### Aging, Comorbidities, & HIV: CROI Update 2023

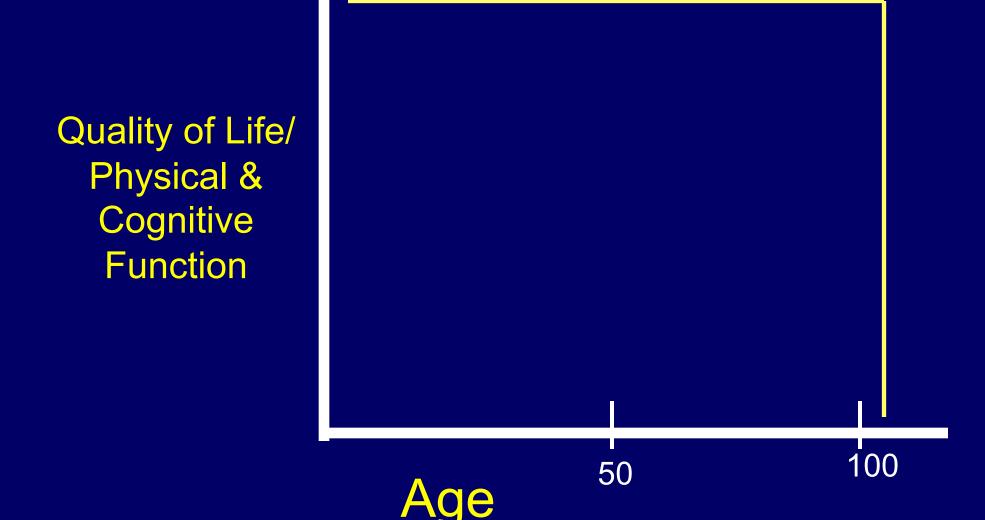


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#### Disclosures

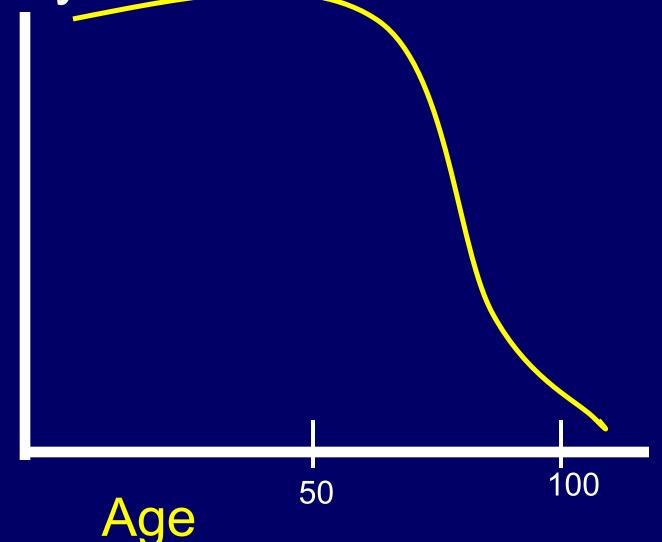
 Dr Brown has served as a consultant to Gilead, ViiV Healthcare, Merck, and Janssen.

#### The Ideal Life: Quality x Time



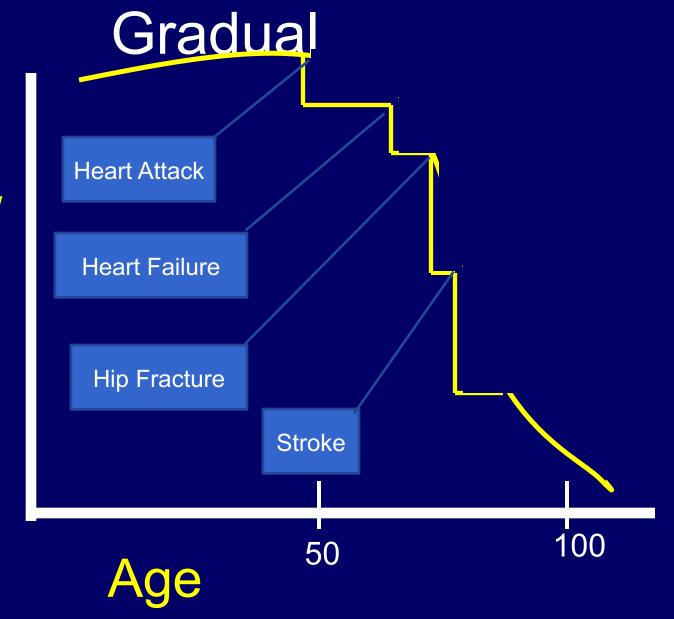
Physical & cognitive function generally declines over time

Quality of Life/
Physical &
Cognitive
Function



### Decline in Function May Not Be

Quality of Life/
Physical &
Cognitive
Function

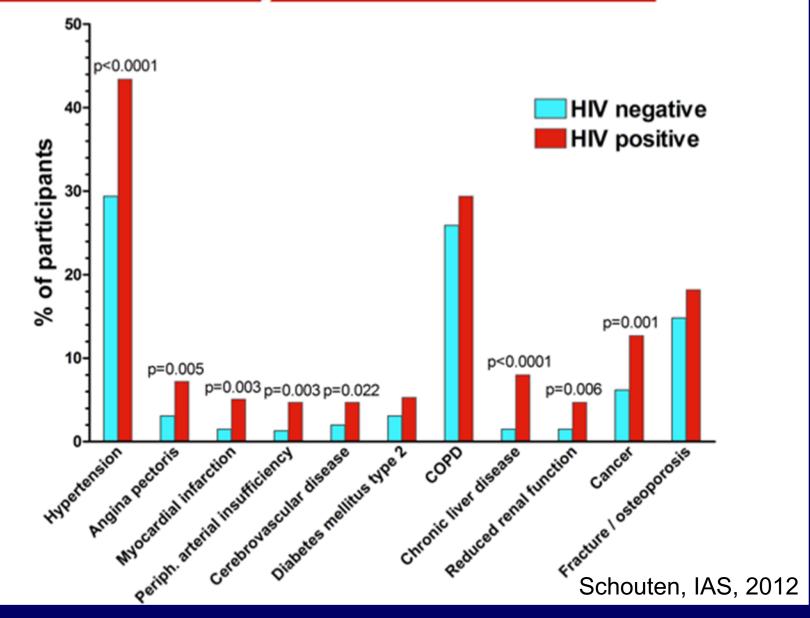


### Prevention of Comorbid Events is Essential and Achievable

- 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

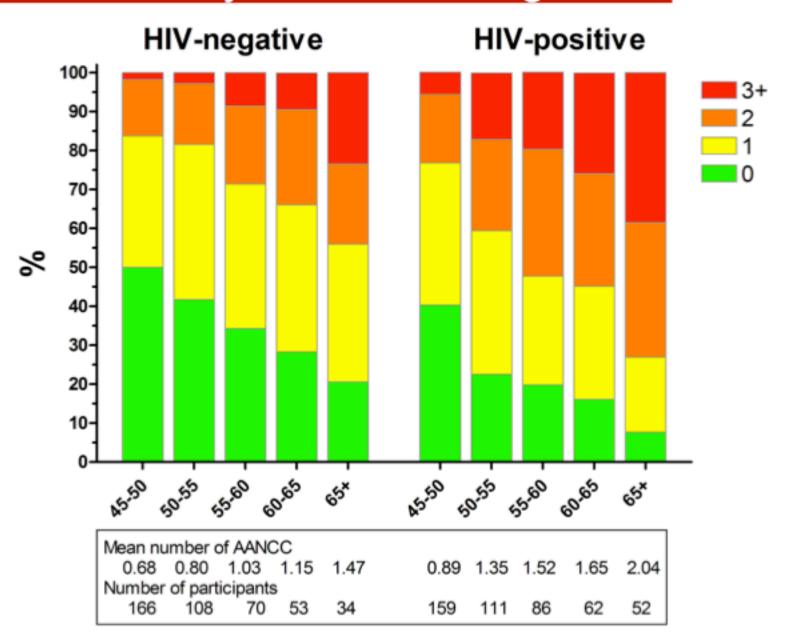






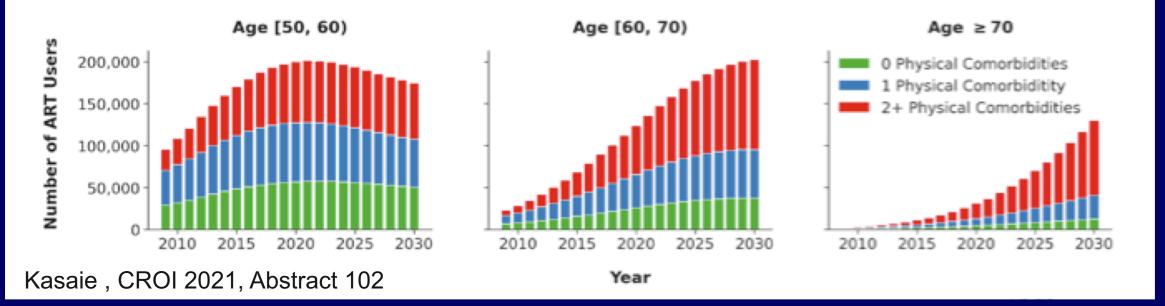
#### Comorbidity in relation to age



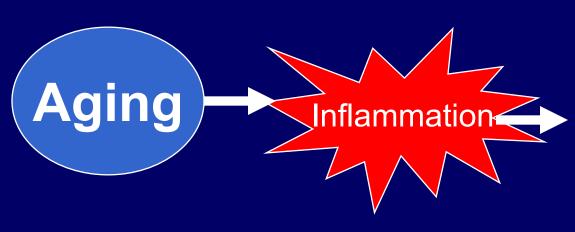


### Multimorbidity will increase markedly in PLWH over the next 10 years

- 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

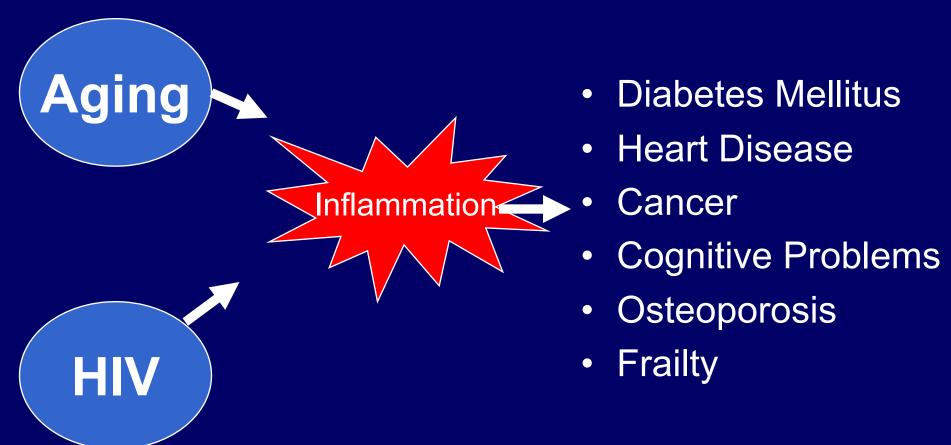


### Inflammation and Immune Dysfunction: A Central Mechanism for Aging

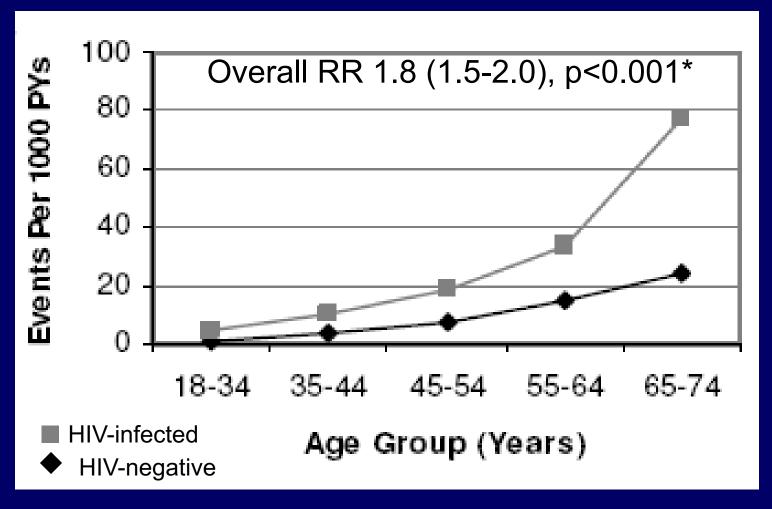


- Diabetes Mellitus
- Heart Disease
- Cancer
- Cognitive Problems
- Osteoporosis
- Frailty

### Aging & HIV: The Inflammation Double Whammy

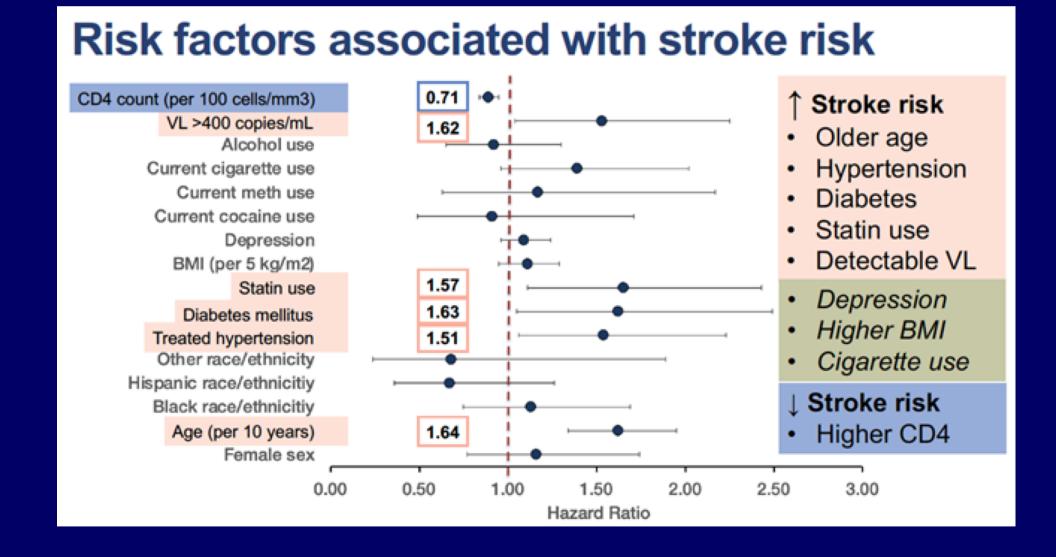


### Myocardial Infarction in People with and Without HIV: MGH Study



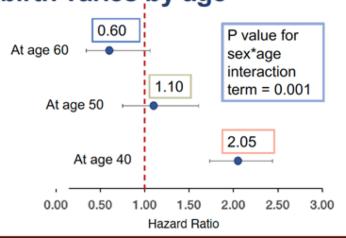
#### Cardiovascular Disease at CROI 2023

#### Risk Factors for Stroke in the CNICS Population



### Stroke More Common in Women than Men at Younger Ages

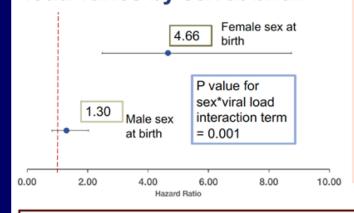
### Risk of stroke associated with female sex at birth varies by age



- Female sex at birth associated with higher risk of stroke at younger ages, independent of stroke disease risk score
- Sex\*age interaction remained significant after additional adjustment for:
  - Viral load
  - · Methamphetamine use
  - Depression

\*Stroke disease risk score based on race/ethnicity, cohort entry year, CNICS site, HIV risk factor, blood pressure, renal function, lipids, cigarette, cocaine + alcohol use, physical activity





- Detectable VL was associated with higher risk of stroke in those assigned female sex at birth, independent of age and stroke disease risk score
- Sex\*viral load interaction remained significant after additional adjustment for:
  - Methamphetamine use

\*Stroke disease risk score based on race/ethnicity, cohort entry year, CNICS site, HIV risk factor, blood pressure, renal function, lipids, cigarette, cocaine + alcohol use, physical activity

Detectable HIV viral load is a risk factor for stroke in women but not men

#### Two types of heart attack:

- 1) Type 1: Plaque in wall of artery ruptures
- 2) Type 2: Demand for oxygen not met

#### **CENTRAL ILLUSTRATION:** Differences in Clinical Characteristics Between Patients With Type 1 and Type 2 Myocardial Infarction

#### Type 1 Myocardial Infarction **Type 2 Myocardial Infarction** Mild or no plaque Plaque rupture or erosion with thrombus Fixed atherosclerosis **Patient Phenotype Patient Phenotype** · More likely to be: · More likely to be: -Male -Older -Younger -Female · Higher prevalence of: Higher prevalence of: -Smoking -Heart failure -Dyslipidemia -Atrial fibrillation -Prior myocardial infarction -Valvular heart disease -Prior PCI -Hypertension -Prior CABG -Renal failure -Cancer · Coronary artery evaluation -Liver disease and treatment: -Depression -57% Coronary angiography -Alcohol use disorder -38.5% PCI -Substance use disorder -7.8% CABG Coronary artery evaluation and treatment -10.9% Coronary angiography -1.7% PCI -0.4% CABG Higher risk of in-hospital death and 30-day Lower risk of in-hospital death and 30-day readmission for MI readmission for MI McCarthy, C.P. et al. J Am Coll Cardiol. 2021;77(7):848-57.

### Depression is related to Type 1 MI in PWH

### Risk of incident Type 1 MI among PWH with versus without a diagnosis of depression or anxiety

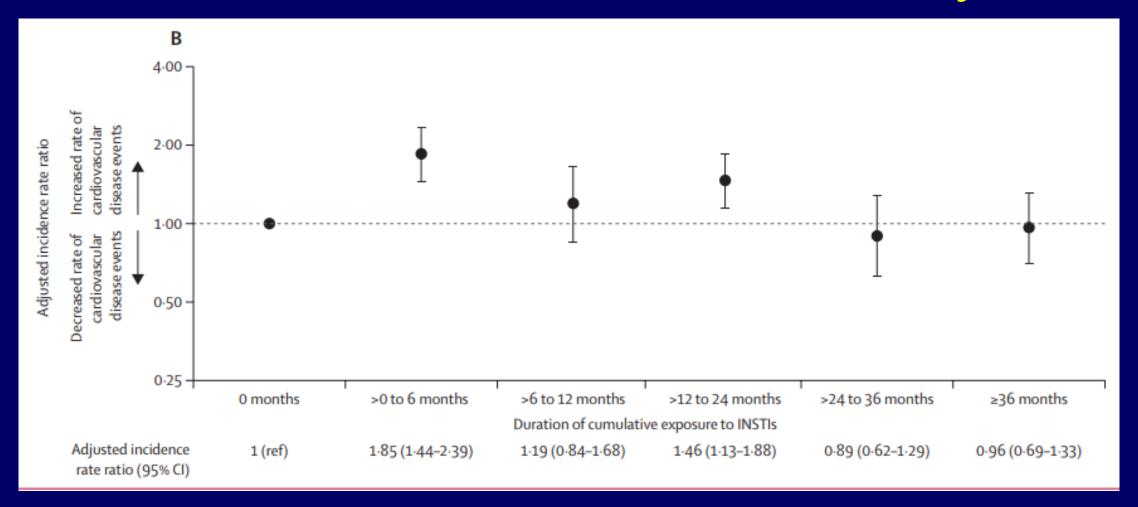
	aHR	95% CI	
Demographics			Model is additionally
Male at birth	1.55	1.13, 2.14	adjusted for:
Age (scaled by 10 years)	1.50	1.35, 1.66	<ul> <li>Race/ethnicity</li> </ul>
Substance use			<ul> <li>HIV acquisition group</li> </ul>
Tobacco (ever/never)	1.88	1.45, 2.43	<ul> <li>At-risk alcohol use</li> </ul>
Cocaine (ever/never)	0.97	0.71, 1.31	<ul> <li>Cannabis use</li> </ul>
Traditional CVD risk factors			<ul> <li>Body mass index</li> </ul>
Hypertension	2.81	2.26, 3.49	<ul> <li>History of AIDS</li> </ul>
Diabetes Mellitus	1.33	1.05, 1.68	<ul> <li>History of HCV</li> </ul>
Elevated total cholesterol or statin use	2.39	1.94, 2.96	<ul> <li>CD4 at ART initiation</li> </ul>
Chronic Kidney Disease (eGFR<60 mL/min)	1.36	1.07, 1.74	<ul> <li>VL at ART initiation</li> </ul>
HIV-related risk factors			<ul> <li>Time-varying CD4</li> </ul>
History of protease inhibitor use (ever/never)	1.49	1.23, 1.81	
History of detectable viral load (ever/never)	1.13	0.85, 1.49	
Mental health comorbidities			
Anxiety	0.92	0.74, 1.16	
Depression	1.23	1.02, 1.49	Cl

### Anxiety is related to Type 2 MI in PWH

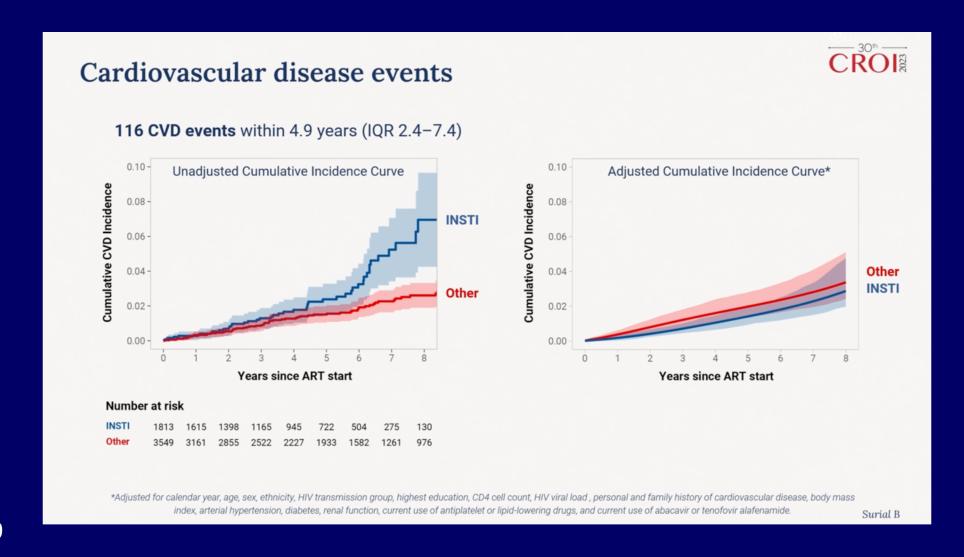
### Risk of incident Type 2 MI among PWH with versus without a diagnosis of depression or anxiety

	aHR	95% CI	
Demographics			Model is additionally
Male at birth	0.98	0.72, 1.32	adjusted for:
Age (scaled by 10 years)	1.18	1.05, 1.33	<ul> <li>Race/ethnicity</li> </ul>
Substance use			<ul> <li>HIV risk acquisition group</li> </ul>
Tobacco (ever/never)	1.36	1.01, 1.84	<ul> <li>At-risk alcohol use</li> </ul>
Cocaine (ever/never)	1.49	1.11, 1.99	<ul> <li>Cannabis use</li> </ul>
Traditional CVD risk factors			<ul> <li>Body mass index</li> </ul>
Hypertension	2.50	1.93, 3.25	<ul> <li>History of AIDS</li> </ul>
Diabetes Mellitus	2.39	1.84, 3.11	<ul> <li>History of HCV</li> </ul>
Elevated total cholesterol or statin use	1.02	0.80, 1.30	<ul> <li>CD4 at ART initiation</li> </ul>
Chronic Kidney Disease (eGFR<60 mL/min)	3.05	2.37, 3.93	<ul> <li>VL at ART initiation</li> </ul>
HIV-related risk factors			<ul> <li>Time-varying CD4</li> </ul>
History of protease inhibitor use (ever/never)	1.07	0.85, 1.34	
History of detectable viral load (ever/never)	1.35	1.02, 1.79	
Mental health comorbidities			
Anxiety	1.42	1.10, 1.83	30 <sup>th</sup> ⋅
Depression	1.20	0.96, 1.51	CRC

### Are integrase inhibitors associated with heart attack?: RESPOND Study



### ART-initiation with integrase inhibitors not associated with CVD events in Swiss Cohort



#### Cancer at CROI 2023

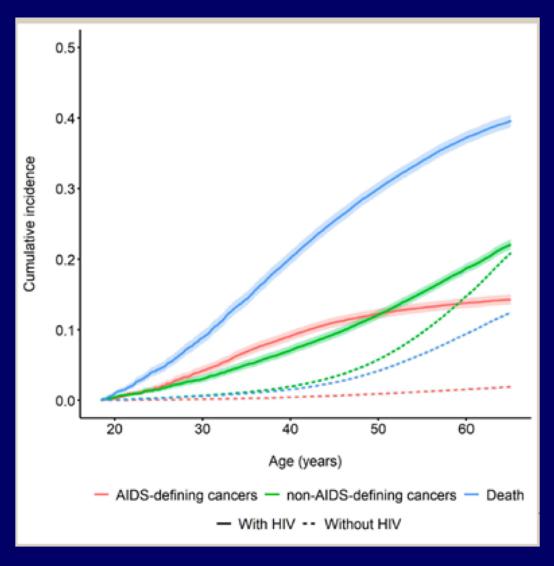
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### New Cancers in Medicare Recipients by HIV Serostatus: 2001-2015

AIDS-defining cancers: Kaposi's sarcoma, cervical, and non-Hodgkin's lymphoma

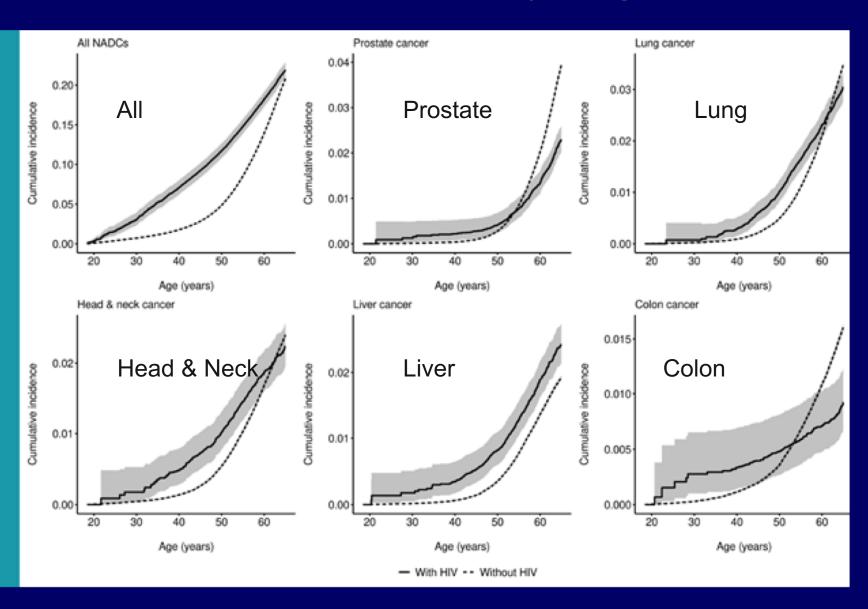
Non-AIDS-defining cancers: breast, colon, head/neck, kidney, larynx, leukemia, liver, lung, oropharynx, pancreatic, prostate, anal, Hodgkin's lymphoma

HIV+: 181, 030 HIV-: 43.9 M



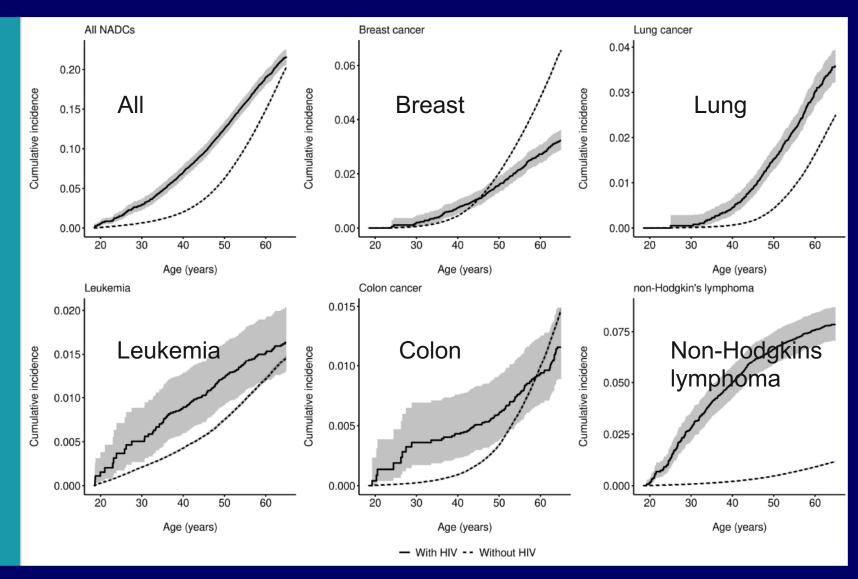
## Beneficiaries Male

### Cancer Incidence by Age: Men

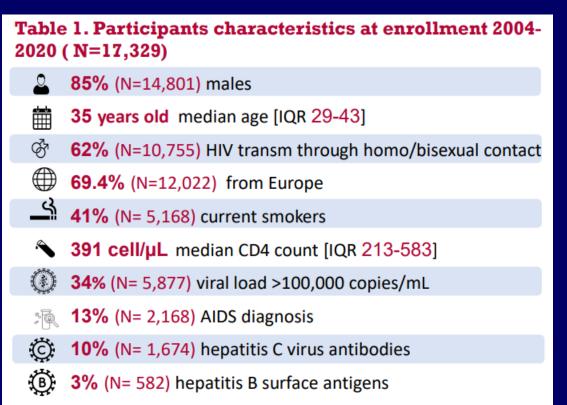


# Beneficiaries Female

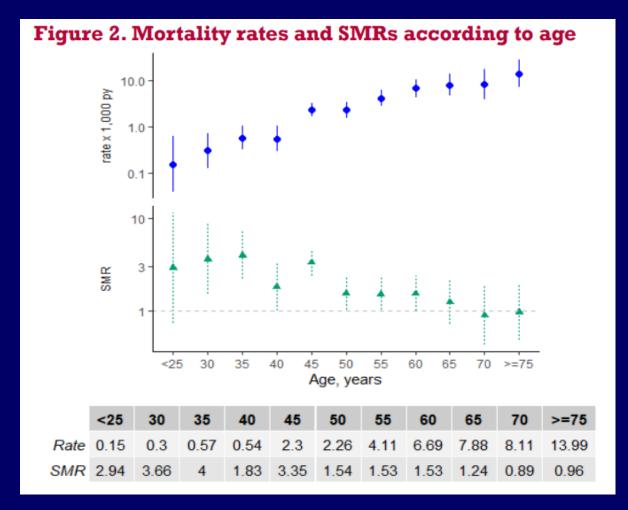
### Cancer Incidence by Age: Women



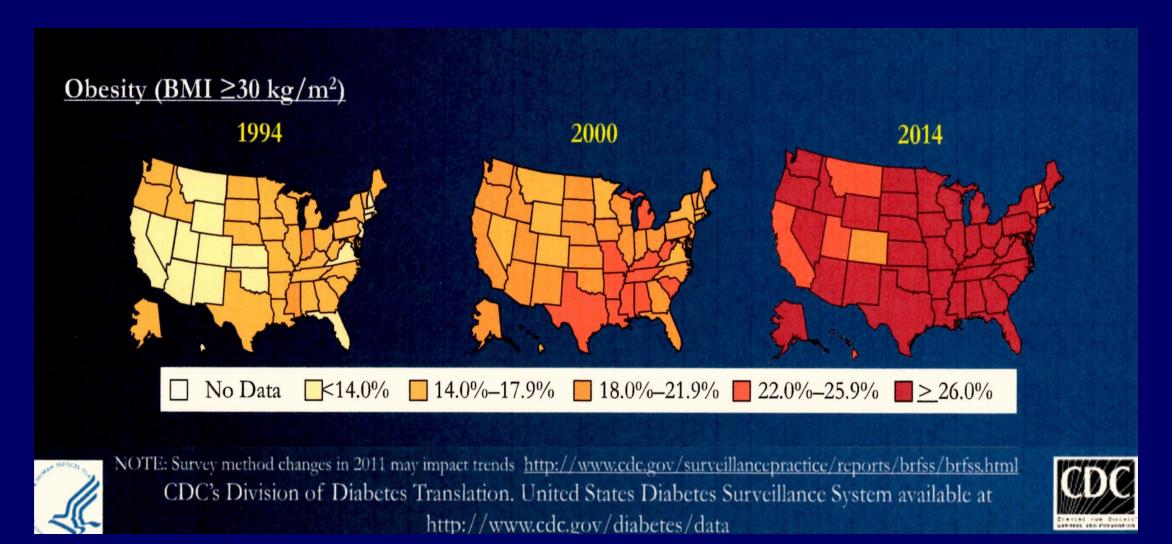
### Cancer Mortality Higher in PWH Compared to General Spanish Population



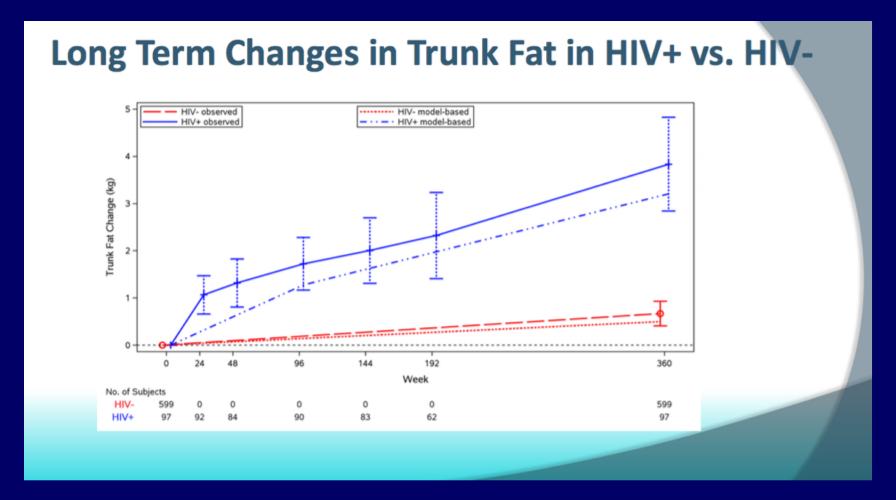
Factors associated with cancer mortality in PWH:
Smoking
Viral Hepatitis
Lower CD4 cell count



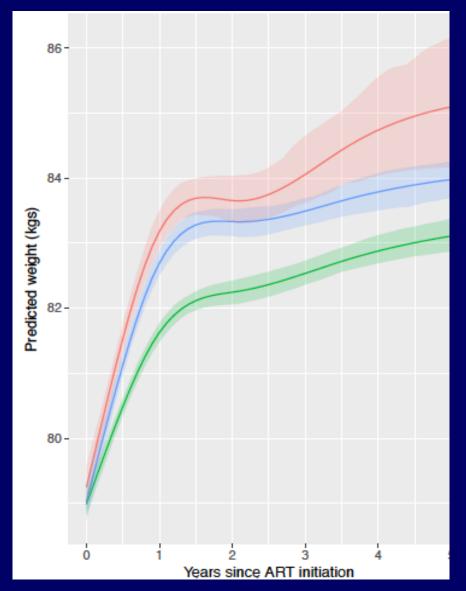
### Increasing Prevalence of Obesity in US



### Central fat increases with ART initiation are greater than expected



#### Weight Gain is Greater with INSTI in NA-ACCORD



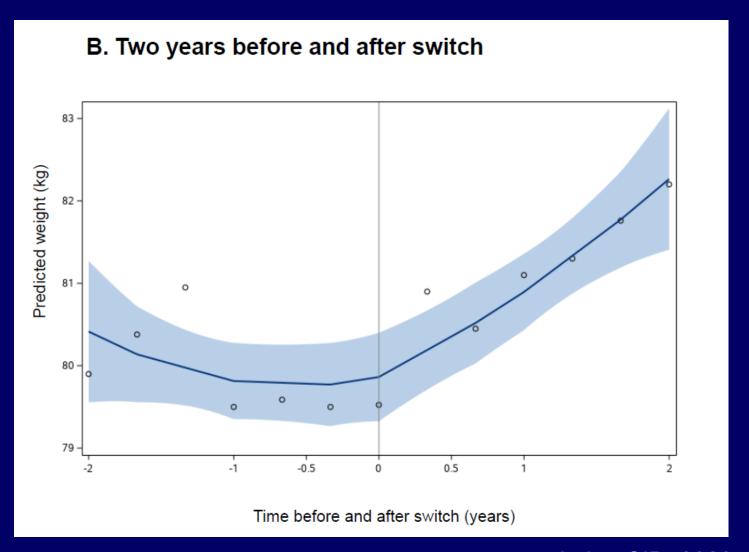
**INSTI** 

PI

**NNRTI** 

Lake, 20th IWCADRH, 2018

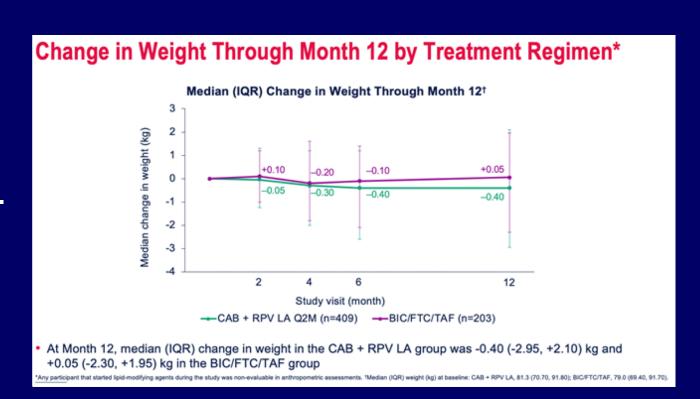
### Switching to INSTI: HAILO Study



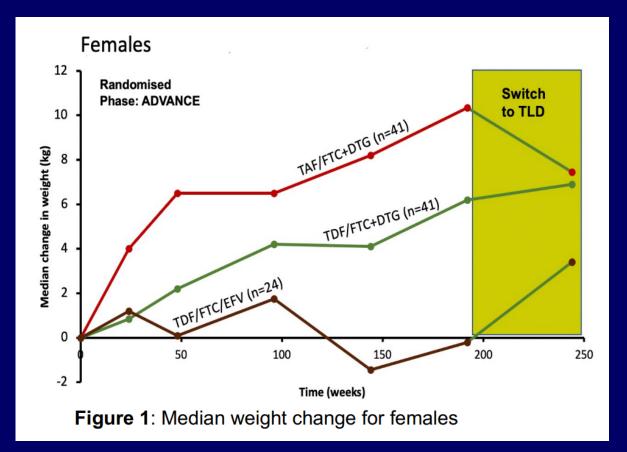
### Does switching off of integrase inhibitors decrease weight?

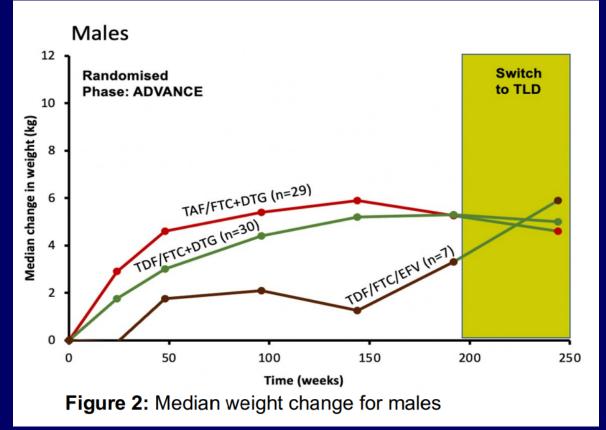
#### SOLAR:

- PWH on F/TAF/BIC randomized 2:1 to CAB LA or stay on F/TAF/BIC over 12M.
- Median age 37, 88% men, 60% overweight or obese.



### Switching off TAF to TDF decreases weight in women: CHARACTERISE





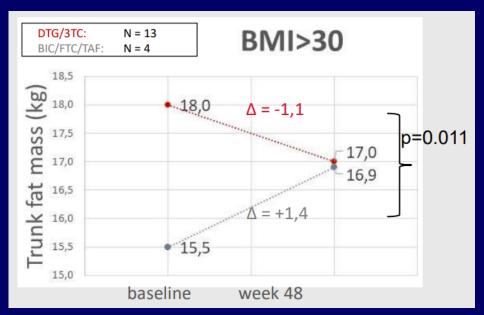
#### Switching from F/TAF/BIC to DTG/3TC

# Randomized, open-label controlled trial (2:1) Longitudinal follow-up: baseline, week 24, week 48 Outcomes (2ary): weight, BMI, waist, lipids, insulin resistance, DXA scan, fibroscan Linear mixed models with covariance patterns

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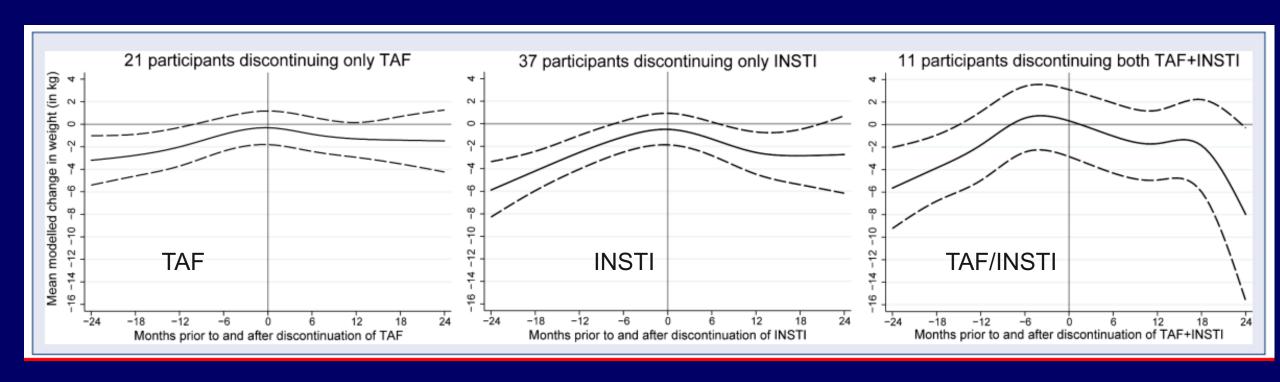
145 screened 134 randomized	ITT-E analysis 130 at baseline
11 screen fails     4 did not take study medication	

	DTG/3TC	BIC/FTC/TAF	p-value
ALT (U/L)	- 0.73	+ 4.55	0.040
HDL (mg/L)	- 0.043	- 2.84	0.043
Lean trunk mass (gram)	+ 112	- 474	0.032
Trunk fat mass (gram)	+ 41	+ 719	0.043
Fat percentage	- 0.04	+ 1.32	0.003

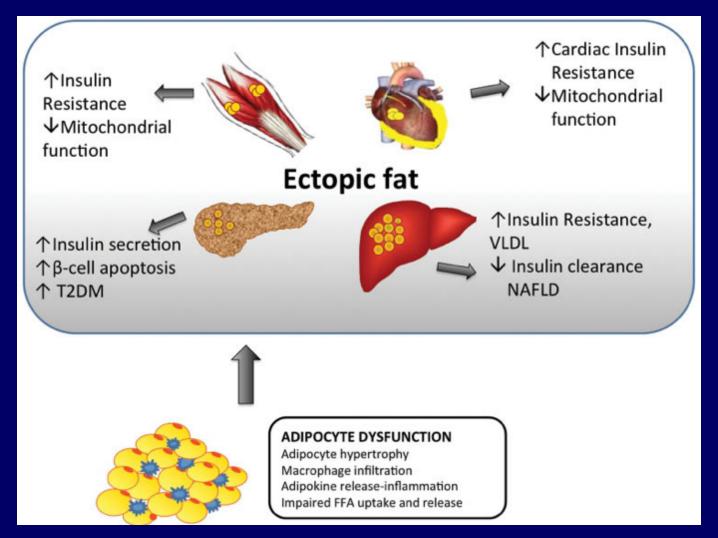


Intention to treat – exposed analysis

### Switching off of TAF, INSTIs, or Both in PWH with >7% weight gain: ATHENA Cohort



#### What is Ectopic Fat?



#### Increase in Liver Fat after switch to INSTIs

Figure 1. Cross
Sectional Study
Schema. One
FibroScan conducted
at varying time-point
post-INSTI switch or
comparable time-point
in non-INSTI group

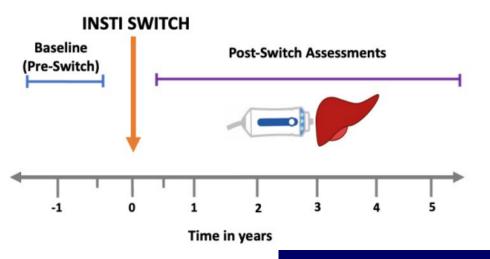
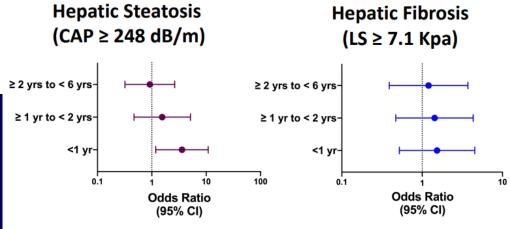


Table 1. Cohort characteristics, n=257

Mean (SD) or n(%)	INSTI N=123	Non-INSTI N=134
Age, years	50 (8)	49 (8)
Black race	82 (67)	107 (80)
BMI, kg/m <sup>2</sup>	32 (8)	32 (8)

Figure 3. Model-adjusted odds of hepatic steatosis and moderate fibrosis in INSTI vs non-INSTI groups. Women on INSTIs had a 3.6 greater odds of having hepatic steatosis within 1 year of switch compared to non-INSTI Controls.



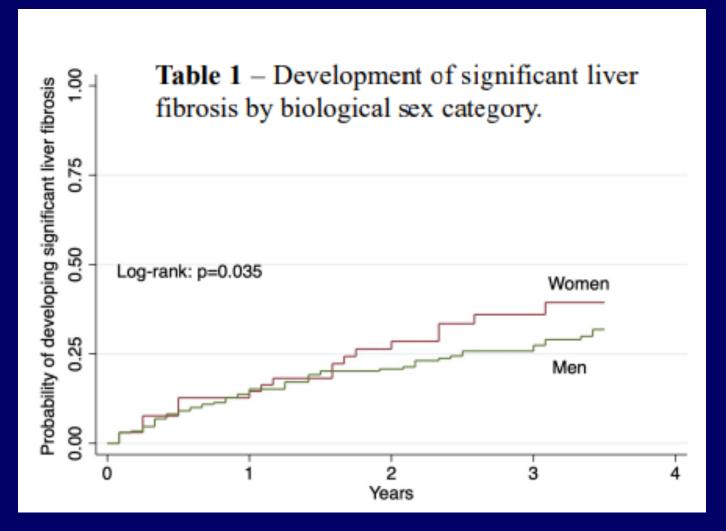
### Women had lower prevalence of fatty liver, but a greater progression to fibrosis

#### Population characteristics

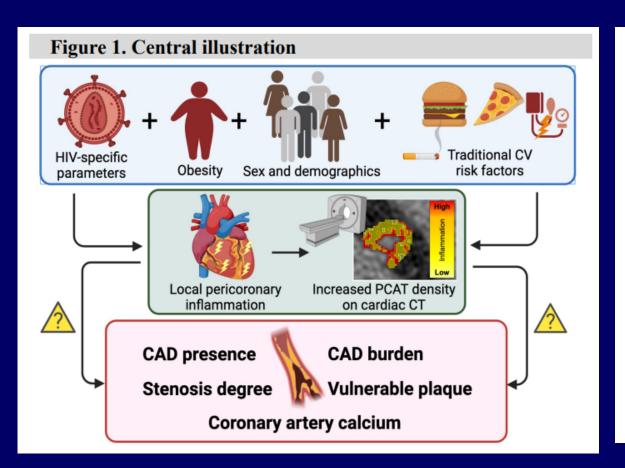
Population characteristics (N= 1359)			
Age	51.8 (9.9)		
Female	25%		
BMI	25.1 (4.4)		
Ethnicity	25% black, 64% white		
HIV duration	17.2 (9.5) years		

#### **Baseline characteristics**

	Female	Male
Prevalence of MAFLD	17.7%	24.3%
Prevalence of liver fibrosis	10.7%	13.4%
Black ethnicity	48%	17%
ALT	26.4	33.4
HDL cholesterol	1.46	1.11
Triglycerides	1.69	2.47



# Inflammation in fat surrounding coronary arteries associated with coronary plaque



### Multivariable regression relating PCAT to plaque phenotypes

•PCAT density was associated with CT-derived CAD measures independent of ASCVD risk score, smoking & substance use, BMI, ART parameters and systemic inflammatory biomarkers (Table 2).

#### Table 2: Association of PCAT density with CAD in REPRIEVE

	Univariable		Model 1			Model 2			
Presence of	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Coronary Plaque	1.3	1.13-1.50	< 0.001	1.3	1.10–1.50	0.002	1.4	1.21-1.70	<0.001
Coronary Calcium	1.5	1.28-1.74	< 0.001	1.5	1.26–1.75	< 0.001	1.6	1.35-1.94	< 0.001
Vulnerable plaque	1.3	1.10-1.54	0.002	1.3	1.06–1.51	0.01	1.3	1.07-1.57	0.008
Leaman >5	1.5	1.27-1.87	< 0.001	1.6	1.27–1.93	< 0.001	1.9	1.47-2.37	< 0.001

**Model 1:** ASCVD risk, substance use, BMI, HIV parameters; **Model 2:** Model 1 + systemic biomarkers (MCP-1, IL-6, LpPLA2, oxLDL, hsCRP). ORs are per 10 HU of PCAT density.

# Fat within the muscle associated with coronary artery disease: REPRIEVE

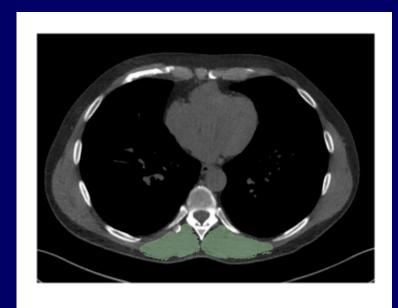
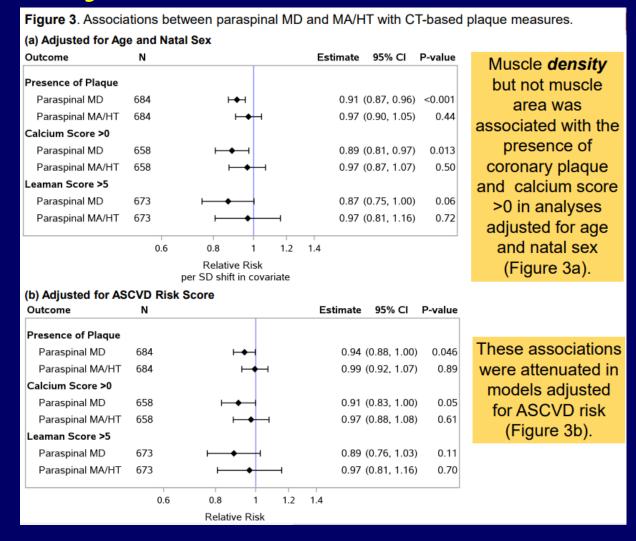
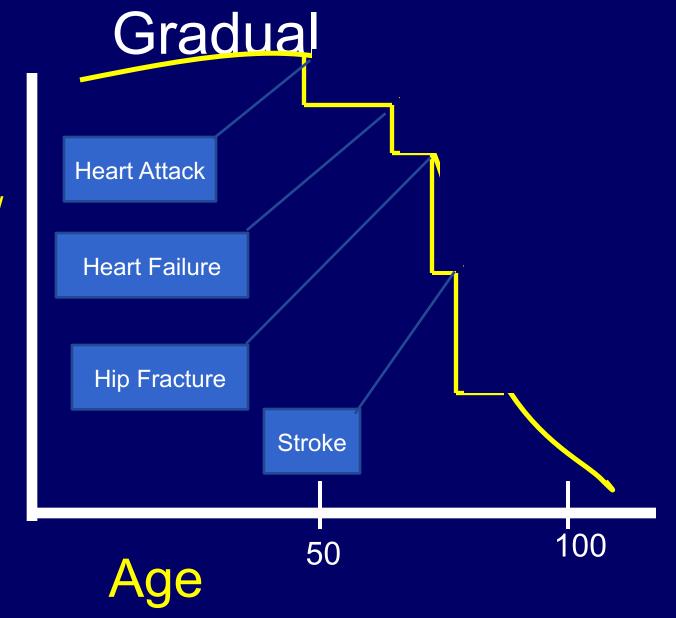


Figure 1. Paraspinal Muscle on Non-Contrast CT Scan, in green



### Decline in Function May Not Be

Quality of Life/
Physical &
Cognitive
Function



Frequency

Yearly

Yearly

At least Yearly

Every 6-12 months

Age 50+

Yearly

debated

Yearly

Yearly

Every 5 years

debated

### Let's Get Screened!

**BP** Measurement

Serum Creatinine

Urine protein test

**DXA Scan** 

Pap test

CT (if smoker)

**Ultrasound** 

(if HBV or HCV+)

Mammogram

Colonoscopy

**PSA** 

Condition	Tests
Diabetes	Fasting Glucose Hgb A1C
High Cholesterol	Lipid Panel

**High Blood Pressure** 

**Anal/Cervical Cancer** 

Kidney Disease

Osteoporosis

Lung Cancer

**Liver Cancer** 

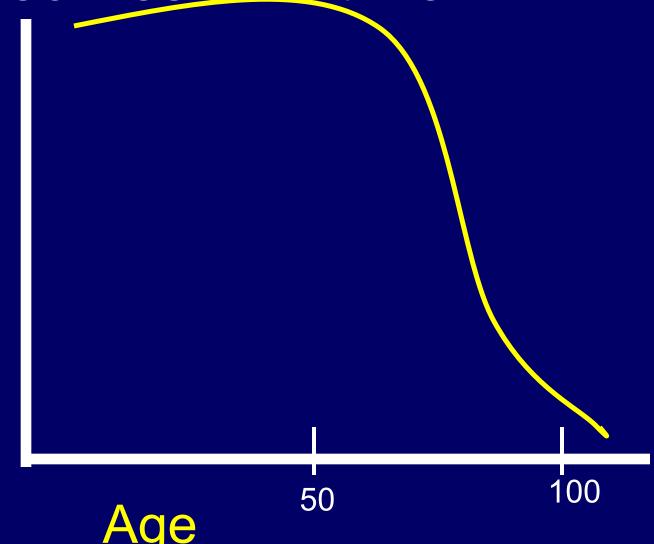
**Breast Cancer** 

Colon Cancer

**Prostate Cancer** 

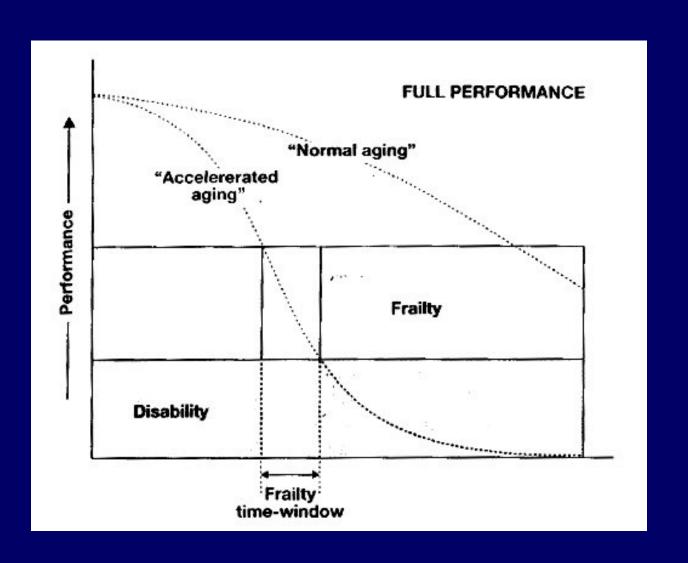
# Physical function generally declines over time

Quality of Life/
Physical &
Cognitive
Function

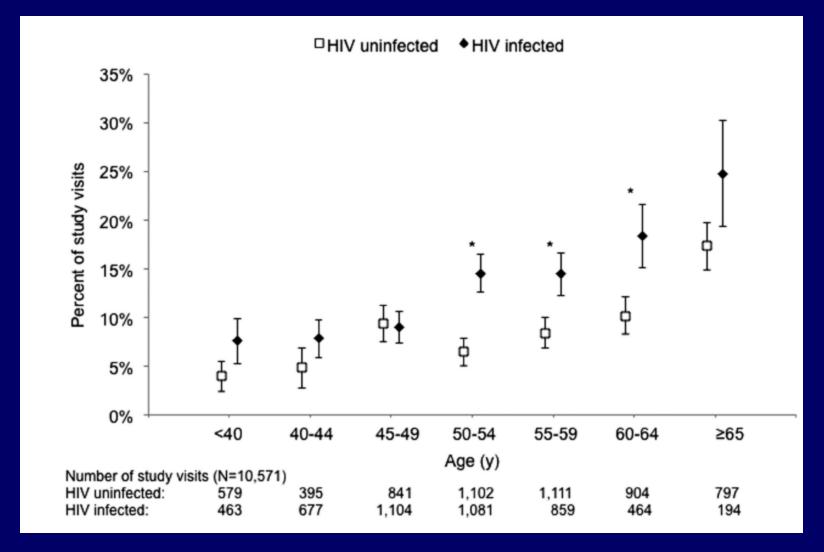


### Frailty: A Brief Overview

- Weight loss
- Weakness
- Exhaustion
- Slowness
- Physical Activity



## HIV+ Men Are More Frail At a Younger Age vs HIV- Men: MACS



# Frailty more common PWH compared to Pw/oH: Thai HIV-NAT

### Frailty by HIV Serostatus



Su Lwin, 696

# Lower trunk muscle area associated with lower grip strength

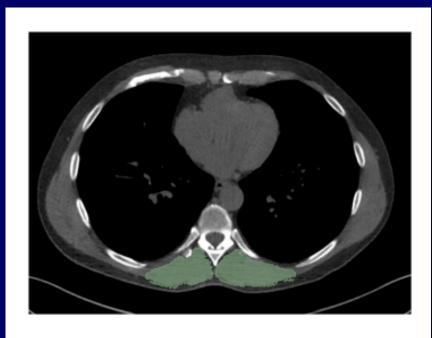
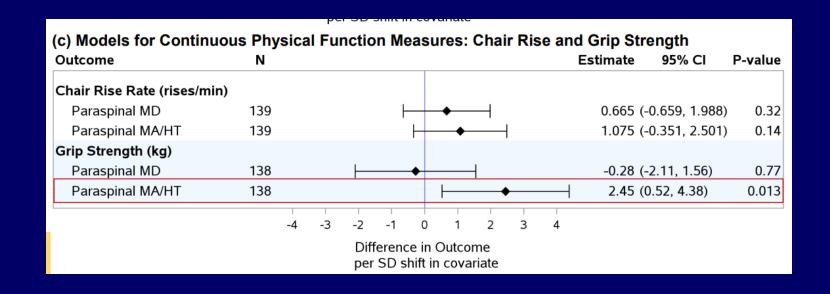


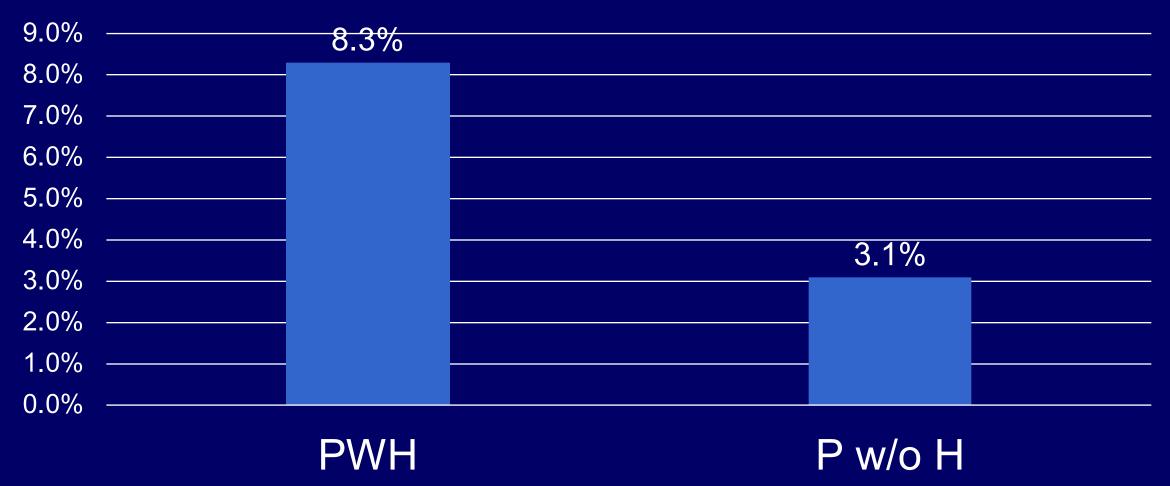
Figure 1. Paraspinal Muscle on Non-Contrast CT Scan, in green

#### **RESULTS** (continued)

- Lower MD (as outcome) was associated with older age, female sex, thymidine analogue exposure, greater BMI and waist circumference, and hsCRP, MCP-1, sTNFR-1, and the inflammatory index score (data not shown).
- Smaller MA/HT (as outcome) was associated with older age, female sex, non-Black race, greater ASCVD risk, and MCP-1 (data not shown).



## Sarcopenia more common in PWH vs Pw/oH: Thai HIV-NAT



Sarcopenia: low grip strength, low walk speed, and low muscle mass

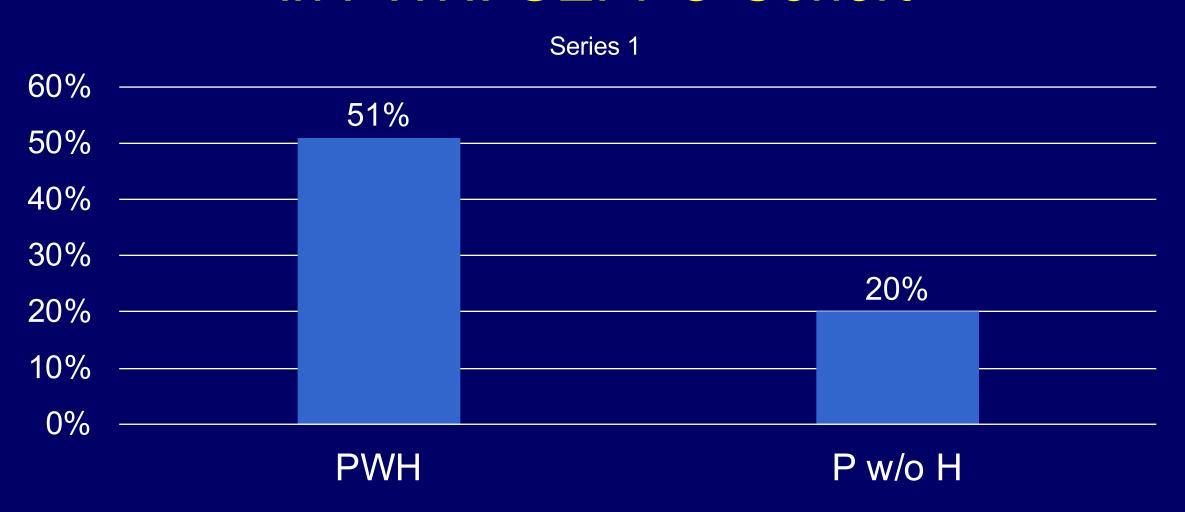
### Factors associated with falls in CNICS

		Any Falls (N=435)	1 vs 0 Falls (N=218)	2 vs 0 Falls (N=120)	3 ws 0 Falls (N=97)
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Neuropathy symptoms:	Not/ a little bothersome	1.74 (1.41, 2.15)	1.50 (1.12, 2.01)	1.69 (1.06, 2.69)	2.35 (1.47, 3.77)
(None = REF)	Bothersome/ highly bothersome	2.85 (2.34, 3.46)	1.76 (1.30, 2.40)	2.41 (1.62, 3.59)	6.77 (4.39, 10.4)
Difficulty remembering:	Not/ a little bothersome	2.18 (1.79, 2.65)	1.62 (1.24, 2.13)	3.35 (2.29, 4.90)	1.65 (1.06, 2.60)
(None = REF)	Bothersome/ highly bothersome	3.18 (2.67, 3.95)	1.71 (1.21, 2.42)	3.98 (2.63, 6.01)	4.37 (2.81, 6.80)
Fatigue or Loss of Energy:	Not/ a little bothersome	2.39 (1.89, 3.02)	1.59 (1.18, 2.15)	3.24 (2.08, 5.03)	2.09 (1.25, 3.51)
(None = REF)	Bothersome/ highly bothersome	3.57 (2.83, 4.51)	2.04 (1.49, 2.79)	4.09 (2.62, 6.40)	4.81 (2.93,7.92)
Feeling dizzy:	Not/ a little bothersome	2.49 (2.07, 3.00)	1.70 (1.28, 2.24)	2.78 (1.93, 3.99)	3.29 (2.22, 4.89)
(None = REF)	Bothersome/ highly bothersome	3.91 (3.20, 4.77)	1.49 (0.98, 2.30)	4.95 (3.34, 7.34)	6.90 (4.60, 10.3)
Frailty Phenotype:	Prefrail	2.42 (1.94, 3.01)	1.71 (1.30, 2.25)	1.64 (1.10, 2.44)	4.45 (2.82, 7.02)
(None = REF)	Frail	4.67 (3.69, 5.92)	1.69 (1.14, 2.52)	4.22 (2.70, 6.60)	10.13 (6.42, 16.0)
Depression Symptoms:	Mild/ moderate	2.33 (1.95, 2.78)	1.97 (1.52, 2.56)	2.15 (1.50, 3.08)	3.07 (2.06, 4.59)
(None = REF)	Moderately severe/ Severe	3.50 (2.72, 4.50)	1.72 (1.08, 2.75)	2.61 (1.49, 4.56)	6.39 (4.07, 10.04)
Diabetes		1.43 (1.20, 1.72)	1.44 (1.09, 1.90)	1.34 (0.91, 1.97)	1.58 (1.04, 2.42)
Quality of Life index	per 1 standard deviation	0.41 (0.35, 0.47)	0.54 (0.46, 0.62)	0.45 (0.38, 0.53)	0.30 (0.25, 0.36)
# Emergency visits ( in the past 2 years)	per visit	1.07 (1.05, 1.09)	1.09 (1.03, 1.15)	1.10 (1.03, 1.17)	1.18 (1.12, 1.25)

- Neuropathy
- Cognitive Problems
- Dizziness
- Depression
- Frailty
- Diabetes
- Low QOL
- ED visits

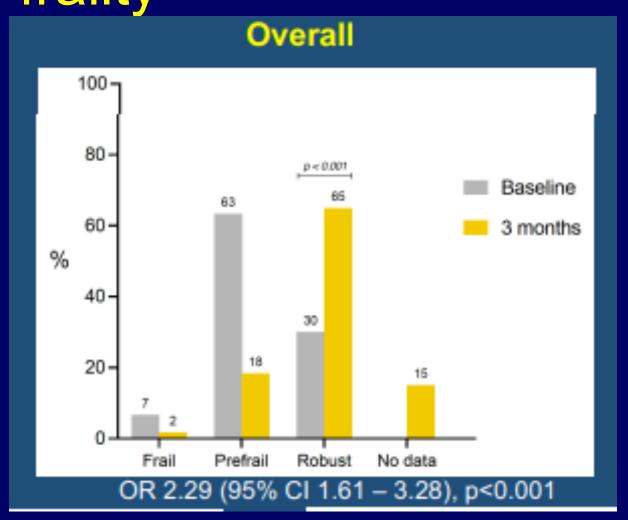
### Among people over 65, falls more common

in PWH: GEPPO Cohort



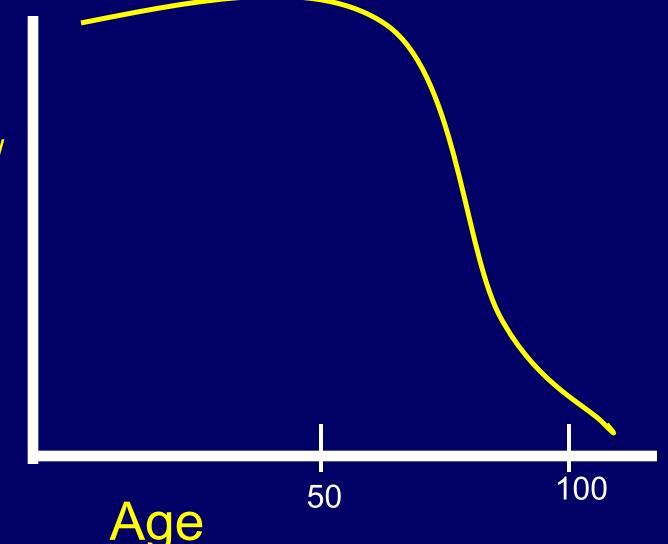
# 12 week exercise program can reverse frailty

- 51 participants (31 HIV+, 20 HIV)
- Median age 57 (53-63) years
- 25% women.
- Personalized multicomponent exercise program (resistance, endurance, balance, and flexibility training)
- Also, improvements in quality of life
- Intervention worked regardless of HIV status



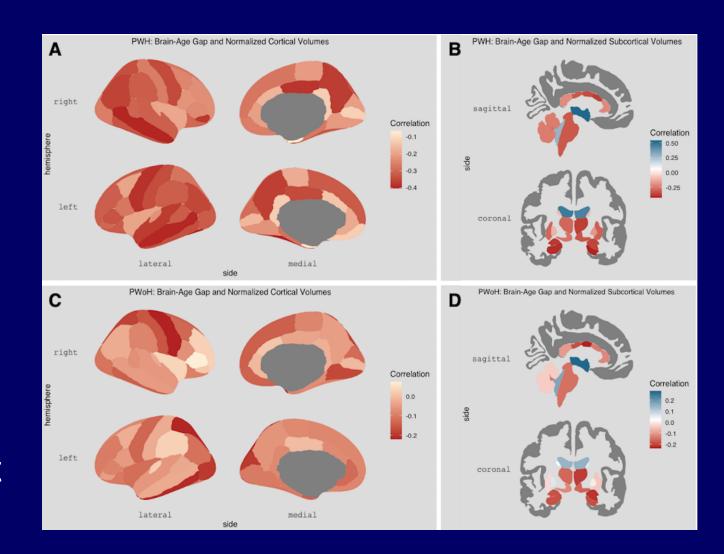
# Cognitive function generally declines over time

Quality of Life/
Physical &
Cognitive
Function

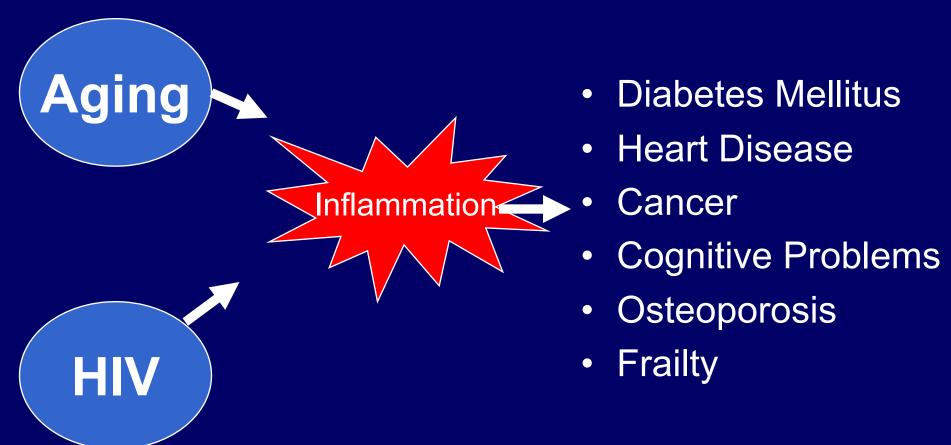


### Brain-age gap greater in PWH vs Pw/oH

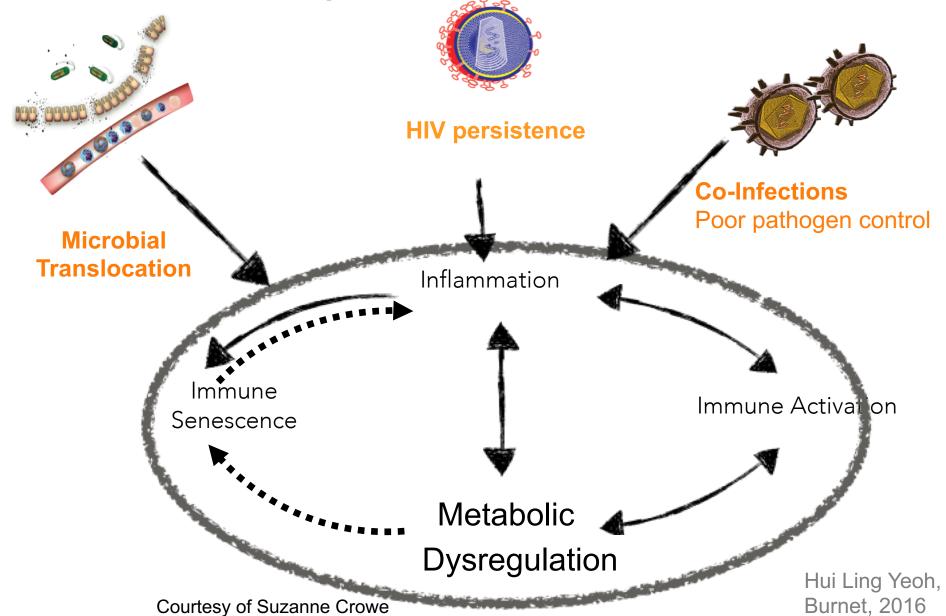
- Brain-age gap related to:
  - CVD risk
  - HCV
  - Detectable VL
  - Early life stress
  - Socioeconomic challenges
- Brain regions were affected differently in those with and without HIV



# Aging & HIV: The Inflammation Double Whammy



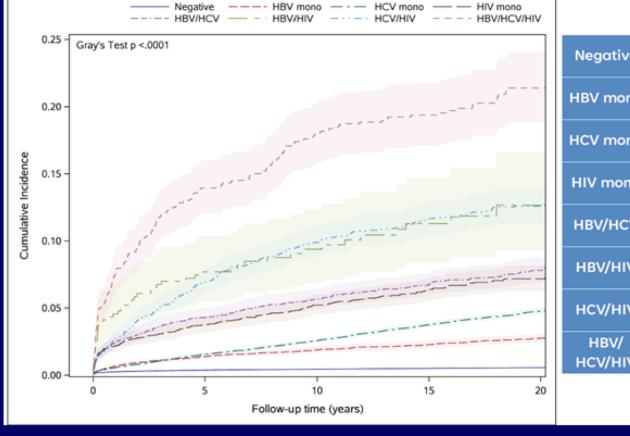
### Microbial translocation, HIV persistence and coinfections cause persistent innate immune activation



## Viral hepatitis increases risk of kidney failure

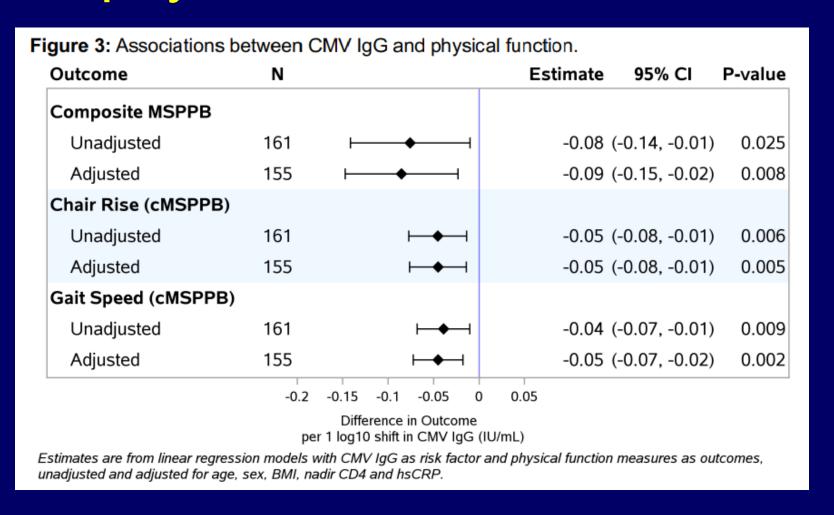
- n=690,873
- 5552 ESRD,49753 deaths over6.3 years
- Results even stronger in those with diabetes or hypertension

Figure 1. Cumulative incidence curves for incident ESRD among individuals with chronic viral infections, incidence rates (95% CI) per 1,000 person-years of follow-up (Table)



Negative	0.55 (0.53-0.57)				
HBV mono	1.58 (1.42-1.76)				
HCV mono	2.83 (2.7-2.97)				
HIV mono	4.75 (4.18-5.41)				
HBV/HCV	5.8 (5.14-6.54)				
HBV/HIV	11.39 (8.59-15.12)				
HCV/HIV	10.32 (9.28-11.47)				
HBV/ HCV/HIV	23.23 (20.4-26.46)				

# Antibody titer for CMV associated with poorer physical function in REPRIEVE



# Serious Non-AIDS Events associated with low level viremia

#### Definitions for the primary exposure of interest

- Non-suppressed viremia
  - A single VL ≥ 1000 copies/mL, OR
  - VL ≥ 200 copies/mL on two or more consecutive determinations at least 3 months apart
- High-level viremia: VL of 200-999 copies/mL, that does not meet the criteria for a blip or non suppressed viremia
- Low-level viremia: VL of 51-199 copies/mL which do not met criteria for a blip
- Virological suppression
  - $VL \le 50$  copies/mL OR
  - Blips: Isolated VL of 51-999 copies/mL which is preceded and followed by a VL ≤ 50 copies/mL

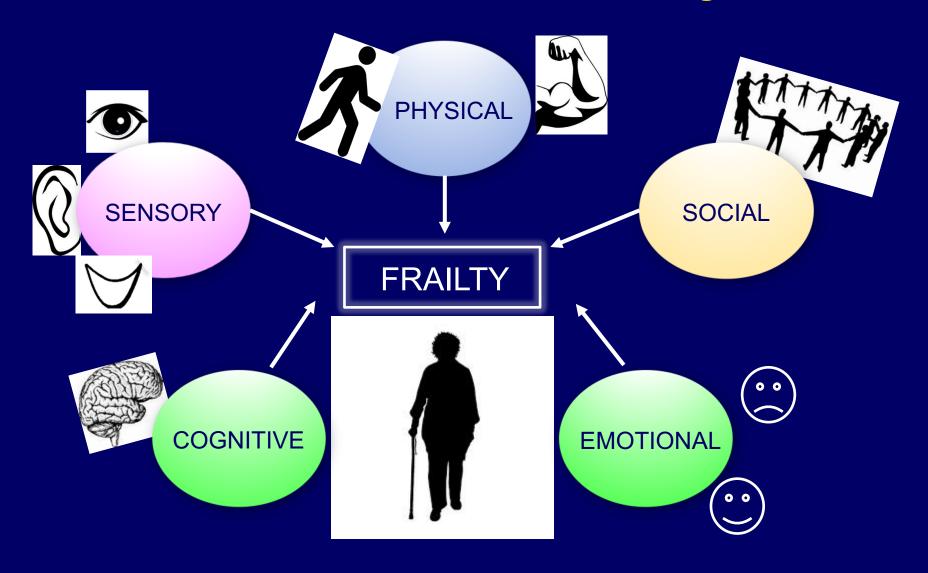
Highest Viremia Status	Overall (n=2815)	No SNAEs (n-2326)	SNAEs (n=489)
VS	1220 (43.3)	1094 (47)	126 (25.8)
Blips	325 (11.5)	266 (11.4)	59 (12.1)
LLV	221 (7.9)	194 (8.3)	27 (5.5)
hLV	122 (4.3)	102 (4.4)	20 (4.1)
NS	927 (32.9)	670 (28.8)	257 (52.6)

	Adjusted				
	HR	95%	P		
Time updated viral load categories (Reference: VS)					
LLV	1.249	1.161	1.343	<.0001	
hLV	1.566	1.453	1.689	<.0001	
NS	1.713	1.641	1.788	<.0001	
Gender					
Female vs. Male	1.355	1.28	1.436	<.0001	

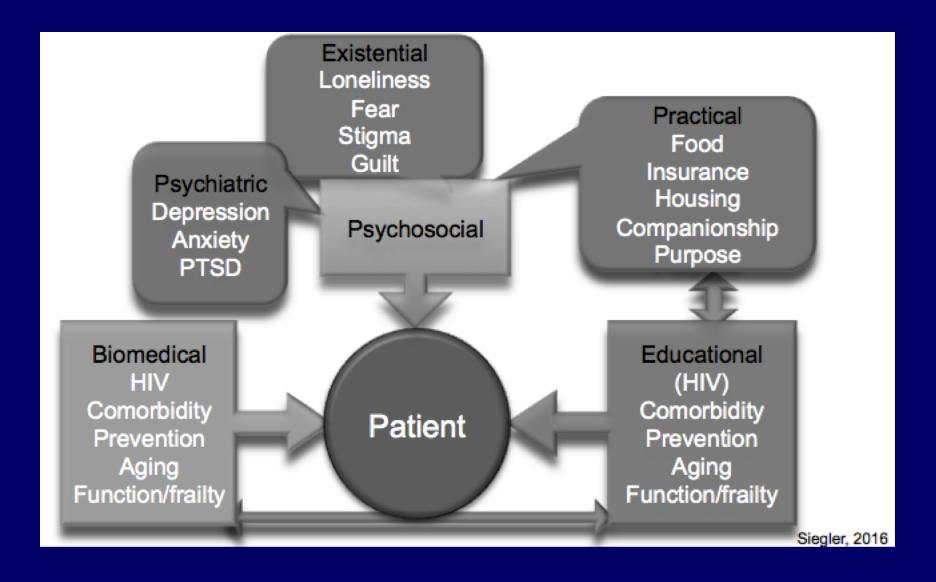
### How to Beat Inflammation: A Patient's Guide

- 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



### Treating the Whole Patient

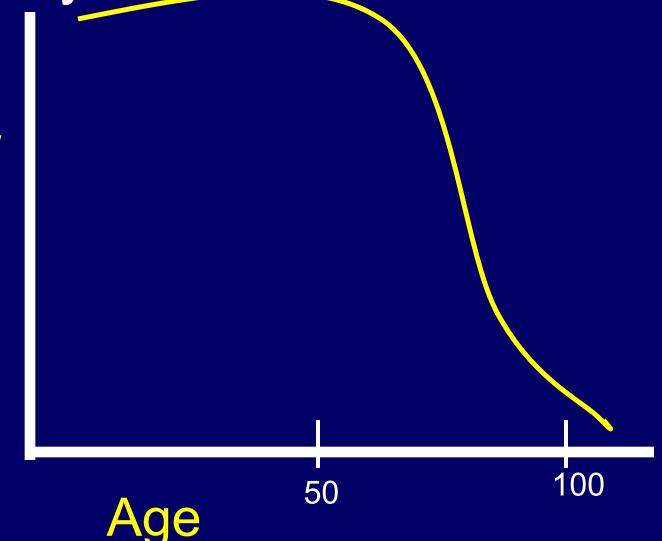


### Major Challenges for Aging PLWH

- 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
- Relative lack of data in women

Physical & cognitive function generally declines over time

Quality of Life/
Physical &
Cognitive
Function



Bending the Curve Upwards is the Essential Goal of Healthy Aging

Quality of Life/
Physical &
Cognitive
Function

