI, 2022
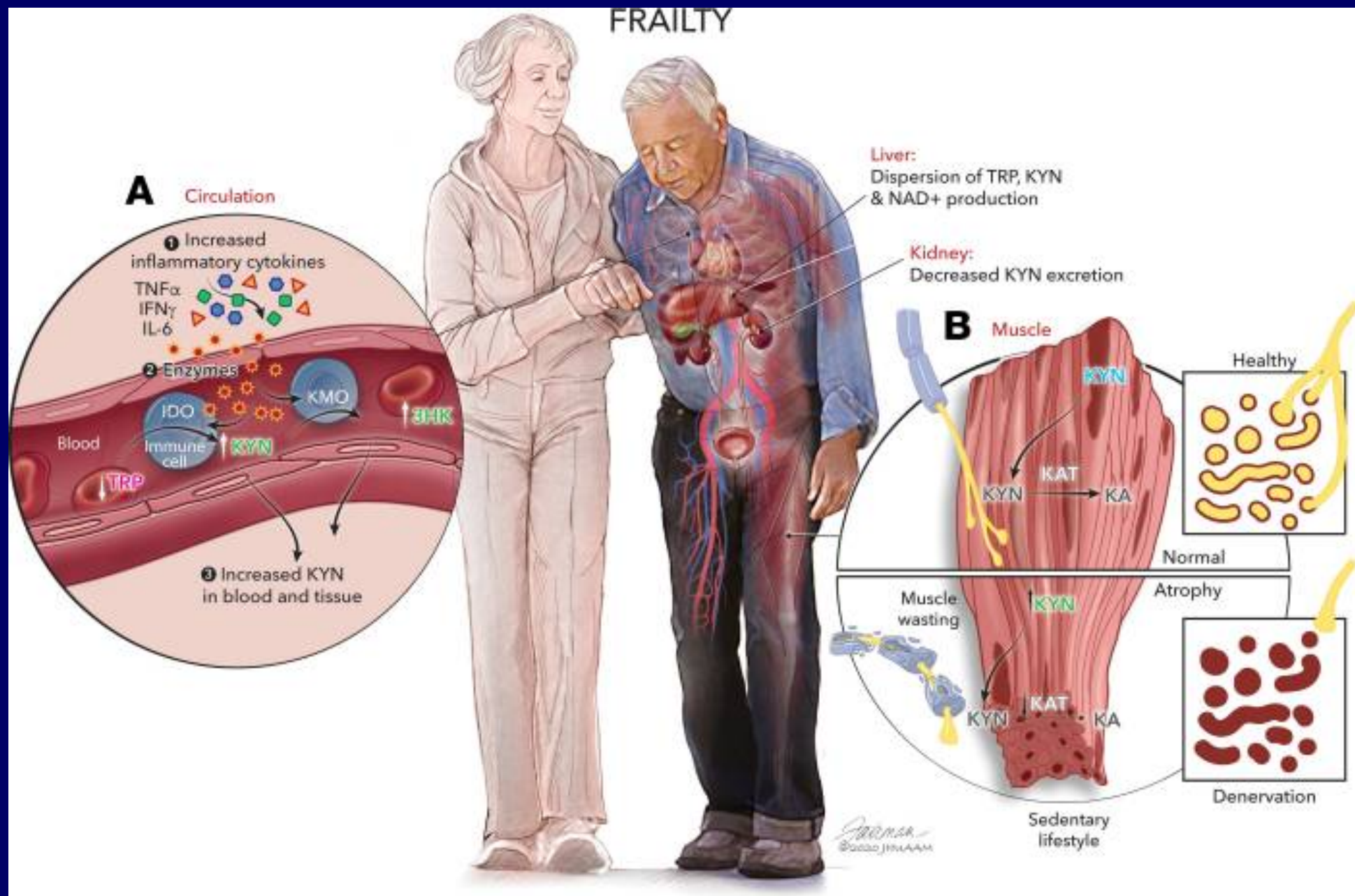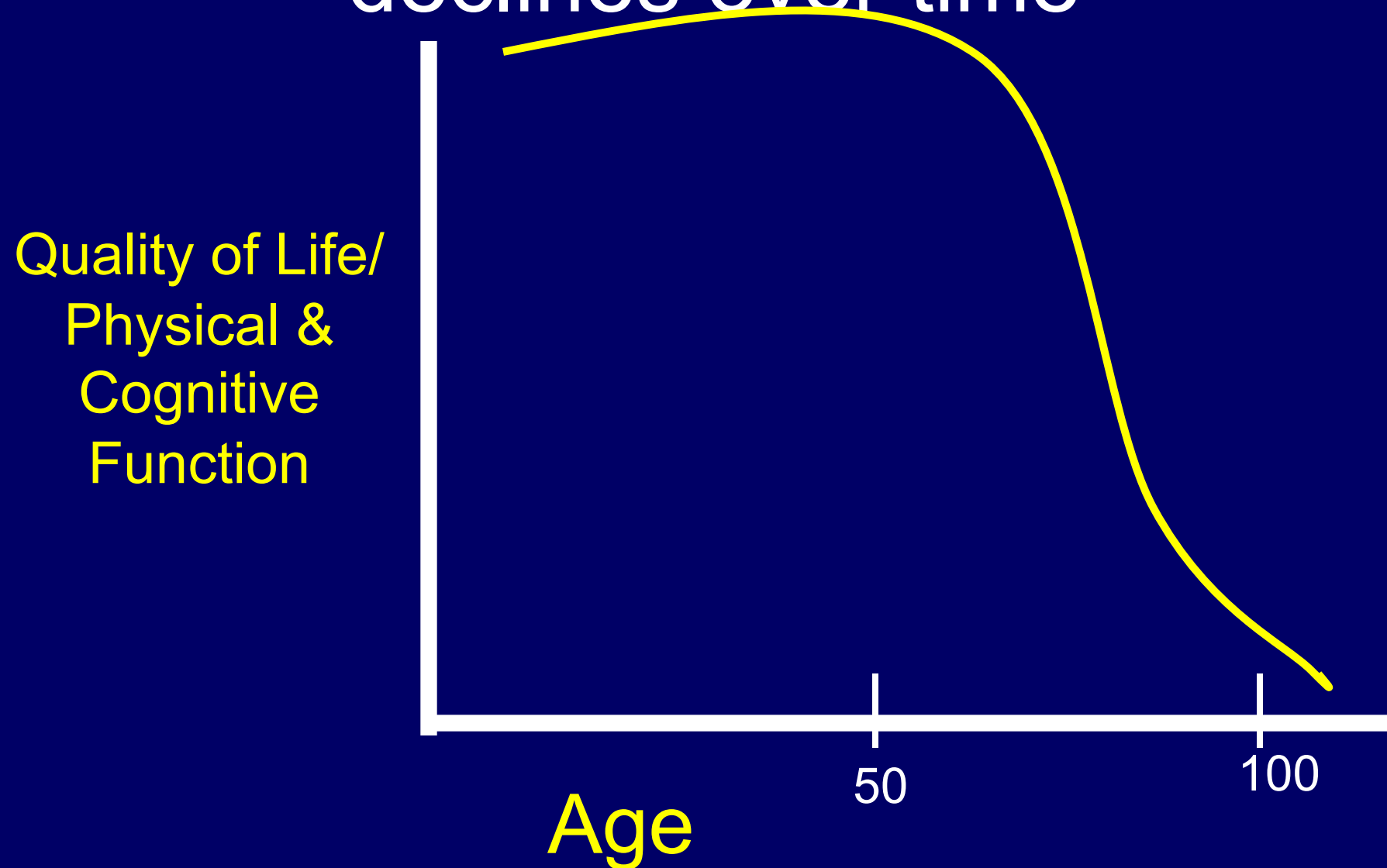
A novel comorbidity index predicts 12 y cognitive change in people with chronic HIV

- Depression
- COPD
- Hypertension

- Performed better than:
  - Charlson
  - VACS
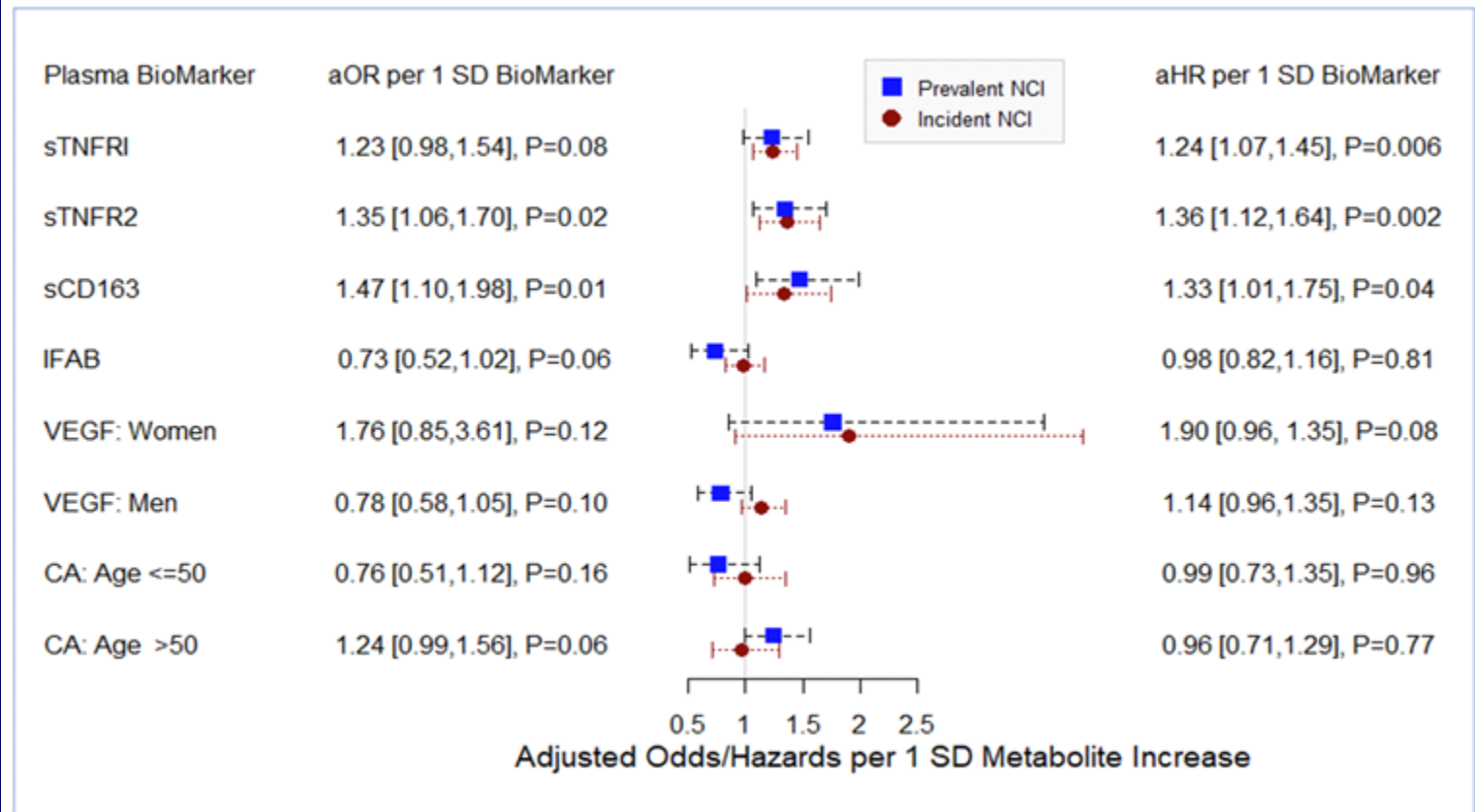 - Framingham

Participants with higher SCI at baseline had significantly worse NC performance over 12 years

Figure. Bar plots of global summary change score at each level of the SCI. Error bars denote 95% confidence intervals

Ellis, CROI, 2022
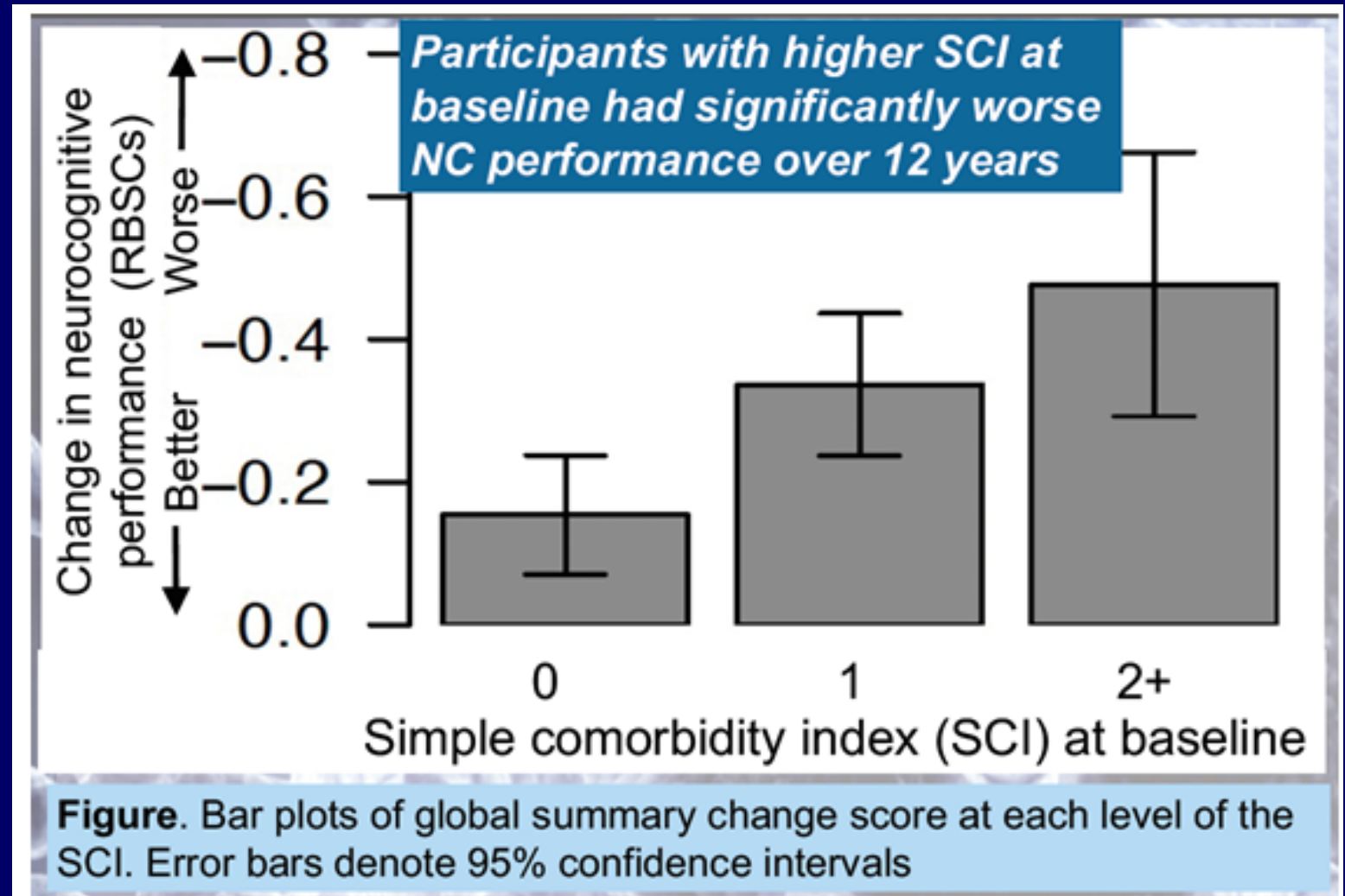
Associations Between Plasma Biomarkers and Neurocognition in ART-Treated PWH

Table 1: Baseline Characteristics, *n=376*

| Age vrs		
	(median, IQR)	51 (46, 56)
	Men (n, %)	306 (81%)
	Women (n, %)	70 (19%)
	Black not Hispanic (n, %)	107 (28%)
	White (n, %)	178 (47%)
	Hispanic regardless of race (n, %)	91 (24%)
CD4	(median, IQR)	614 (449, 825)
VL<50 copies/mL	(n, %)	349 (93%)
NCI	(n, %)*	101 (27%)
*There were 104 incident NCI cases during a median follow-up of 173 wks		

FIGURE 1: Adjusted Odds & Hazard Ratios for Baseline Associations by Plasma Biomarkers with Prev. & Inc. NCI*

Plasma BioMarker	aOR per 1 SD BioMarker		aHR per 1 SD BioMarker
sTNFRI	1.23 [0.98,1.54], P=0.08		1.24 [1.07,1.45], P=0.006
sTNFR2	1.35 [1.06,1.70], P=0.02		1.36 [1.12,1.64], P=0.002
sCD163	1.47 [1.10,1.98], P=0.01		1.33 [1.01,1.75], P=0.04
IFAB	0.73 [0.52,1.02], P=0.06		0.98 [0.82,1.16], P=0.81
VEGF: Women	1.76 [0.85,3.61], P=0.12		1.90 [0.96, 1.35], P=0.08
VEGF: Men	0.78 [0.58,1.05], P=0.10		1.14 [0.96,1.35], P=0.13
CA: Age <=50	0.76 [0.51,1.12], P=0.16		0.99 [0.73,1.35], P=0.96
CA: Age >50	1.24 [0.99,1.56], P=0.06		0.96 [0.71,1.29], P=0.77

Legend: ■ Prevalent NCI ● Incident NCI

0.5 1 1.5 2 2.5
Adjusted Odds/Hazards per 1 SD Metabolite Increase

*No associations were evident with IL-6 or sCD14 (data not shown).

Kalayjian, CROI, 2022

Decline in Function May Not Be Gradual

Quality of Life/ Physical & Cognitive Function

Heart Attack

Heart Failure

Hip Fracture

Stroke

Age

50

100
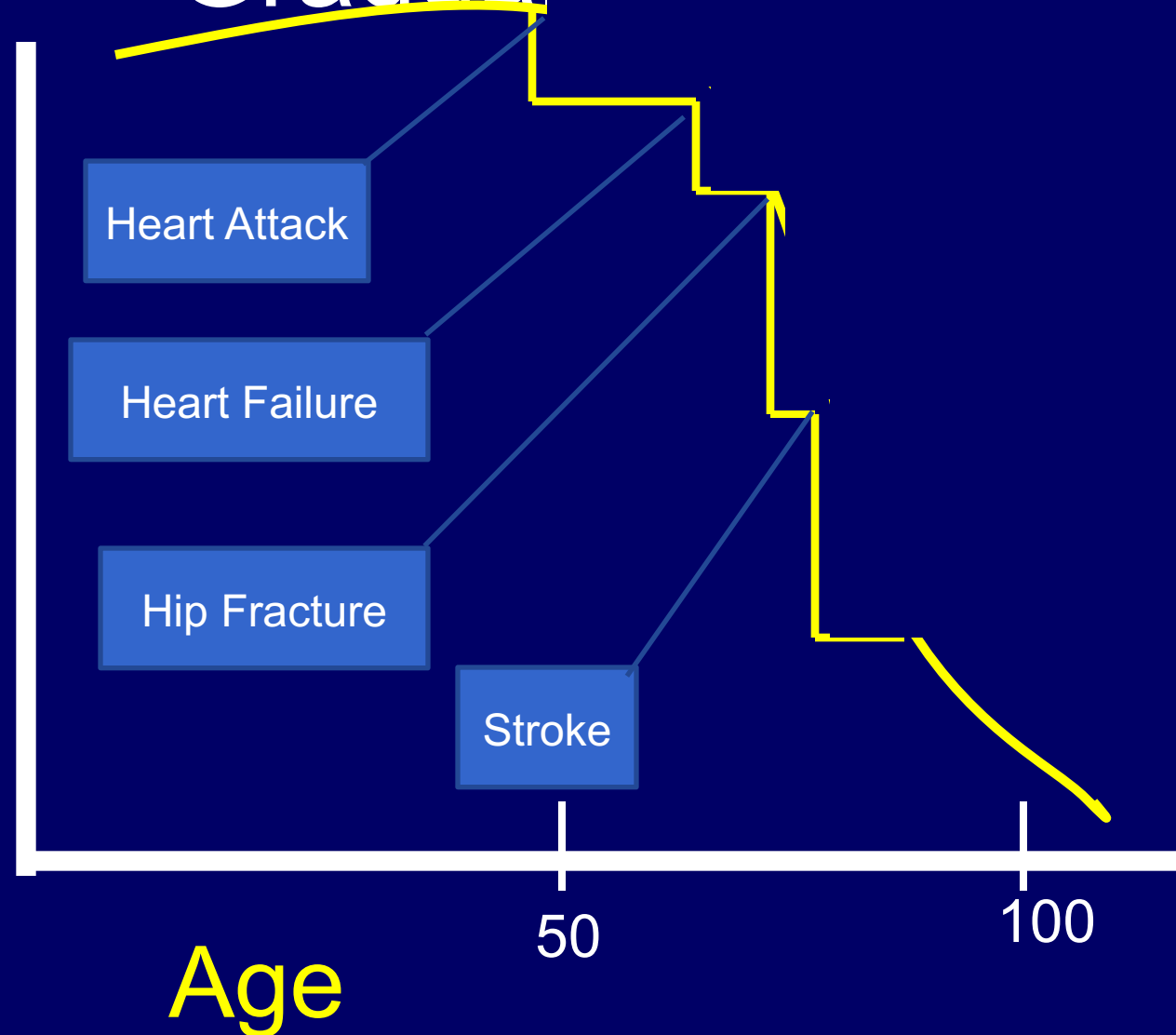
Let's Get Screened!

Condition	Tests	Frequency
Diabetes	Fasting Glucose Hgb A1C	Yearly
High Cholesterol	Lipid Panel	Yearly
High Blood Pressure	BP Measurement	At least Yearly
Kidney Disease	Serum Creatinine Urine protein test	Every 6-12 months
Osteoporosis	DXA Scan	Age 50+
Anal/Cervical Cancer	Pap test	Yearly
Lung Cancer	CT (if smoker)	debated
Liver Cancer	Ultrasound (if HBV or HCV+)	Yearly
Breast Cancer	Mammogram	Yearly
Colon Cancer	Colonoscopy	Every 5 years
Prostate Cancer	PSA	debated

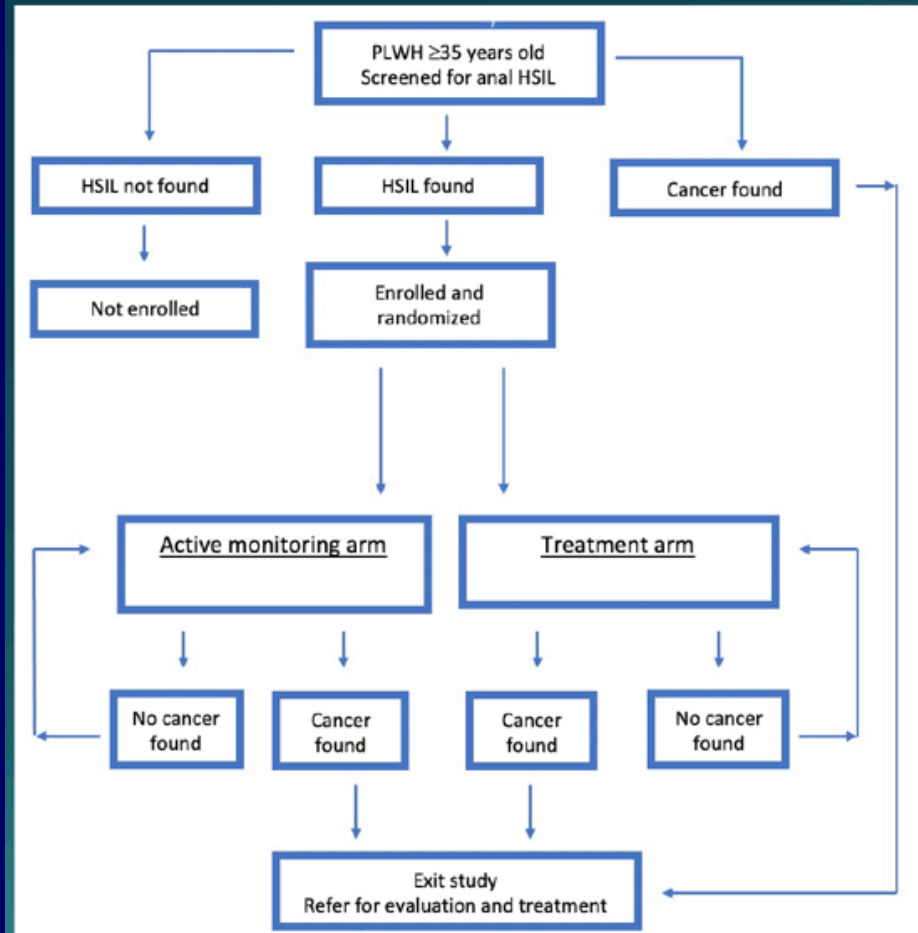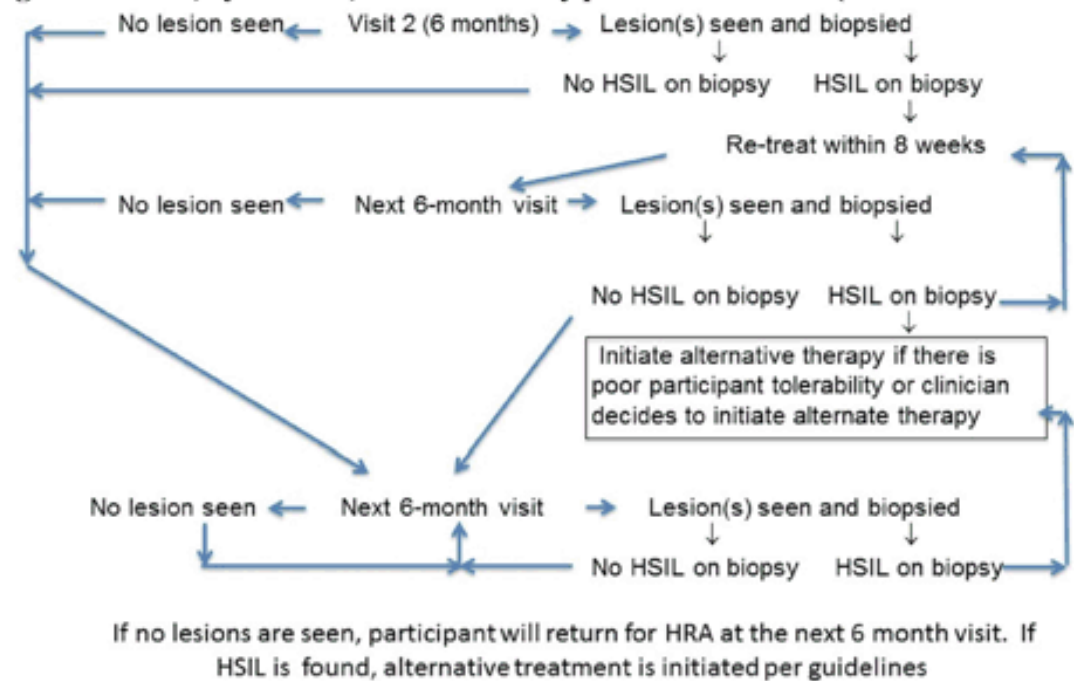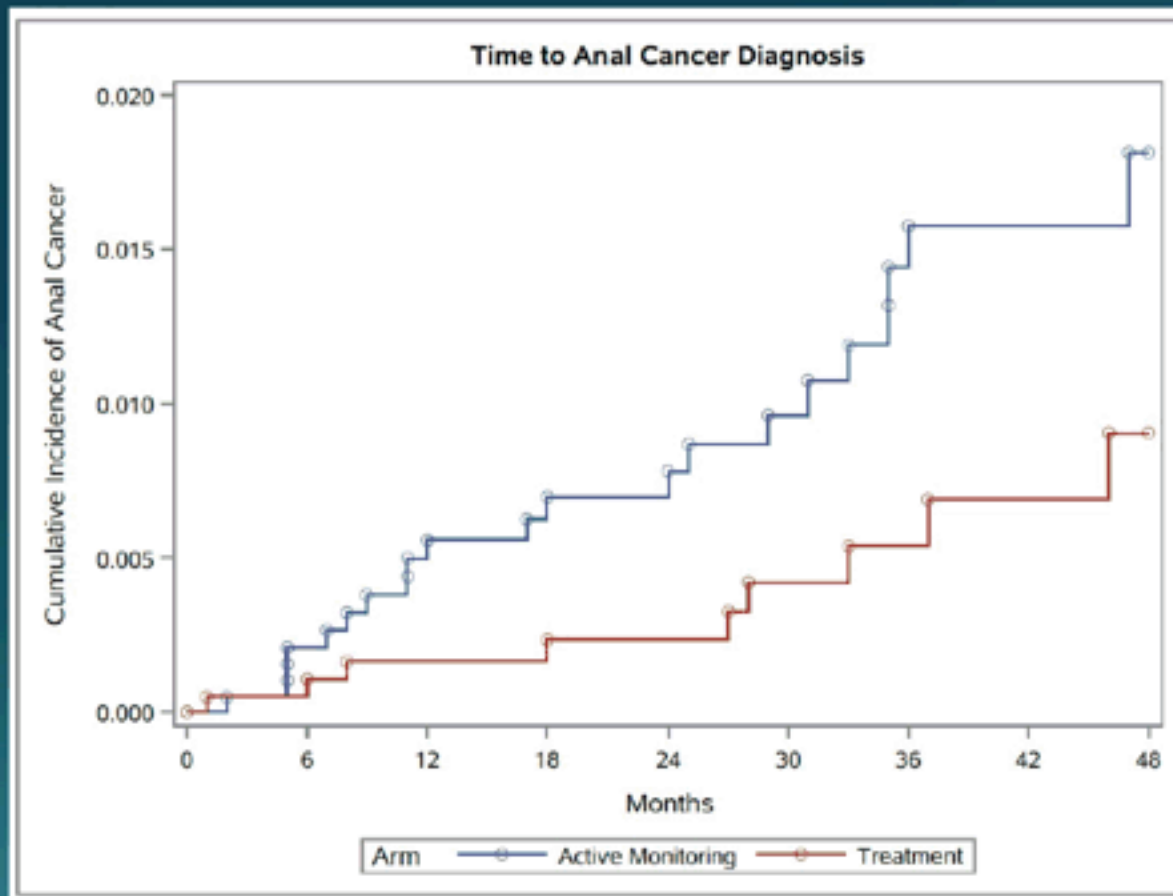# ANCHOR Study: Treatment of Anal High-Grade Lesions to Prevent Anal Cancer

ANCHOR Study: Treatment of Anal High-Grade Lesions to Prevent Anal Cancer

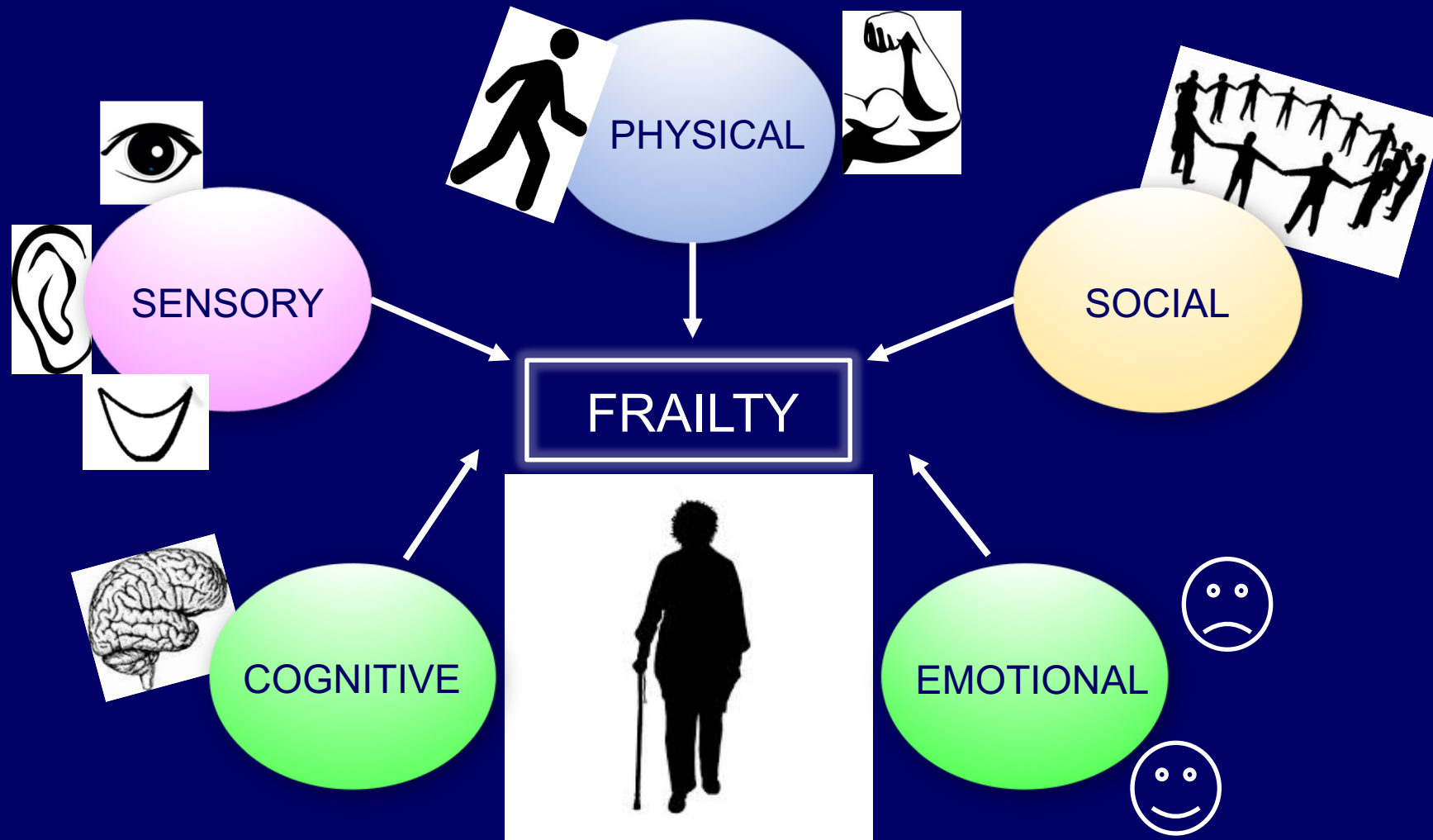**Kaplan-Meier curve of time-to-confirmed cancer cases**

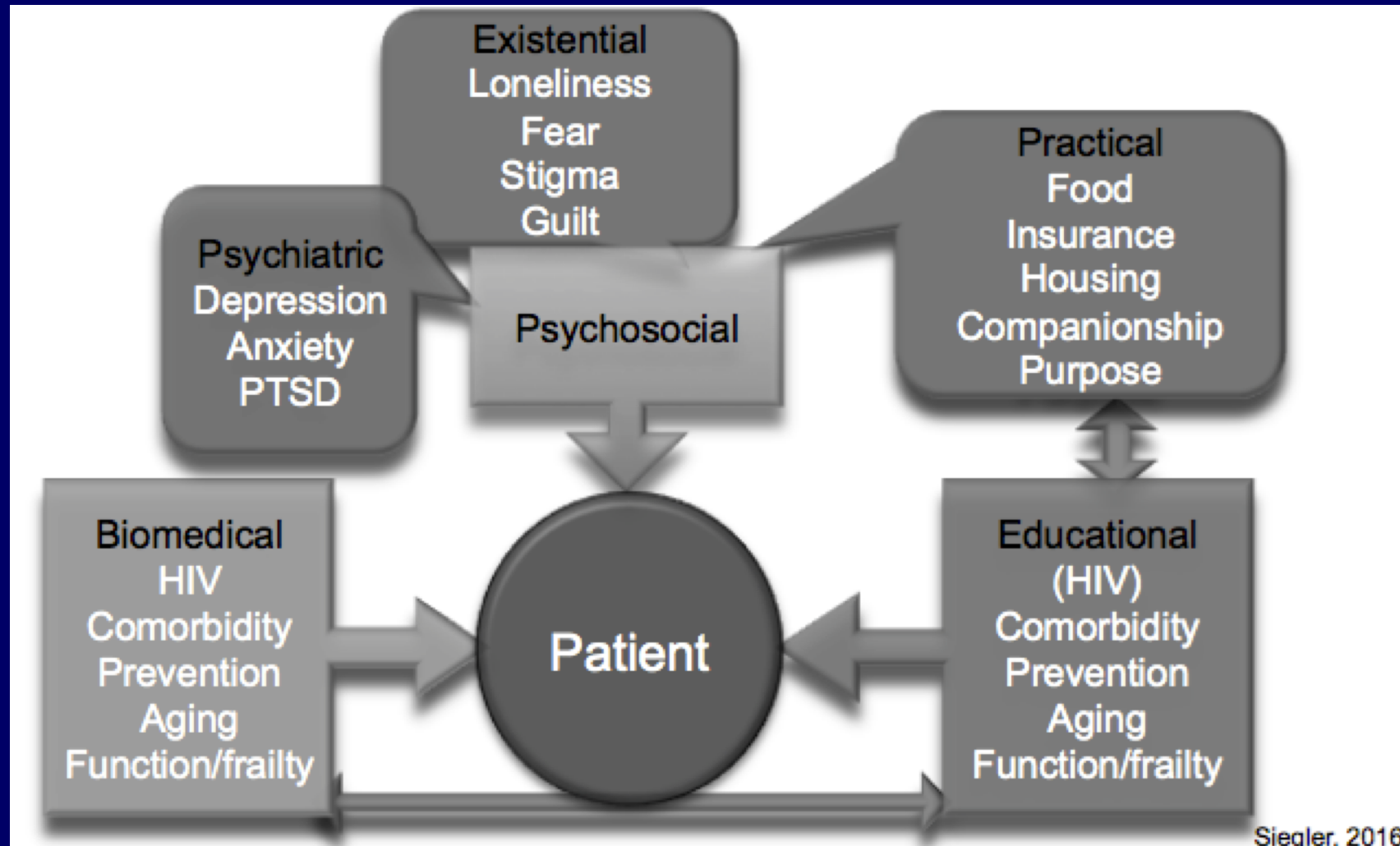57% reduction in incident anal cancer

How to Beat Inflammation: A Patient's Guide

- Continue your HIV medications. Stay undetectable
- Stop smoking
- Maintain normal weight
- If overweight, lose at least 5-10% of body weight
- Exercise
- Have a healthy diet
- Cut down on alcohol, avoid drugs
- Get your hepatitis C cured
- Maintain dental health
- Practice good sleep hygiene

The Faces of Frailty

SENSORY

PHYSICAL

SOCIAL

FRAILTY

COGNITIVE

EMOTIONAL

Thurn & Gustafson, *Current HIV/AIDS Reports,* 2017.

Treating the Whole Patient

Siegler, 2016

Major Challenges for Aging PLWH

- Multimorbidity: What is the best model for care?
- Access to Geriatric Care
- Health care navigation
- Access to mental health services
- Access to social services
- Prevention of disability
- Bias in long term care
- Health disparities by race/sexual minority

More HIV Research Highlights from CROI 2022 with
Dr. Carl Dieffenbach

Dr Dieffenbach: "The care of people living with HIV has NOT kept up with the reality of this aging population"
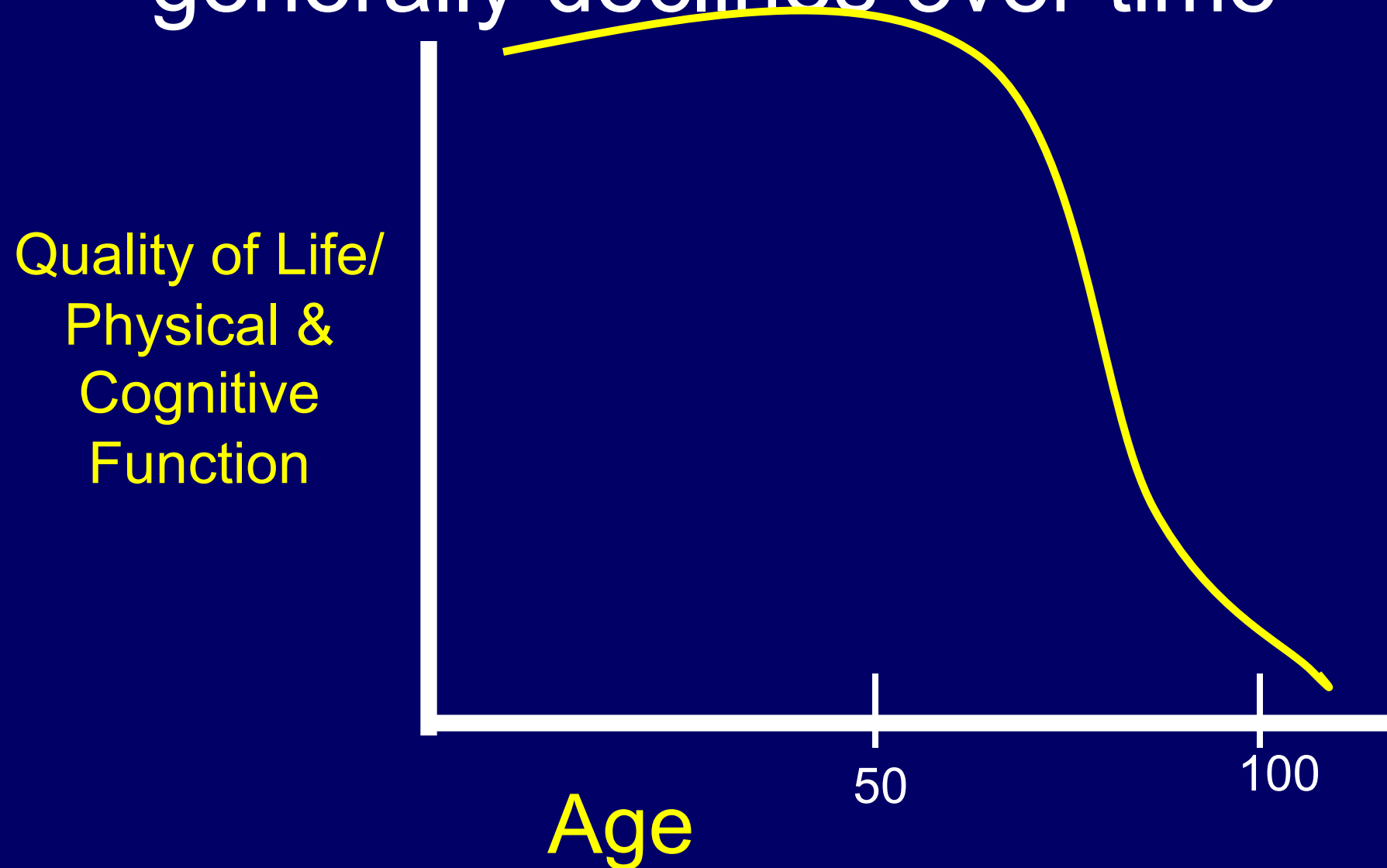
Bending the Curve Upwards is the Essential Goal of Healthy Aging

Quality of Life/
Physical &
Cognitive
Function

50

100

Age