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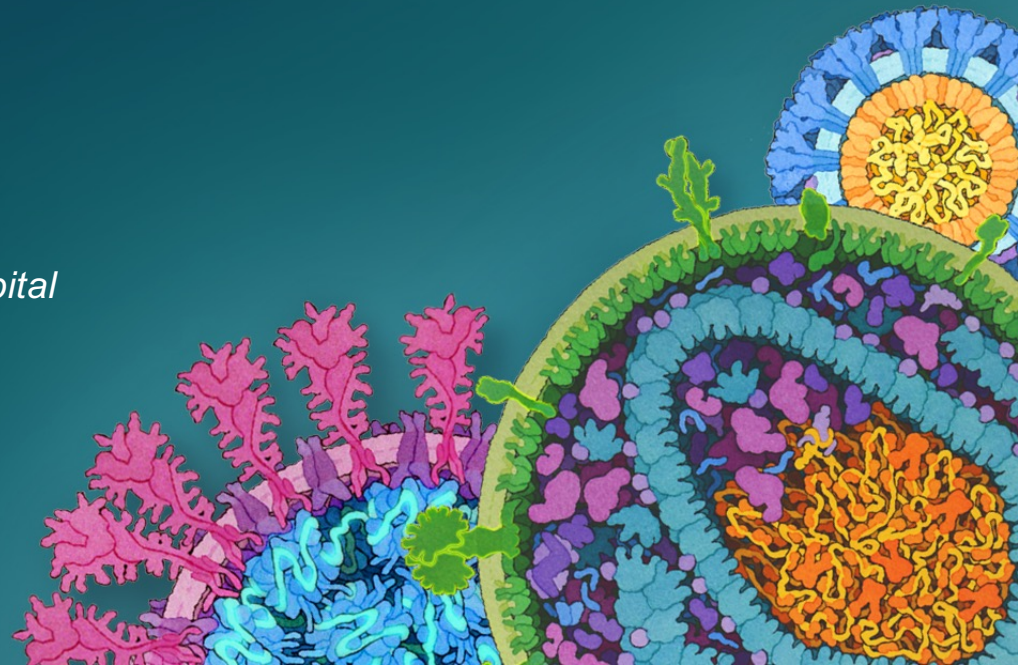
CLINICAL EPIDEMIOLOGY OF AGING & COMORBIDITY WITH HIV INFECTION: A GLOBAL PERSPECTIVE

Mark Siedner

Harvard Medical School/Massachusetts General Hospital

Boston, MA USA

Disclosures: None



Talk Summary

- What 30 years of research has taught us about the epidemiology of co-morbidities among people with HIV
- Could much of what we believe about the epidemiology of co-morbidities among people with HIV be wrong?
 - Sub-Saharan Africa perspective
 - Global North perspective through a social science lens
- Summary and research priorities

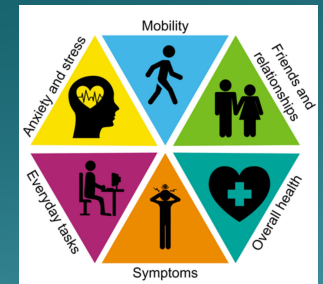
HIV and Health in the Pre-ART Era



**HIV
Infection**



**Longevity,
Health and
Wellbeing**



Combination ART & the Sea Change

The New England Journal of Medicine

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VOLUME 335

OCTOBER 10, 1996

NUMBER 15



A TRIAL COMPARING NUCLEOSIDE MONOTHERAPY WITH COMBINATION THERAPY IN HIV-INFECTED ADULTS WITH CD4 CELL COUNTS FROM 200 TO 500 PER CUBIC MILLIMETER

SCOTT M. HAMMER, M.D., DAVID A. KATZENSTEIN, M.D., MICHAEL D. HUGHES, PH.D., HOLLY GUNDACKER, M.S.,
ROBERT T. SCHOOLEY, M.D., RICHARD H. HAUBRICH, M.D., W. KEITH HENRY, M.D., MICHAEL M. LEDERMAN, M.D.,
JOHN P. PHAIR, M.D., MANETTE NIU, M.D., MARTIN S. HIRSCH, M.D., AND THOMAS C. MERIGAN, M.D.,
FOR THE AIDS CLINICAL TRIALS GROUP STUDY 175 STUDY TEAM*



Hammer et al, *NEJM*, 1996

HIV and Health in the ART Era

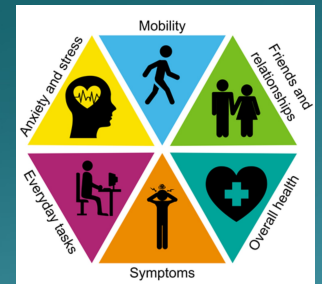


HIV
Infection

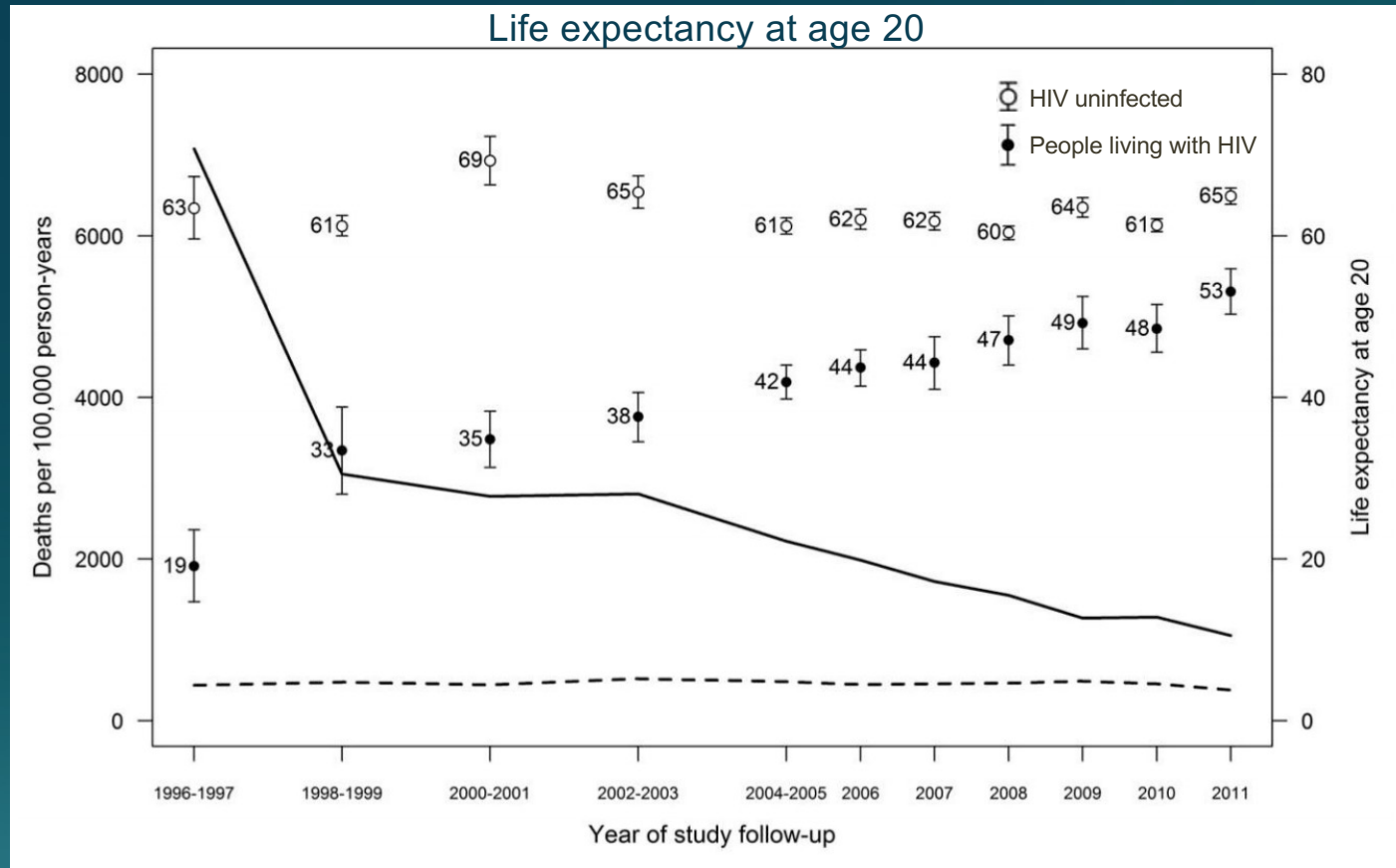
ART



Longevity,
Health and
Wellbeing

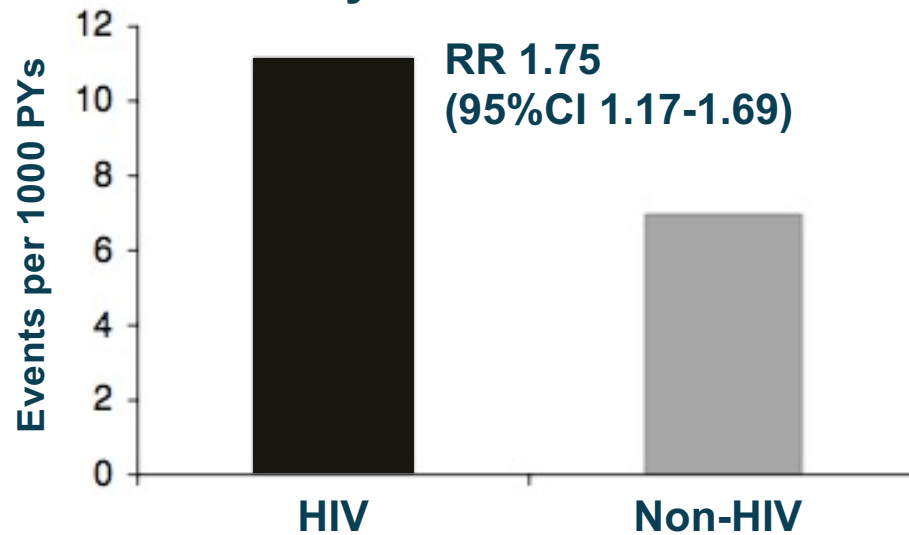


HIV and Life Expectancy in ART Era

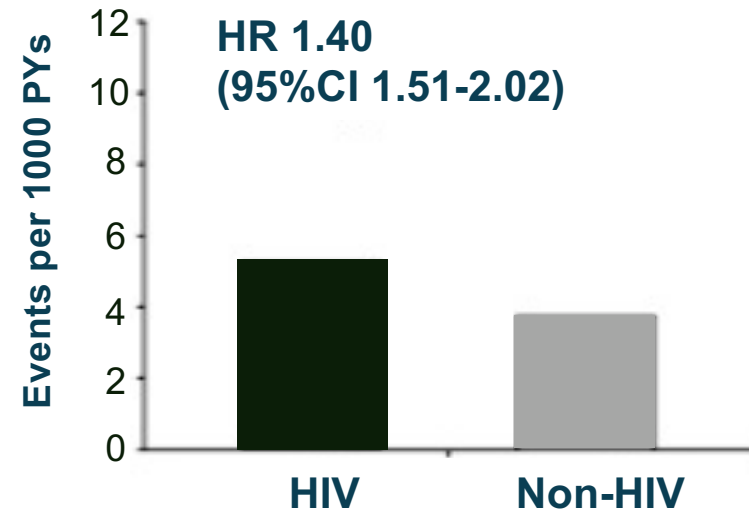


HIV Infection and Myocardial Infarction

Incidence of Myocardial Infarction

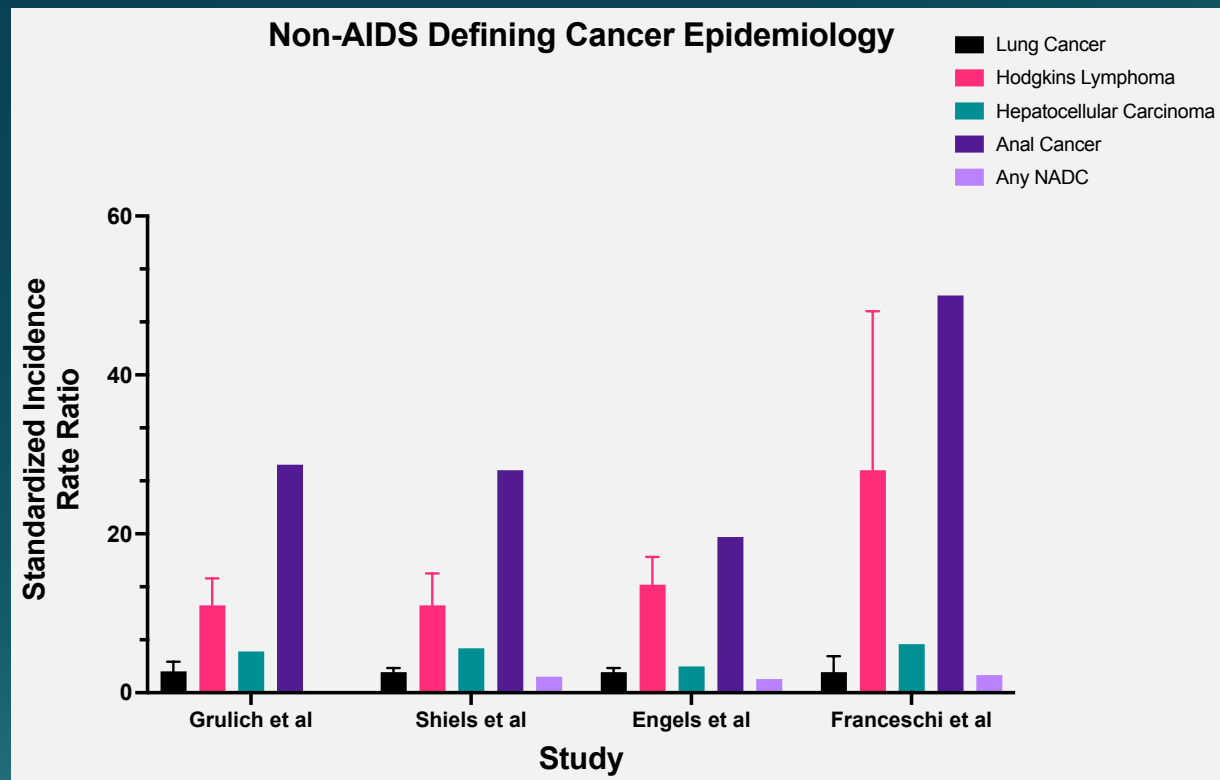


Incidence of Stroke

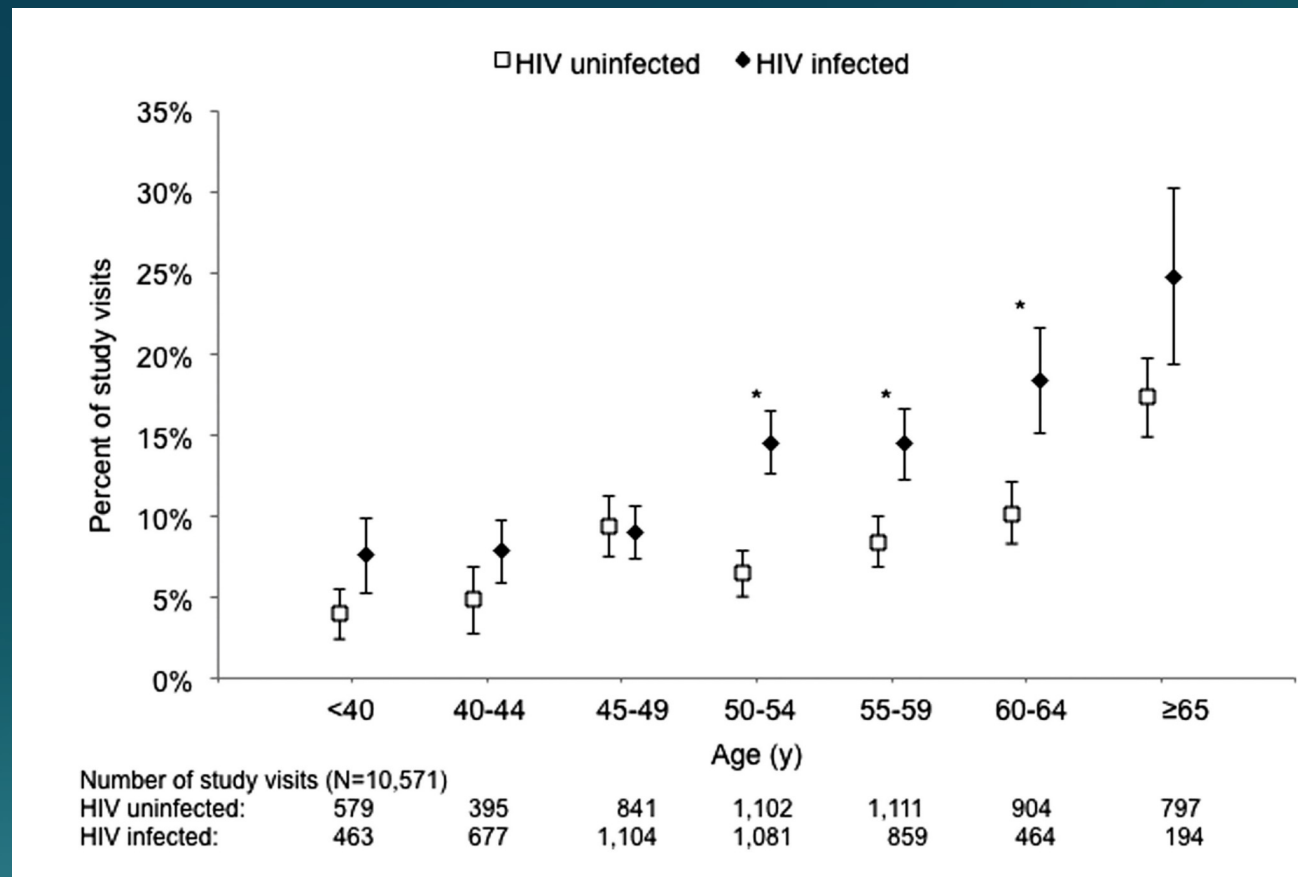


Triant et al, J Clin Endo, 2007
Chow et al, AIDS 2012
Currier et al, JAIDS, 2003
Frieberg et al, Ann Int Med, 2013
Althoff et al, Clin Inf Dis, 2015

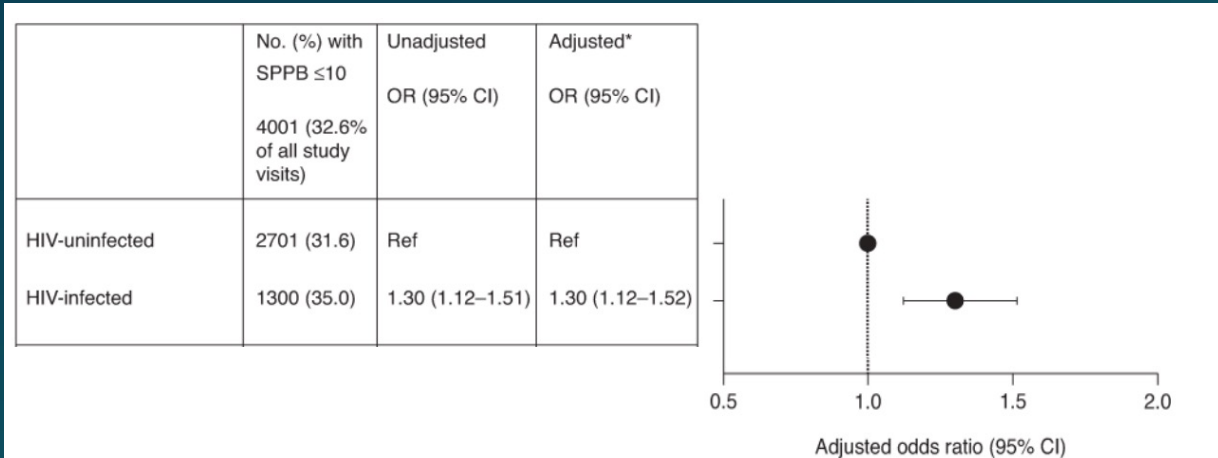
HIV Infection and Cancer



HIV and Frailty



HIV and Reduced Physical Function

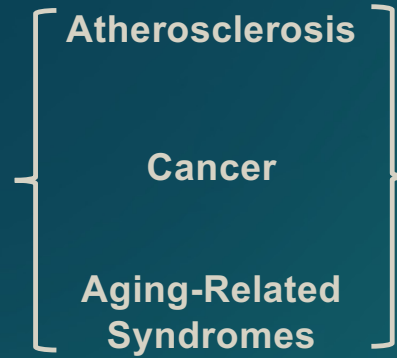


Conceptual Framework

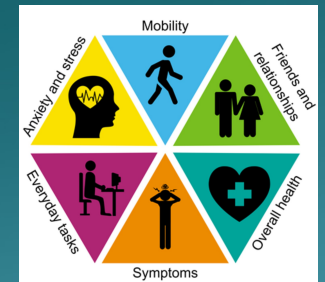


**HIV
Infection**

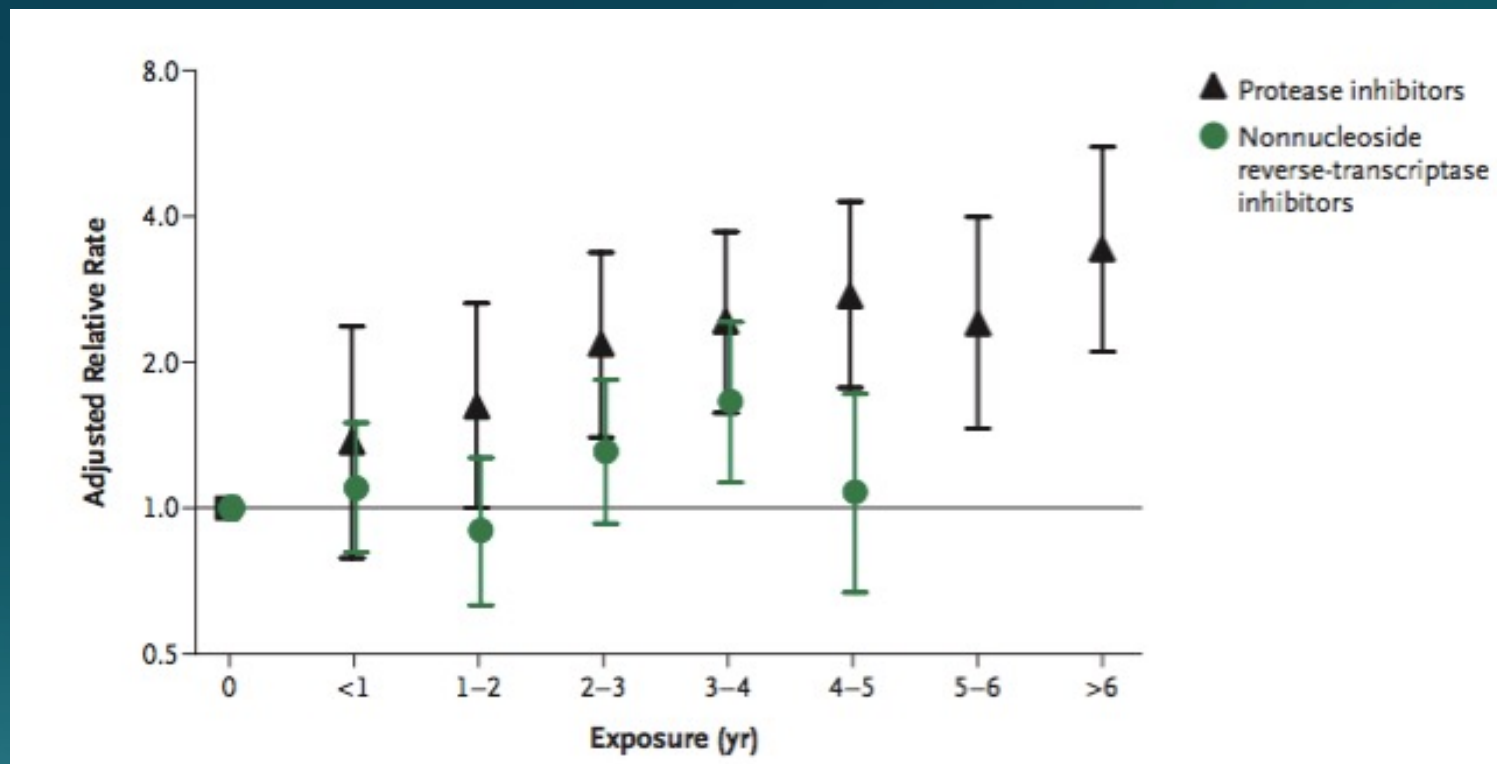
ART



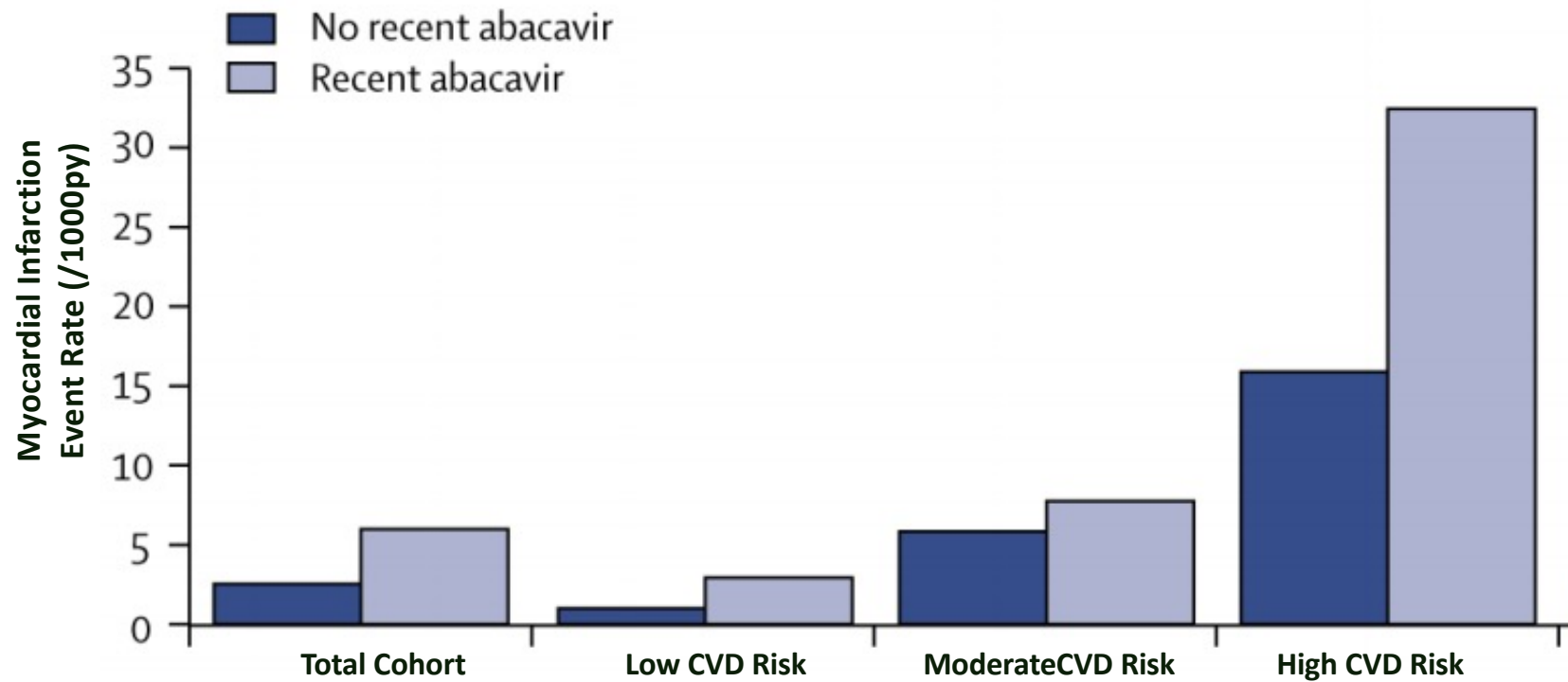
**Longevity,
Health and
Wellbeing**



ART-related toxicity



ART-related toxicity

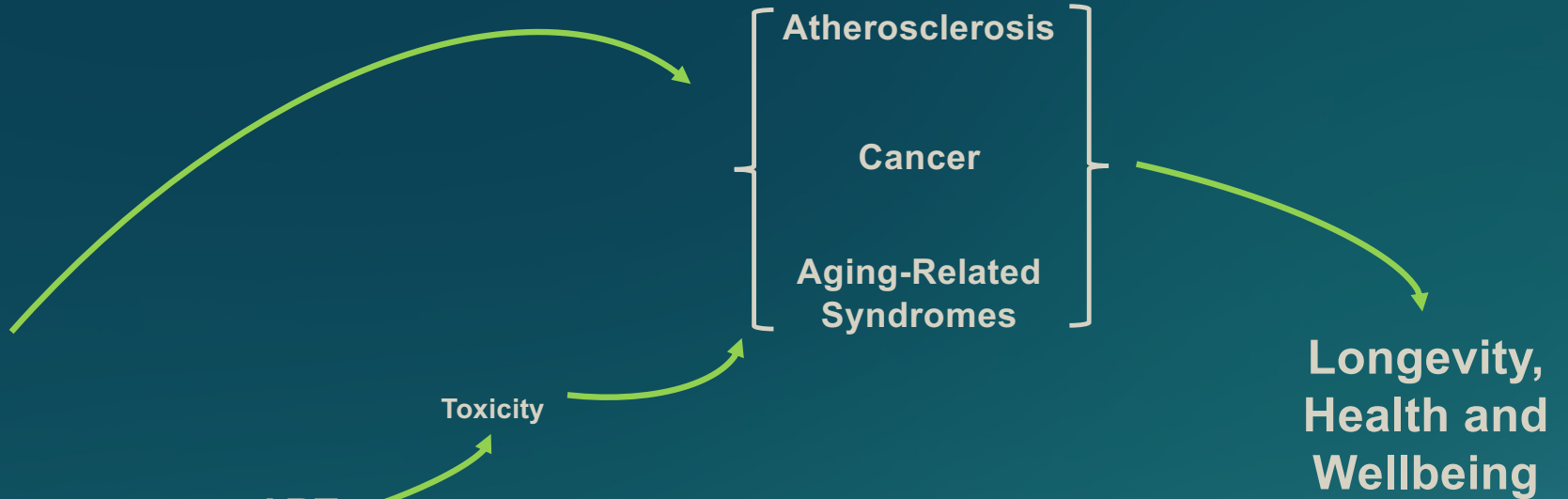


Monforte et al, *AIDS*, 2013
Lang et al, *JAMA Int Med*, 2010

Conceptual Framework



**HIV
Infection**



The disease or its treatment?

| Outcome | Relative Risk for Treatment Interruption* | P-value | Total Events |
|---------|---|---------|--------------|
| Death | 1.8 (1.2-2.9) | 0.007 | 55 |

***Relative risk comparing those with ART treatment interruption versus those who remain on therapy**

The disease or its treatment?

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| Serious OI | 6.6 (1.5 – 29) | 0.01 | 13 |

***Relative risk comparing those with ART treatment interruption versus those who remain on therapy**

The disease or its treatment?

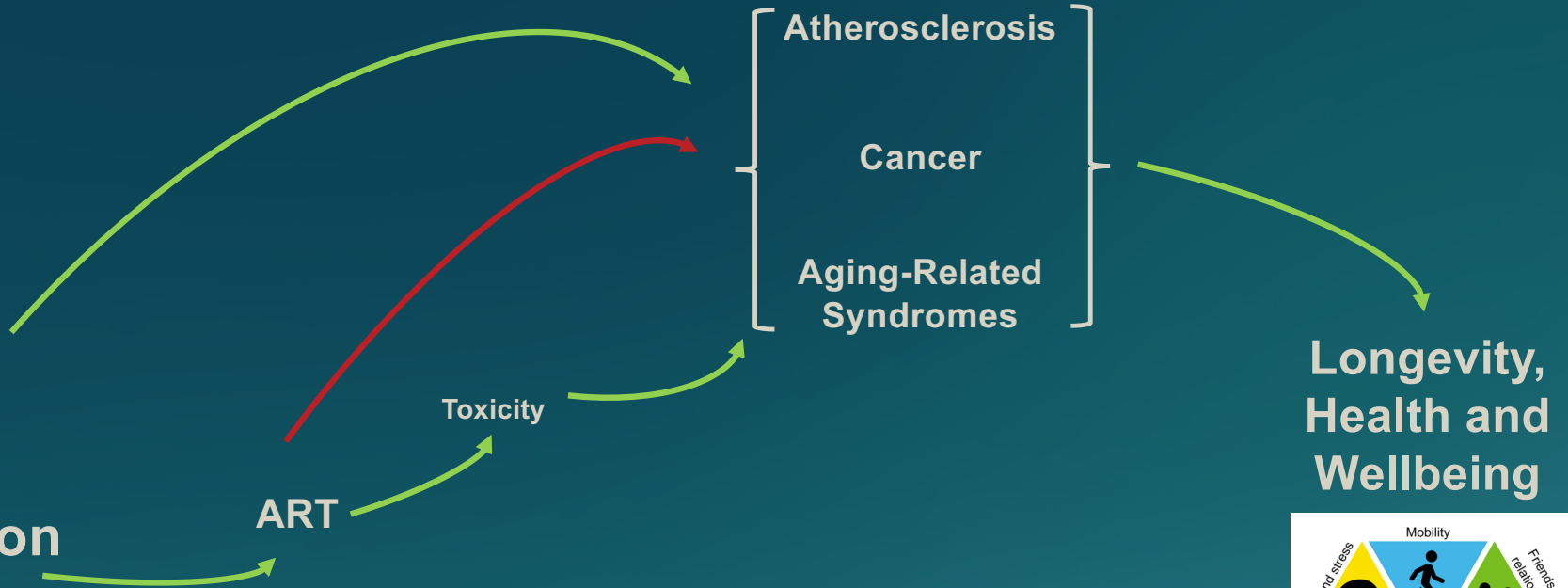
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|-----------------------|---|--------------|--------------|
| Death | 1.8 (1.2-2.9) | 0.007 | 55 |
| Serious OI | 6.6 (1.5 – 29) | 0.01 | 13 |
| Major CV Event | 1.7 (1.1-2.5) | 0.009 | 65 |

***Relative risk comparing those with ART treatment interruption versus those who remain on therapy**

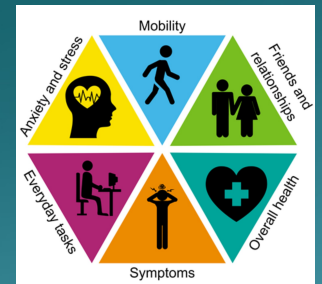
Conceptual Framework



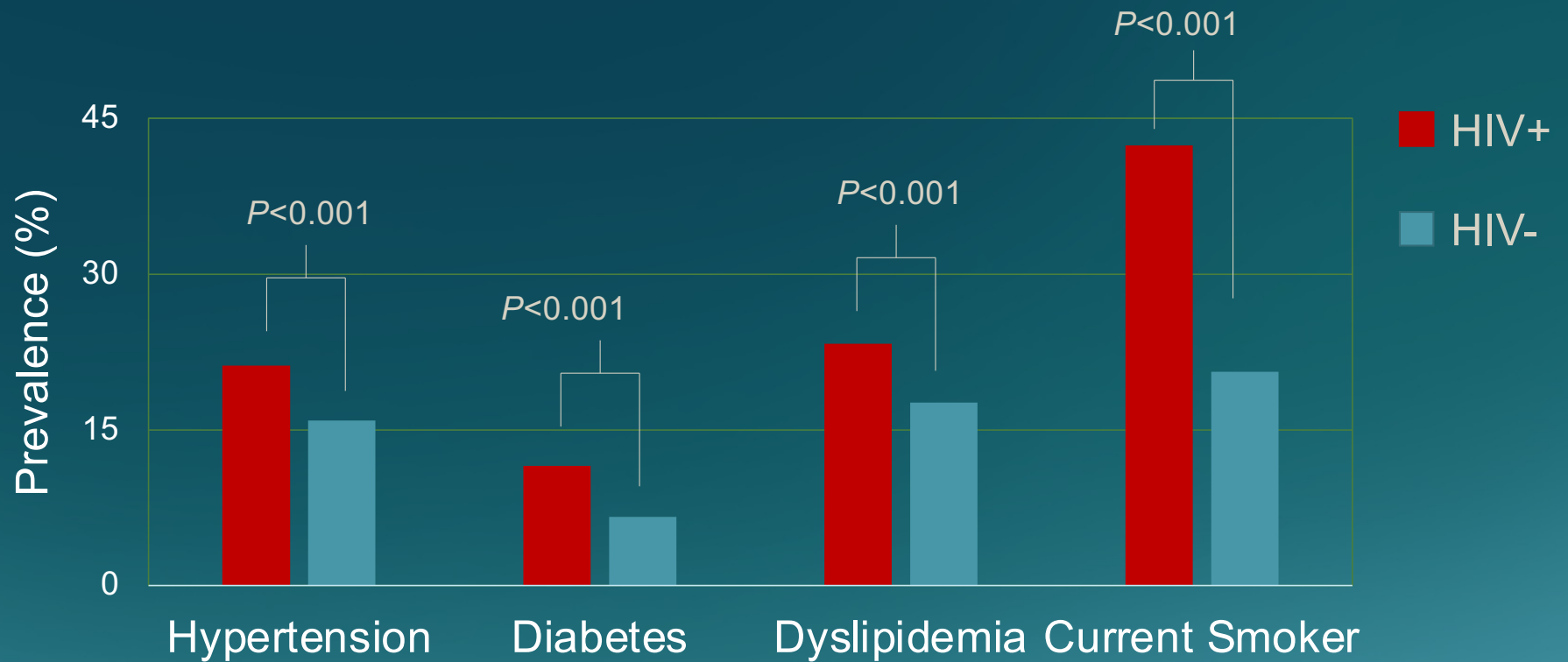
**HIV
Infection**



**Longevity,
Health and
Wellbeing**

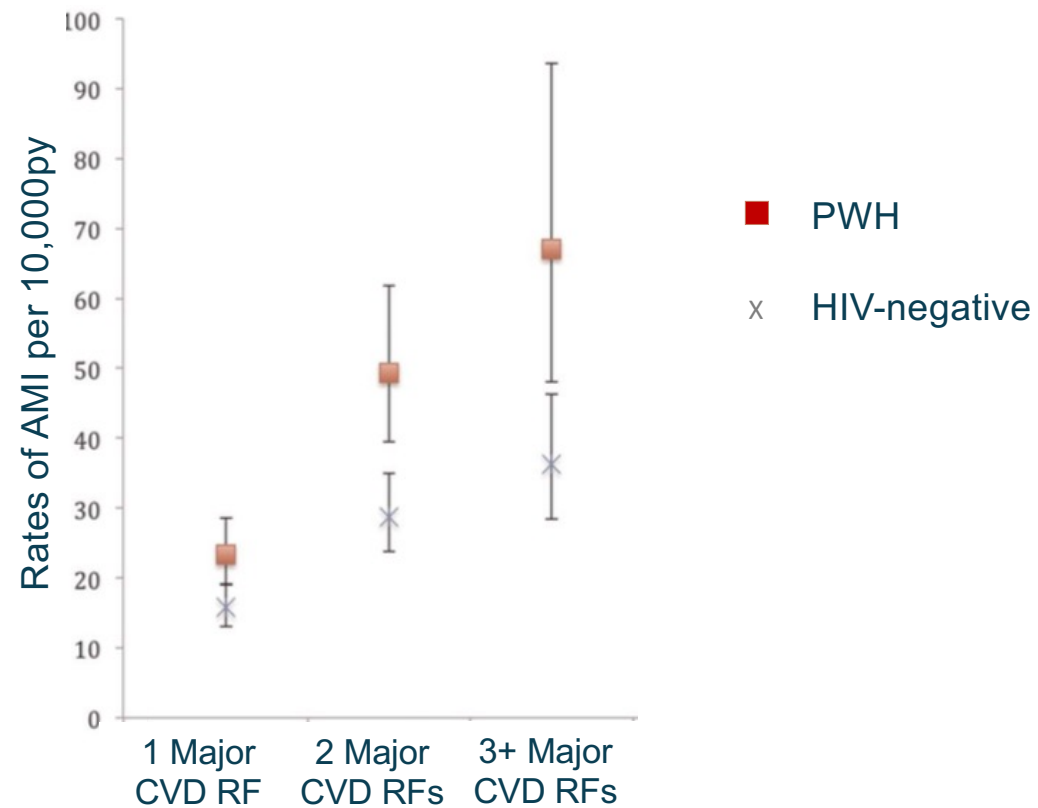


Confounded by Traditional Risk Factors?

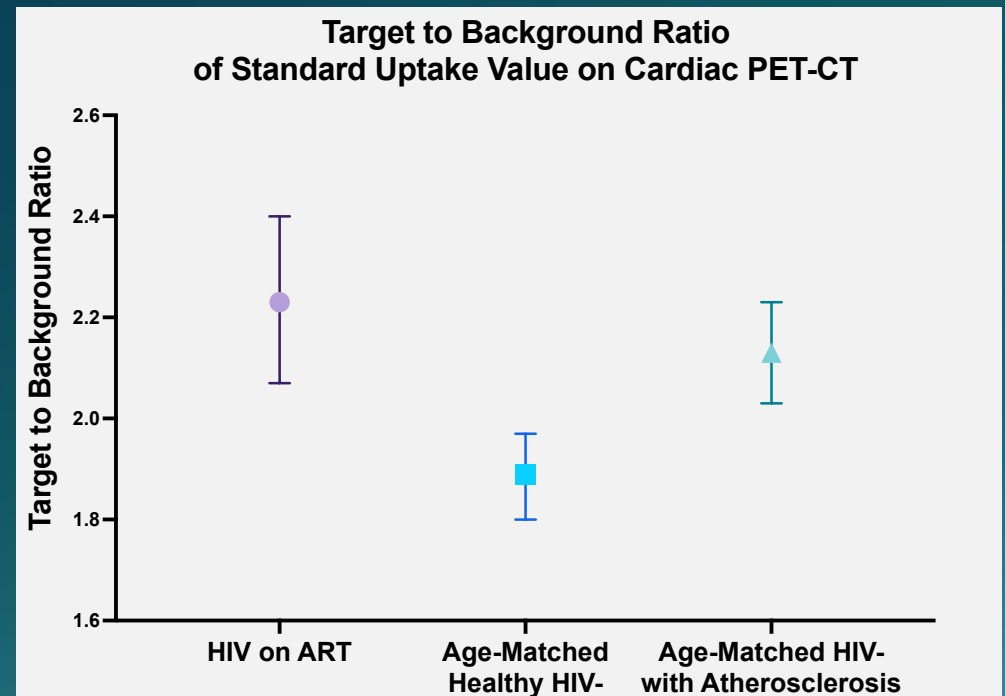
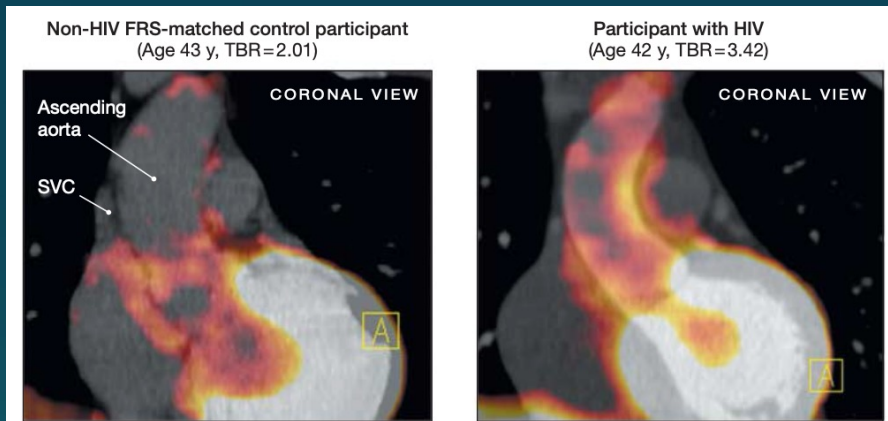


Triant et al, J Clin Endo, 2007
Mdodo, Ann Int Med, 2015

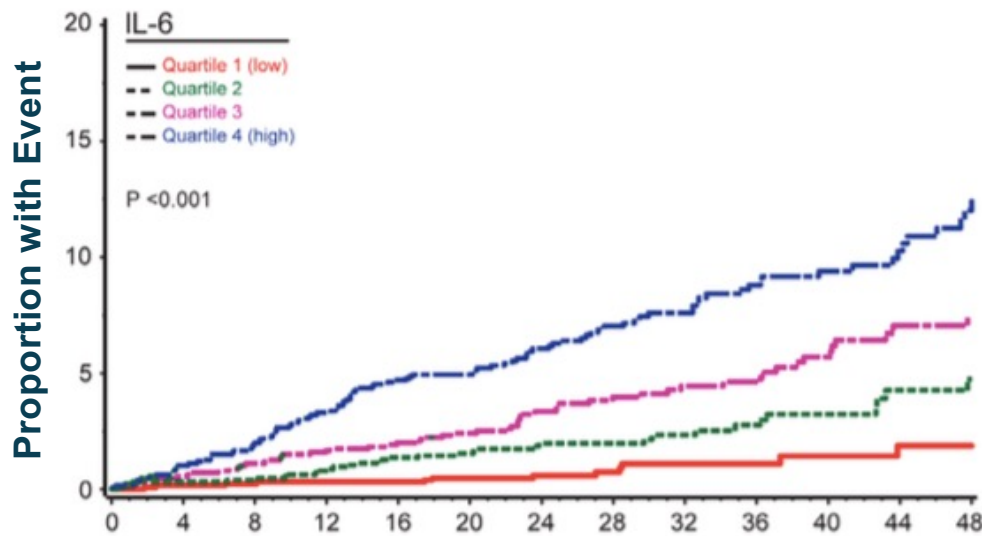
Confounded by CVD Risk Factors?



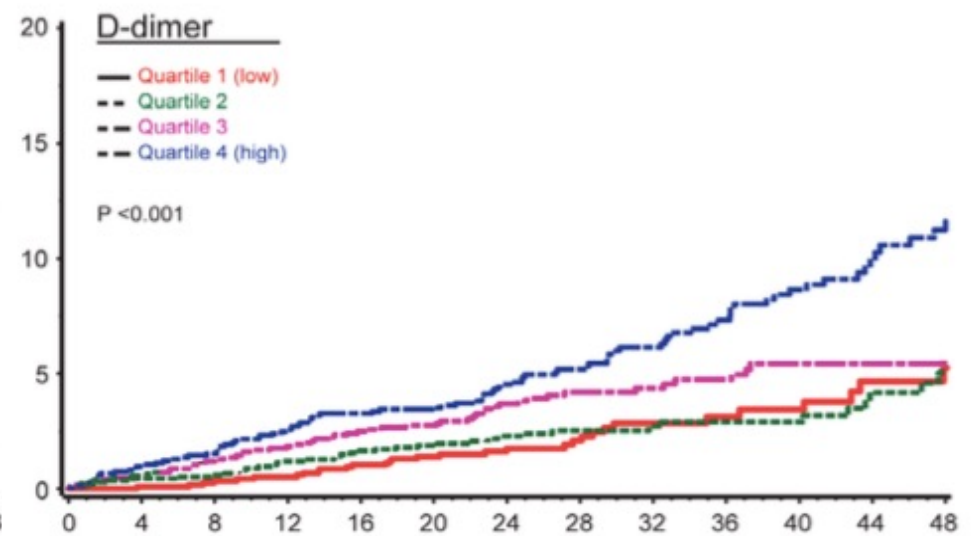
Confounding by CVD Risk Factors?



Inflammation as a Casual Mediator

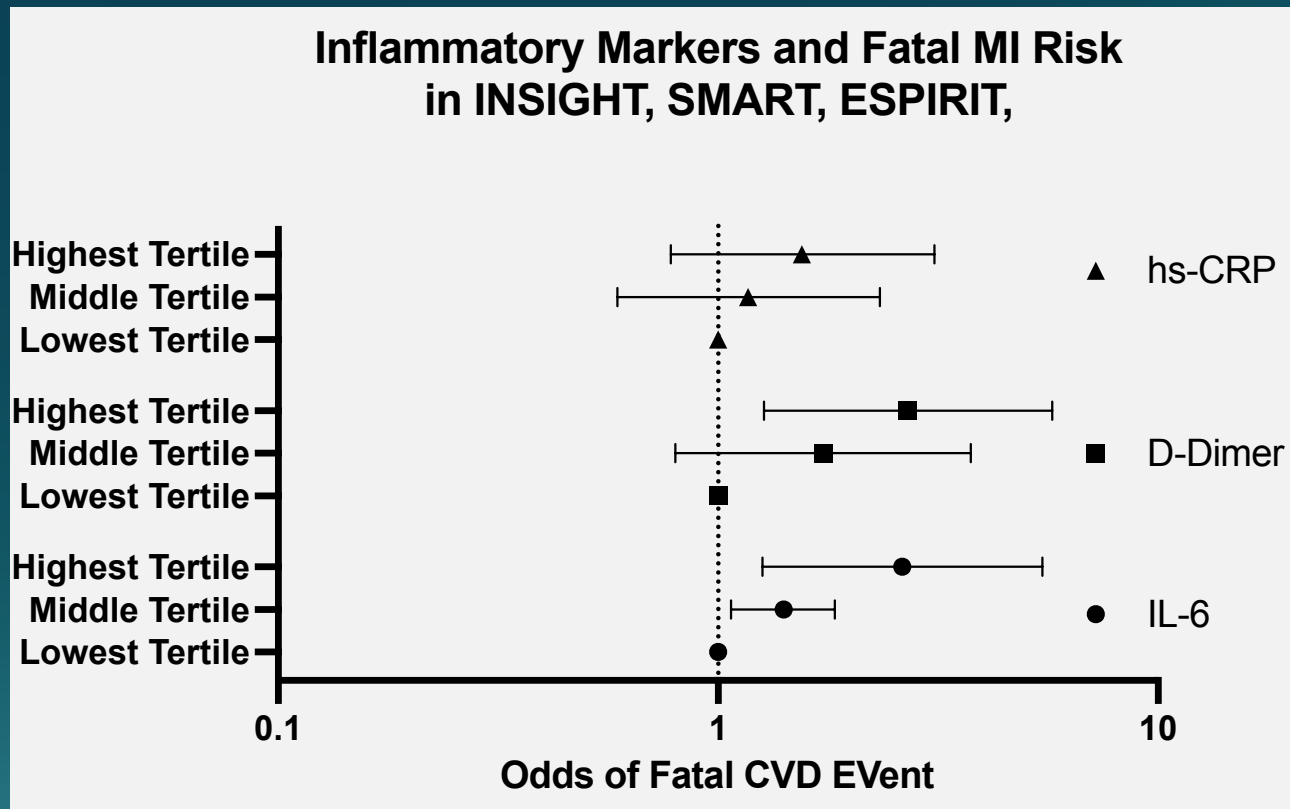


Months from Randomization



Months from Randomization

Inflammation as a Casual Mediator



Conceptual Framework



**HIV
Infection**

Inflammation

ART

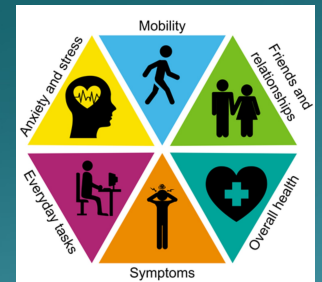
Toxicity

Atherosclerosis

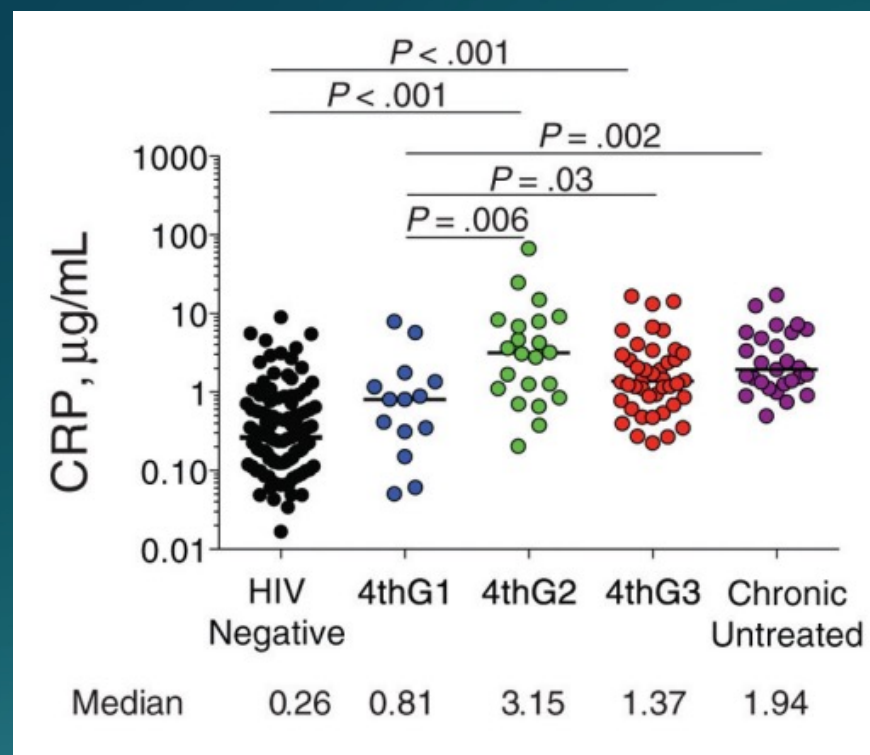
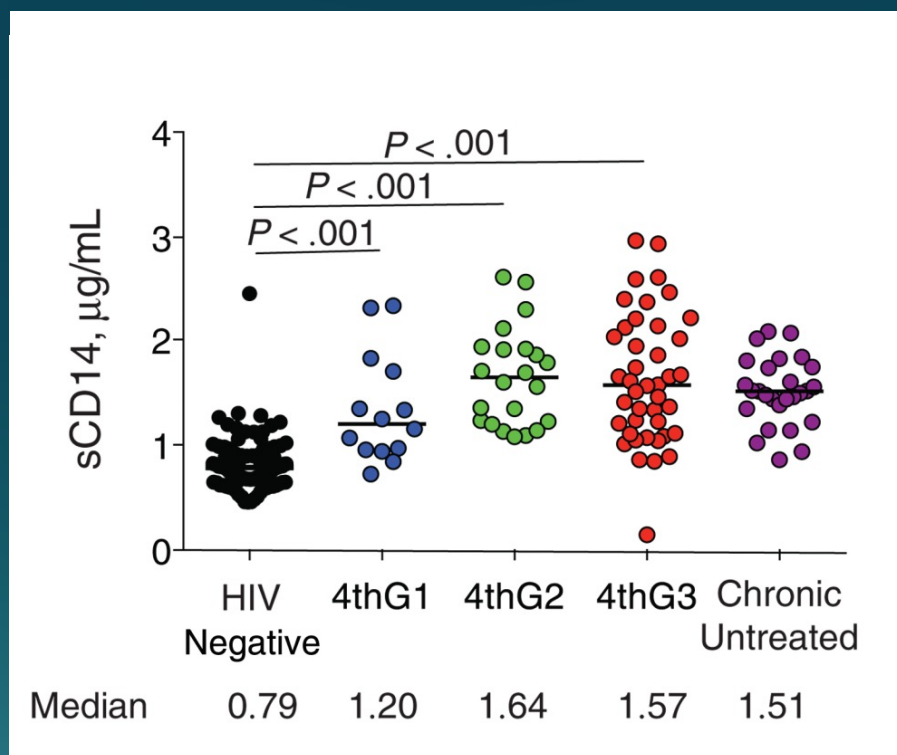
Cancer

**Ageing-Related
Syndromes**

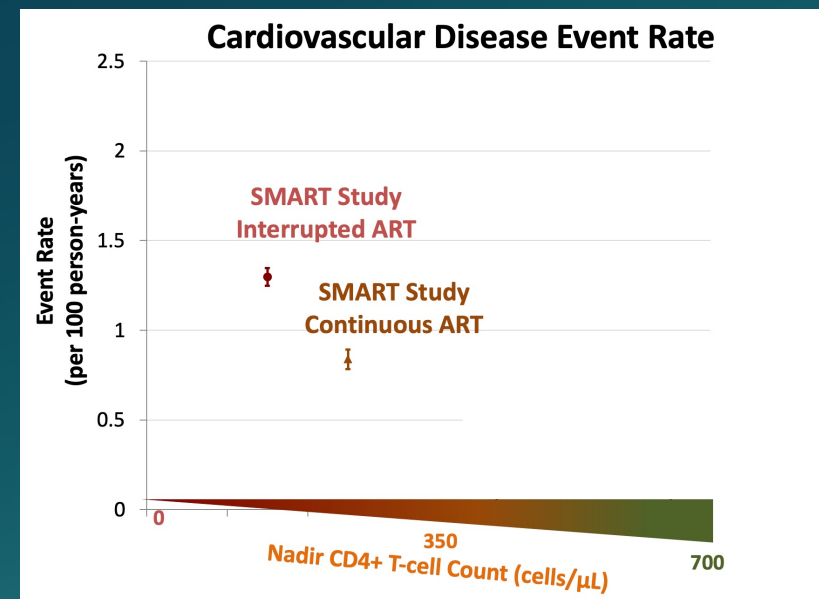
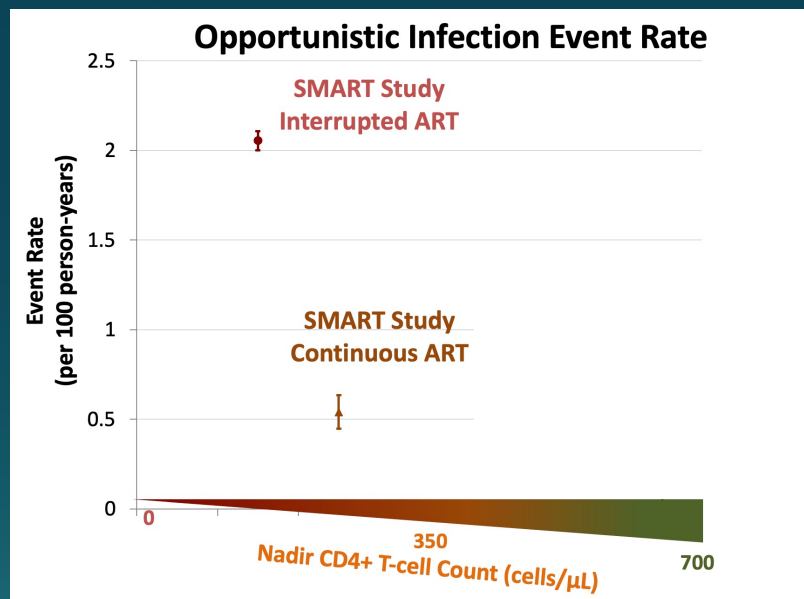
**Longevity,
Health and
Wellbeing**



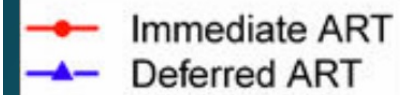
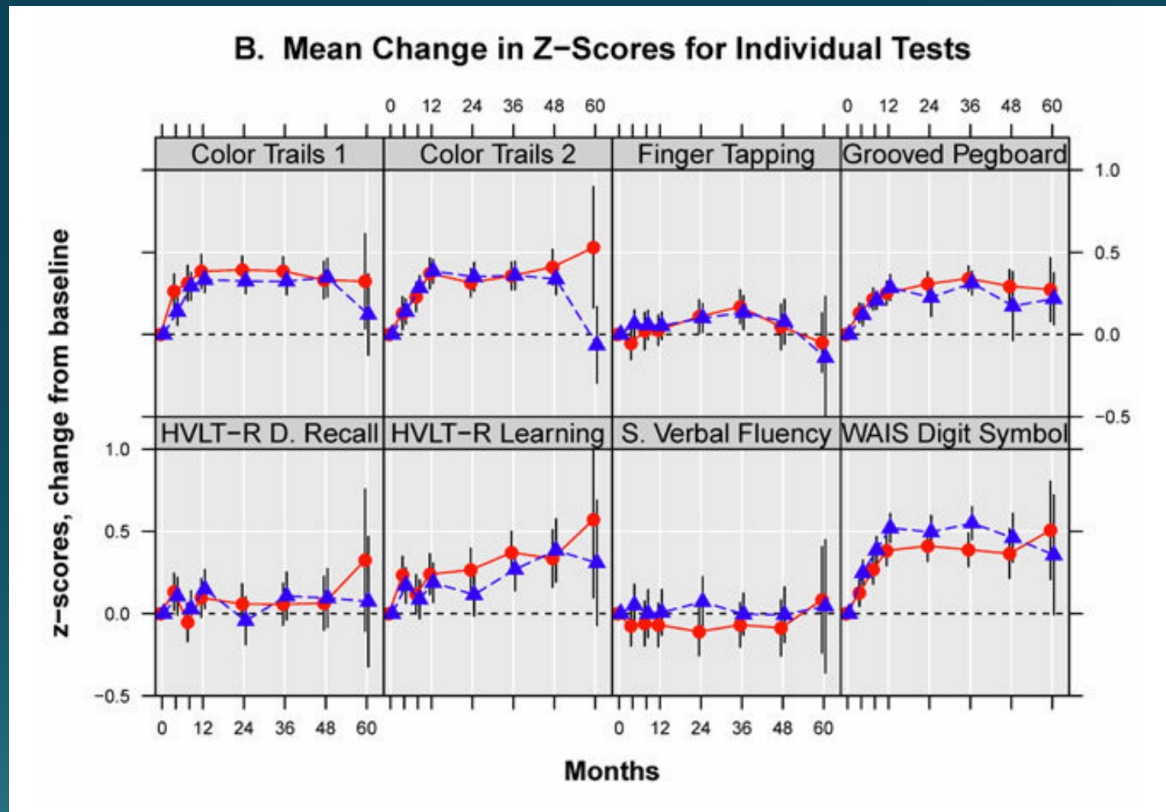
Timing of ART Initiation and Chronic Inflammation



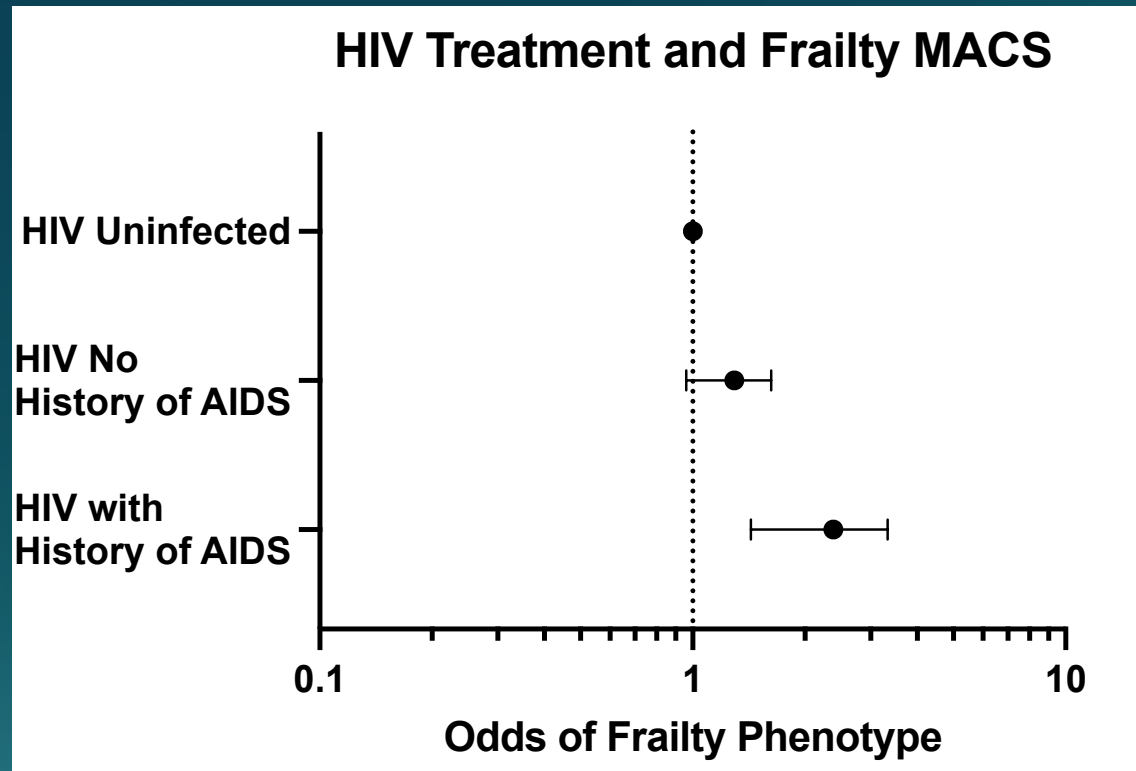
Timing of ART Initiation and CM Risk



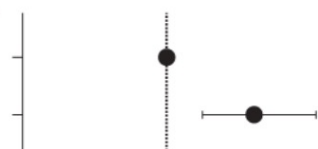
Neurocognition and Early ART Initiation



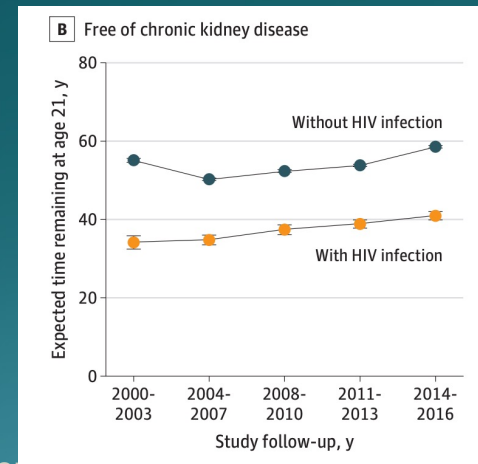
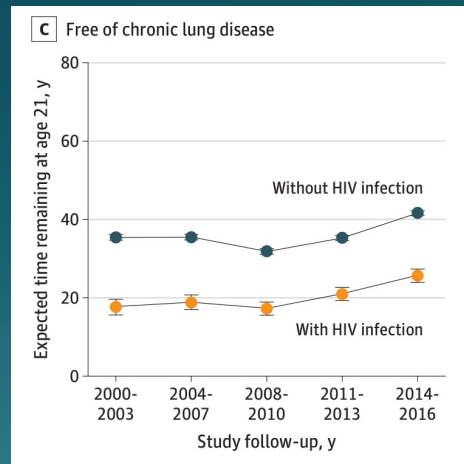
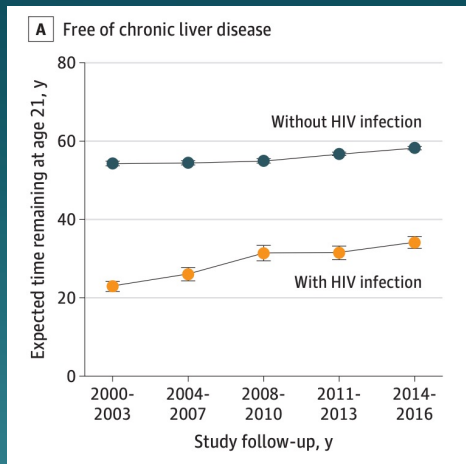
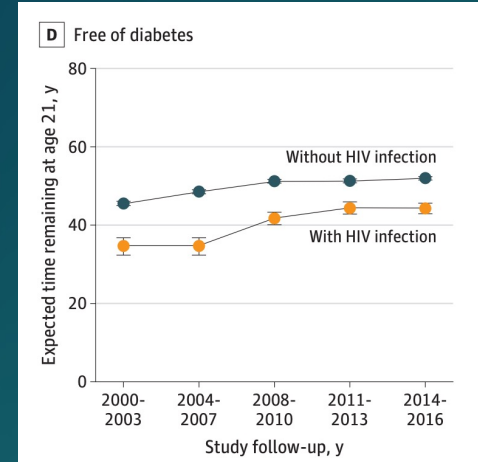
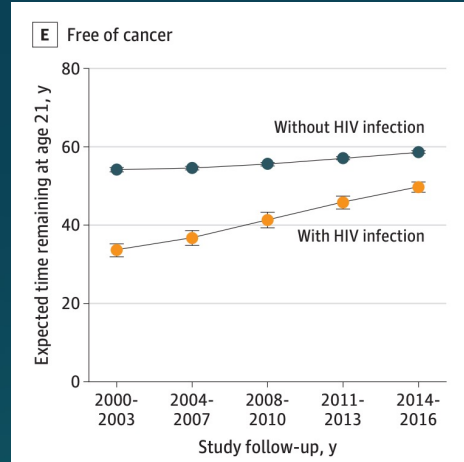
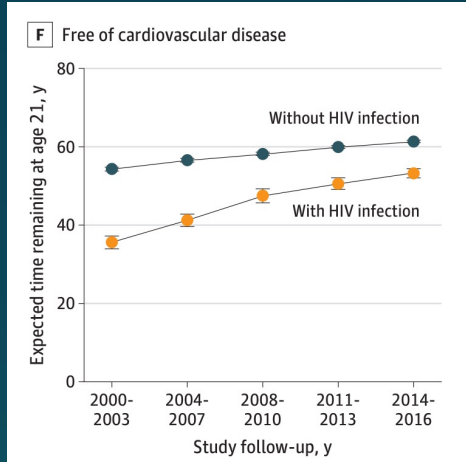
Frailty and HIV by History of AIDS



Physical Function and HIV by Disease Status

| | No. (%) with SPPB ≤ 10 4001 (32.6% of all study visits) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | |
|----------------|---|------------------------|-----------------------|---|
| HIV-uninfected | 2701 (31.6) | Ref | Ref |  |
| HIV-infected | 1300 (35.0) | 1.30 (1.12-1.51) | 1.30 (1.12-1.52) | |

Confounding by ART Use & Timing?



Conceptual Framework



**HIV
Infection**

Inflammation

**Timing of Treatment
Initiation**

Toxicity

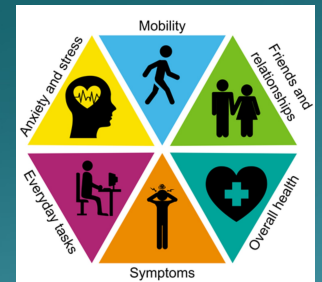
ART

Atherosclerosis

Cancer

**Ageing-Related
Syndromes**

**Longevity,
Health and
Wellbeing**



Halftime Summary

- PWH in Global North with access to ART have persistent, albeit narrowing, gap in life expectancy
- Innumerable conditions are increased with HIV infection (partial list)
 - Atherosclerosis/CVD
 - Chronic lung disease
 - Cancer
 - Geriatric syndromes: frailty, reduced physical functioning, cognitive decline
- Increased inflammation among PWH predicts poor health and outcomes
- Early treatment initiation mitigates risk of some, but not all, conditions

Interventions against causal risk factors

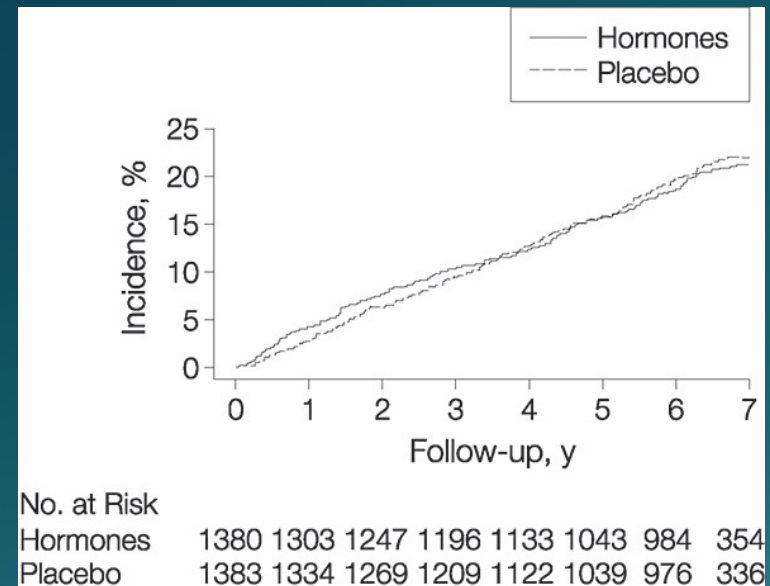
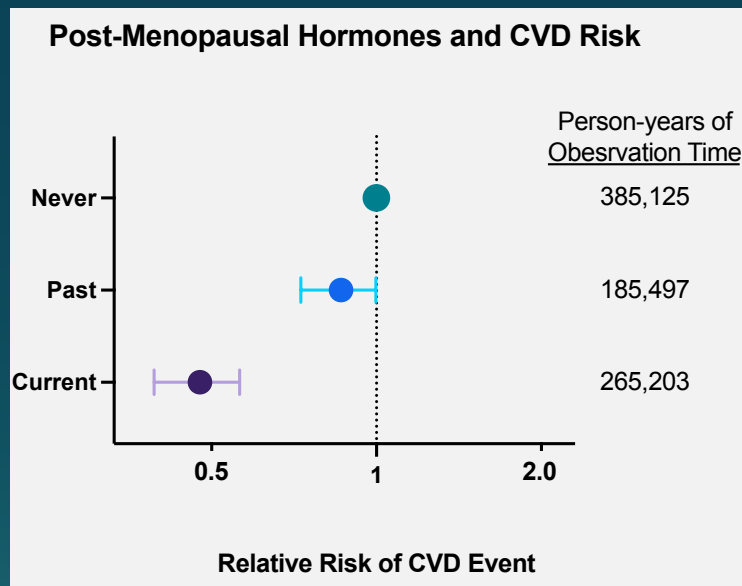
- Early treatment, early treatment, early treatment
- Anti-inflammatory therapies?



REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

On causal effects and mis-specification



*Adjusted for: age, BMI, history of DM, history HTN, cholesterol, age at menopause, smoking, family history

Goldstein et al, AIM, 2000
Grady et al, JAMA, 2002

Is the effect of HIV on chronic co-morbidities *causal*?

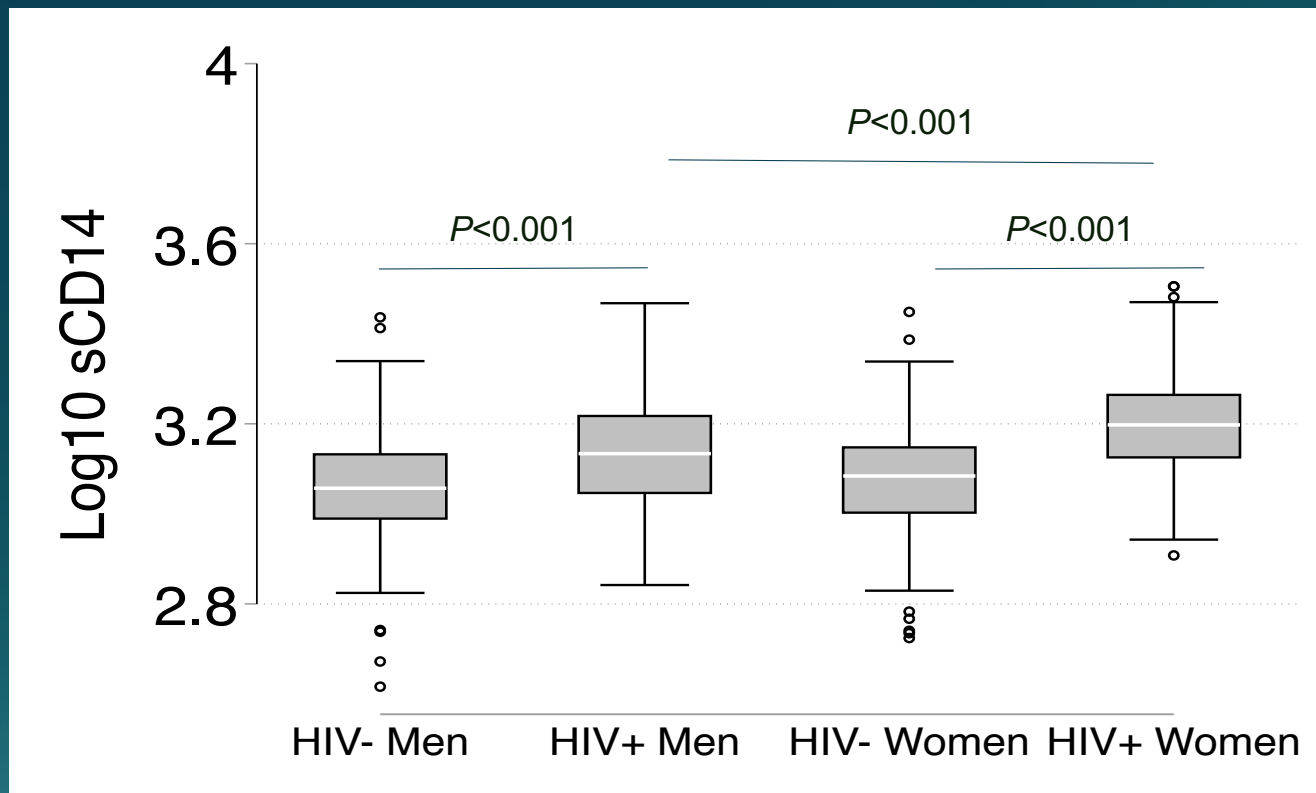
- Sir Bradford-Hill Criteria

- Strength of association
- **Consistency?**
- **Specificity**
- Temporality
- Biologic plausibility
- ~~Dose-response~~
- Coherence
- Experimental proof

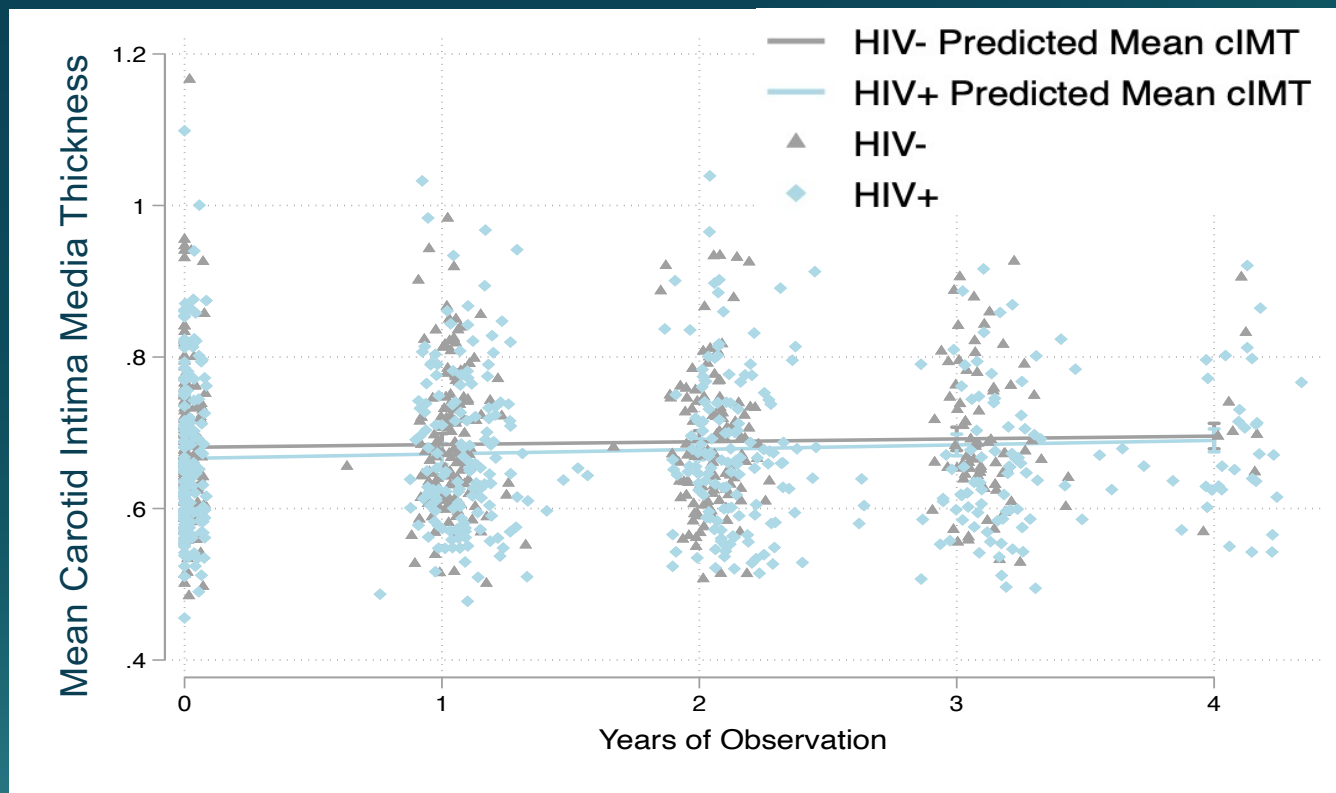
- Consistency

- The case of sub-Saharan Africa

HIV, Gender and Inflammation in Uganda



A global perspective: sub-Saharan Africa

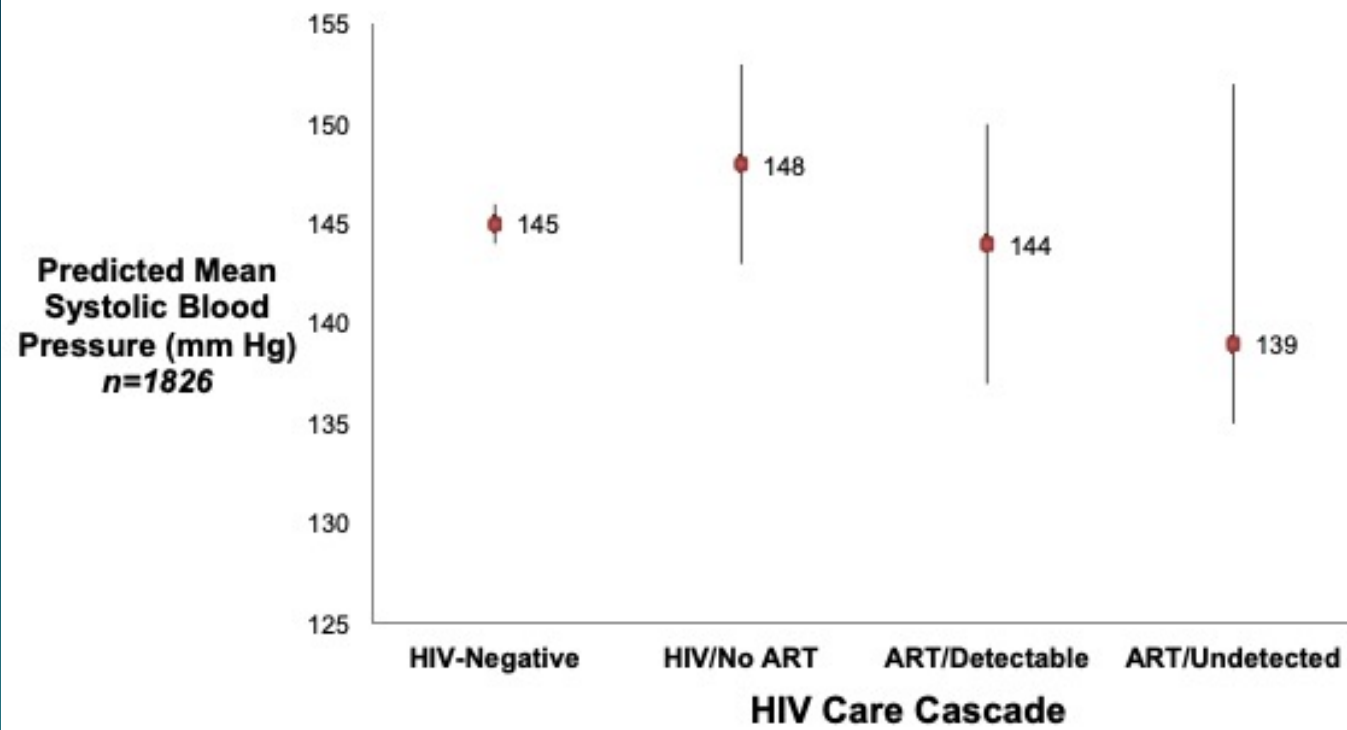


HIV and Stroke Risk

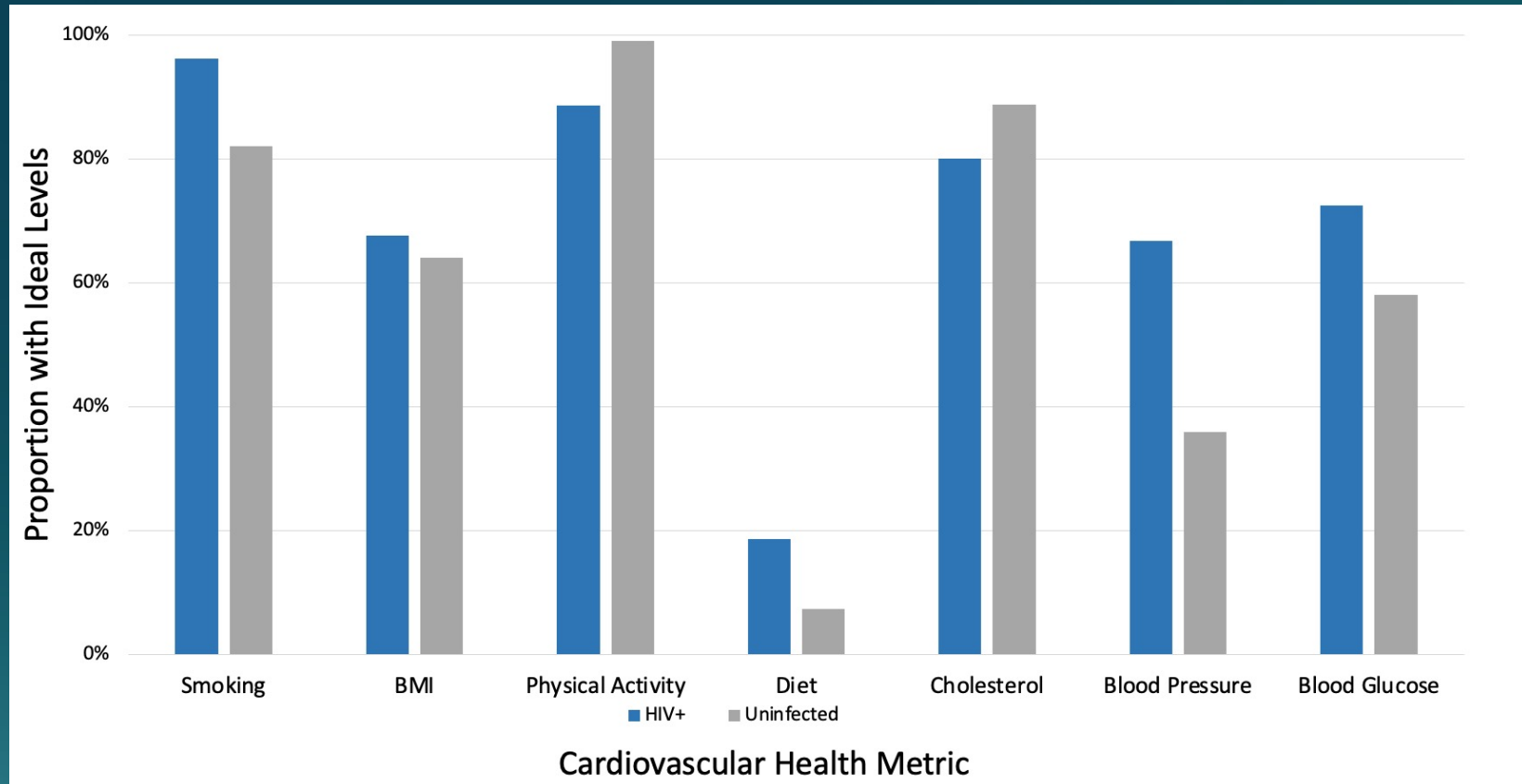
| Characteristic | Adjusted Odds Ratio* | P-value | Population Attributable Fraction |
|----------------------|---------------------------|------------------|----------------------------------|
| Hypertension | 5.01 (3.02 – 8.29) | <0.001 | 46% |
| Diabetes | 3.41 (1.45 - 8.01) | 0.005 | 3% |
| Current Smoker | 2.36 (1.34 - 4.13) | 0.003 | 6% |
| HIV Infection | 3.28 (2.05 – 5.25) | <0.001 | 15% |

HIV and Stroke Risk

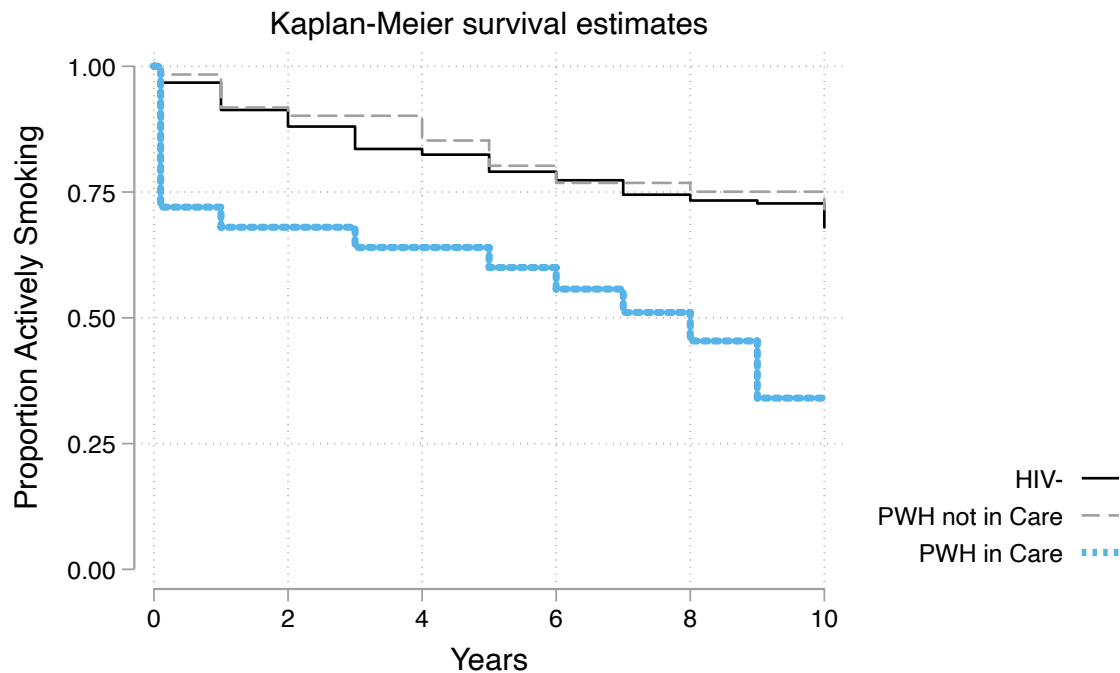
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| HIV Infection | 3.28 (2.05 – 5.25) | <0.001 | 15% |
| Untreated | 4.48 (2.44 – 8.24) | <0.001 | |
| ART >6 months | 1.49 (0.72 – 3.07) | 0.23 | |



HIV and Ideal CVD Risk Factors in Uganda



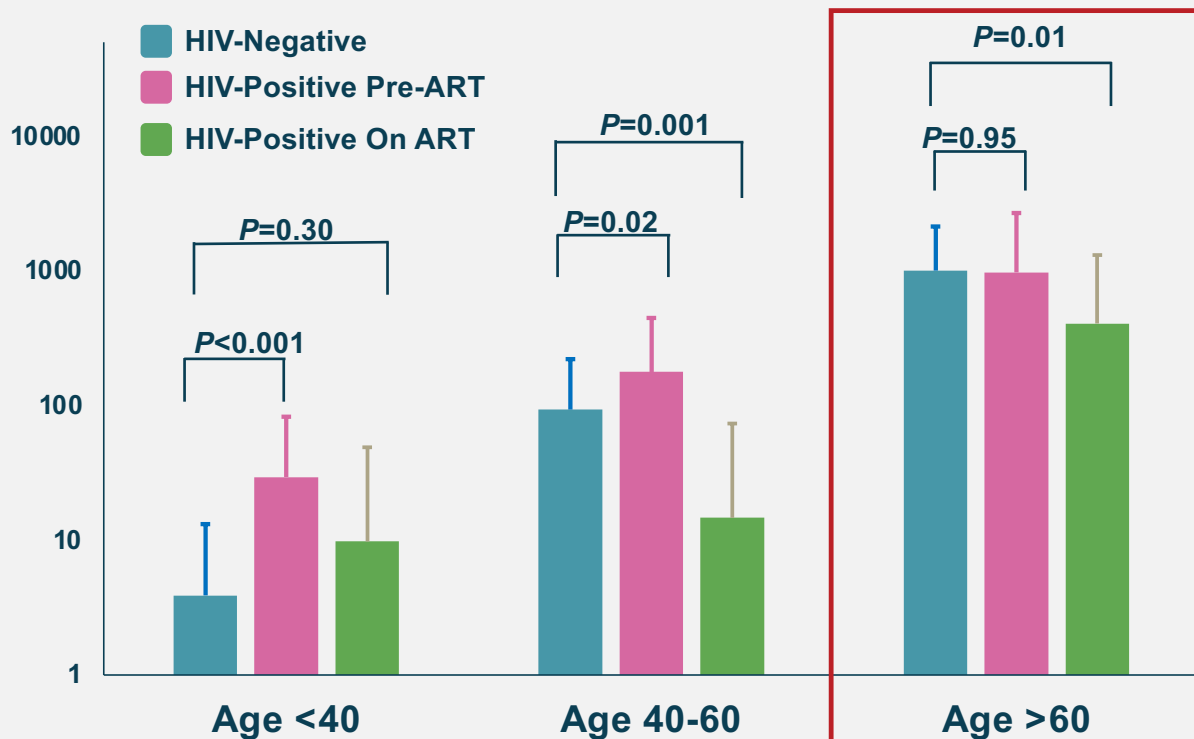
HIV Care and Access to Primary Care



| Number at risk | | | | | | | |
|----------------|-----------------|-----|-----|-----|-----|-----|-----|
| | HIV- | 185 | 166 | 148 | 139 | 129 | 122 |
| | PWH not in Care | 61 | 56 | 55 | 47 | 44 | 43 |
| | PWH in Care | 25 | 17 | 16 | 14 | 9 | 2 |

HIV, ART, and stroke incidence in rural SA

Umkhanyakude District (SA) HIV and Fatal Stroke Incidence



Conceptual Framework: **sub-Saharan Africa**



HIV Infection

Inflammation

Timing of Treatment Initiation

Toxicity

ART

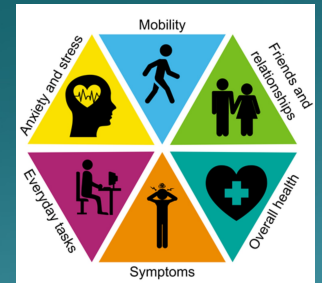
Healthcare Access

Atherosclerosis

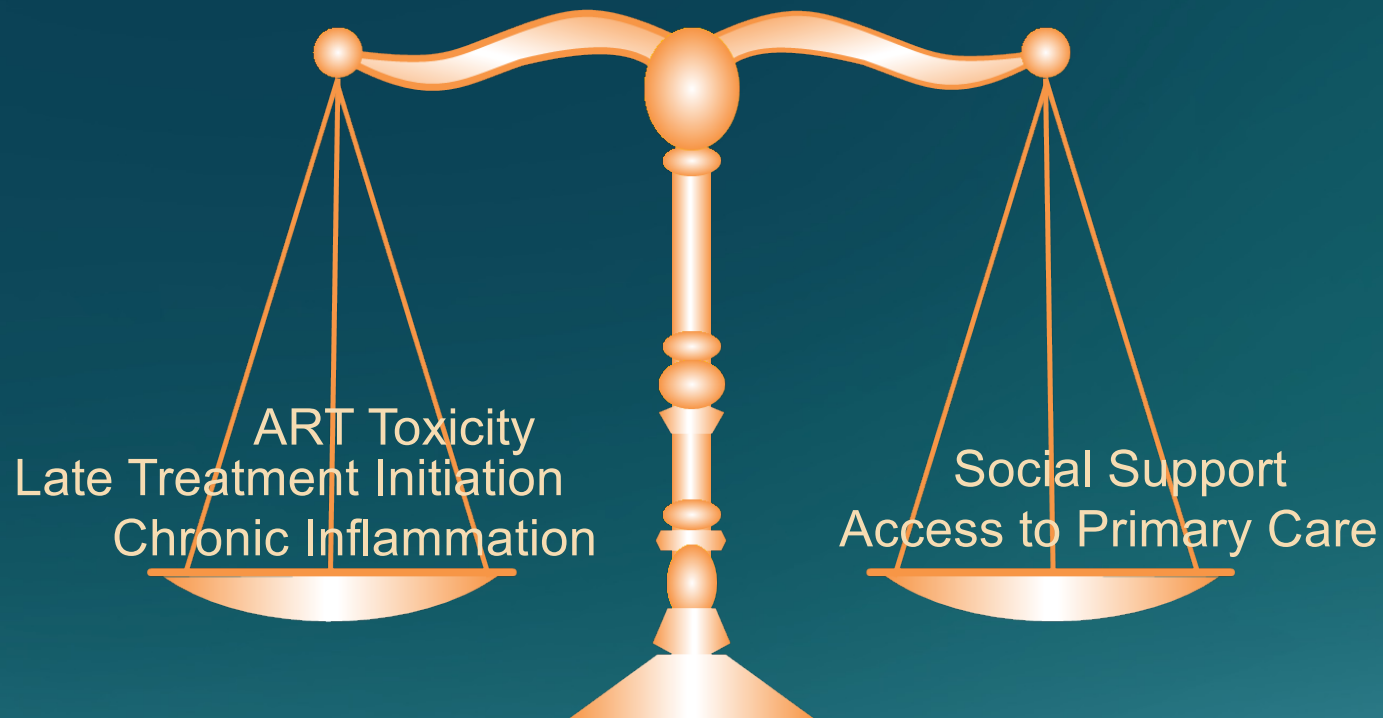
Cancer

Ageing-Related Syndromes

Longevity, Health and Wellbeing



Balance of health determinants for PWH in SSA



Could we be mis-estimating the *causal* effect of HIV on co-morbidities in the US?

Social determinants of health and risk of HIV

- Compared to other races, black MSM in the US and UK:
 - **More** likely to practice HIV prevention behaviors (OR 1.4, 1.2-1.6)
 - **Less** likely to have a history of substance abuse (OR 0.5, 0.4-0.8)
 - **More** likely to have HIV in the US (3.0, 2.1-4.4) and UK (1.9, 1.6-2.2)
 - **More** likely of having at least one structural barrier to care (unemployment, low income, previous incarceration, lower educational attainment), OR>2.0
 - **Less** likely to to initiate ART (22% vs 60%)

Social determinants of health and risk of HIV

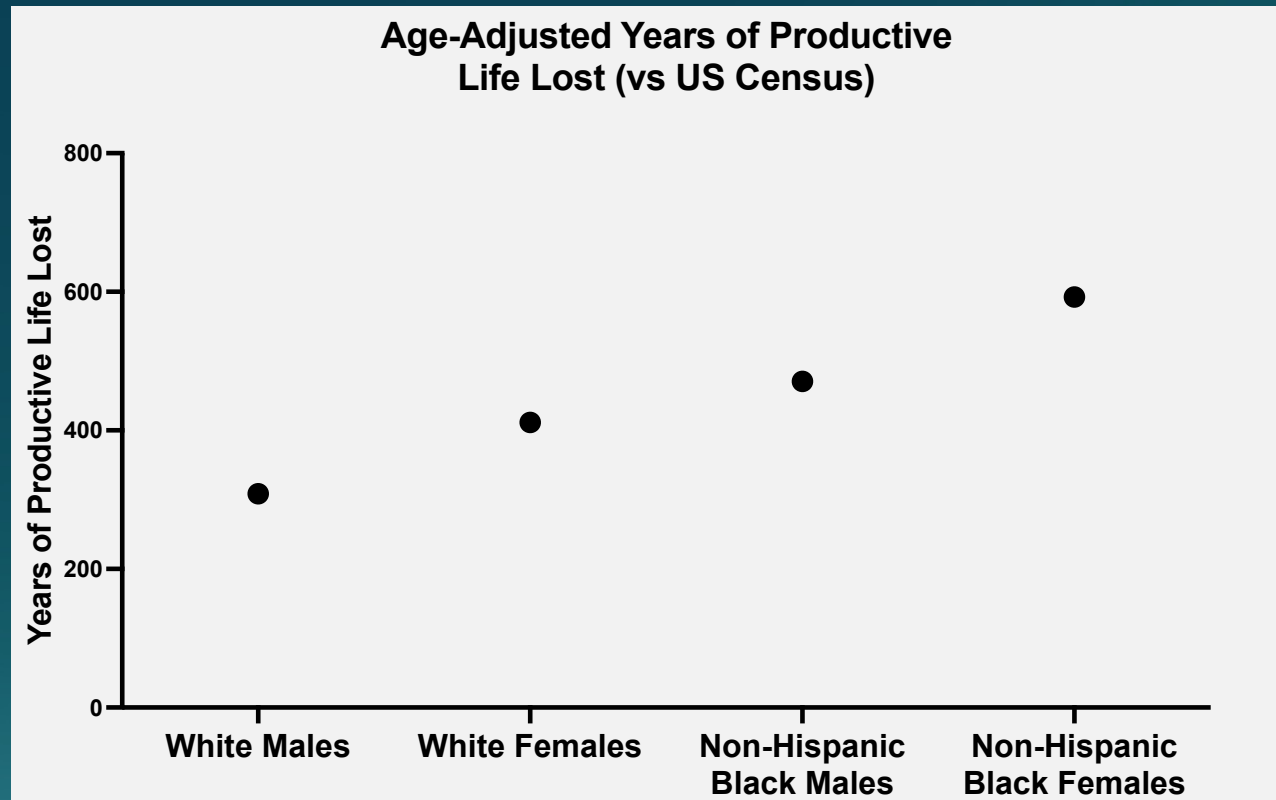
HIV Incidence among women in the US by Race

| Year | HIV diagnoses No. (rate) | | | Overall rate | Absolute rate difference [†] |
|------|-----------------------------|-------------|-------------|--------------|--|
| | Black | Hispanic | White | | |
| 2010 | 6,310 (38.7) | 1,469 (7.8) | 1,540 (1.8) | 7.7 | 36.9 |
| 2011 | 5,856 (35.5) | 1,351 (7.0) | 1,506 (1.7) | 6.9 | 33.8 |
| 2012 | 5,580 (33.4) | 1,229 (6.2) | 1,426 (1.6) | 6.6 | 31.8 |
| 2013 | 5,227 (30.9) | 1,279 (6.3) | 1,418 (1.6) | 6.3 | 29.3 |
| 2014 | 5,128 (30.0) | 1,350 (6.5) | 1,483 (1.7) | 6.4 | 28.3 |

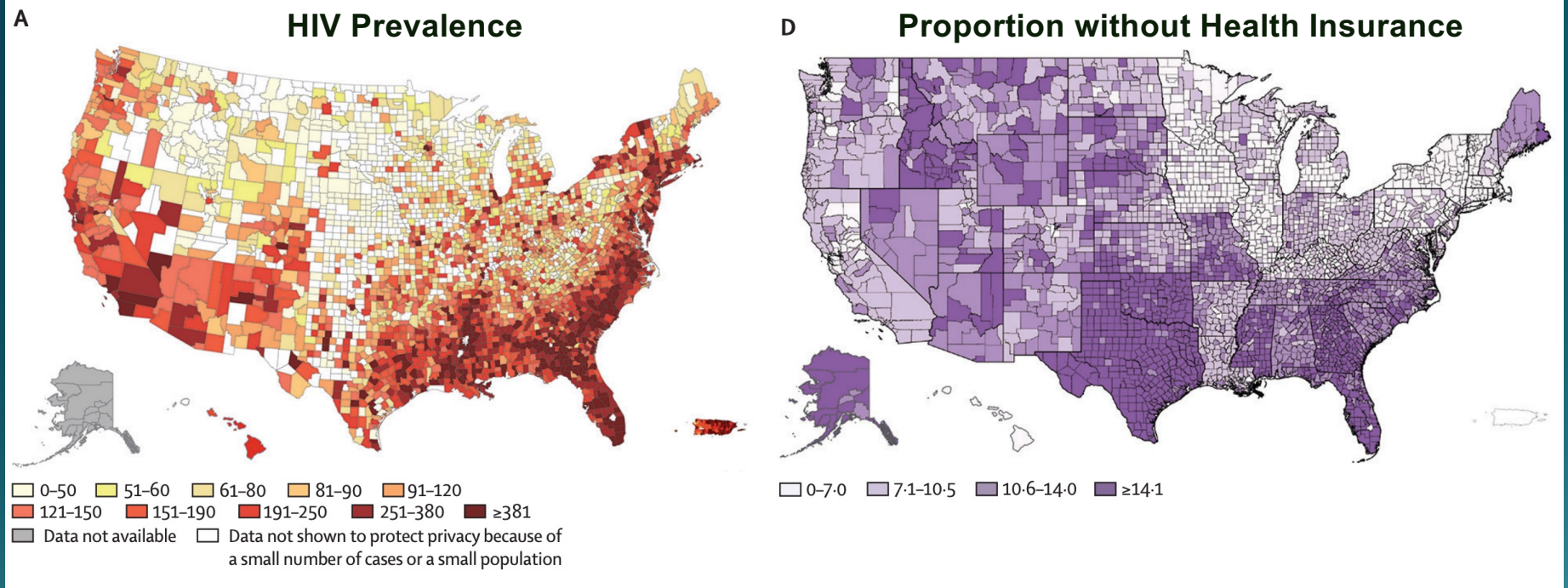
* Per 100,000 population.

- Black MSM in the US 80% more likely to have concurrent sexual partnerships compared to white women

Race, HIV, Infection and Years of Life Lost

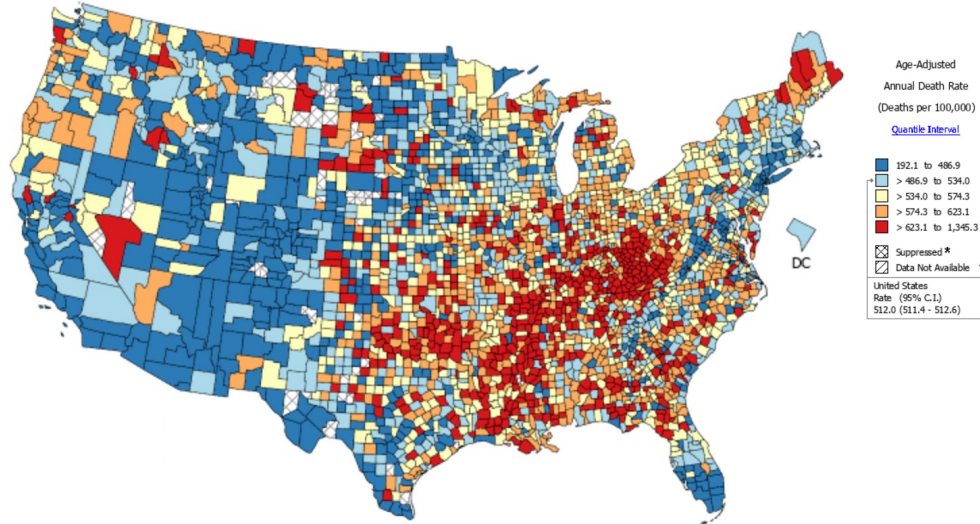


HIV Prevalence and Poverty in the US

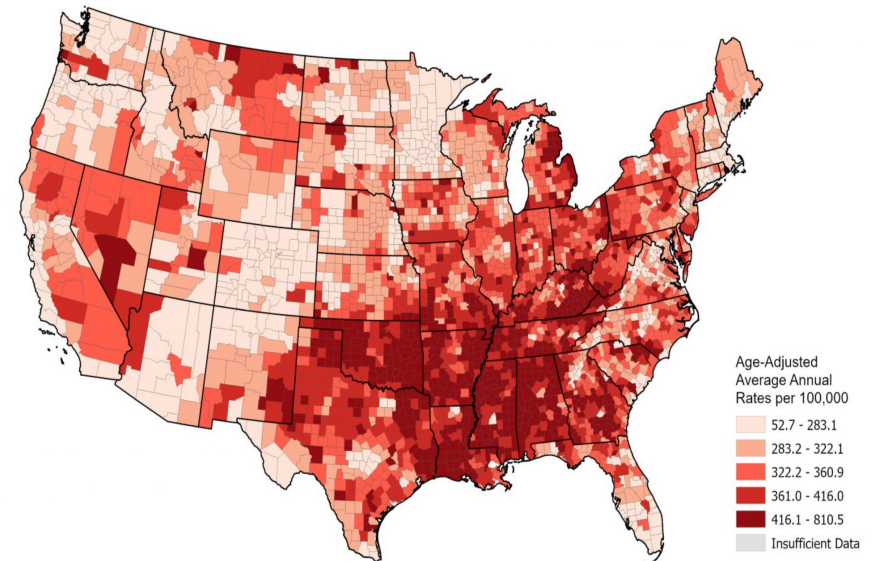


NCD Death Rates and Poverty in the US

Cancer Death Rates among Adults >50 (2015-2019)



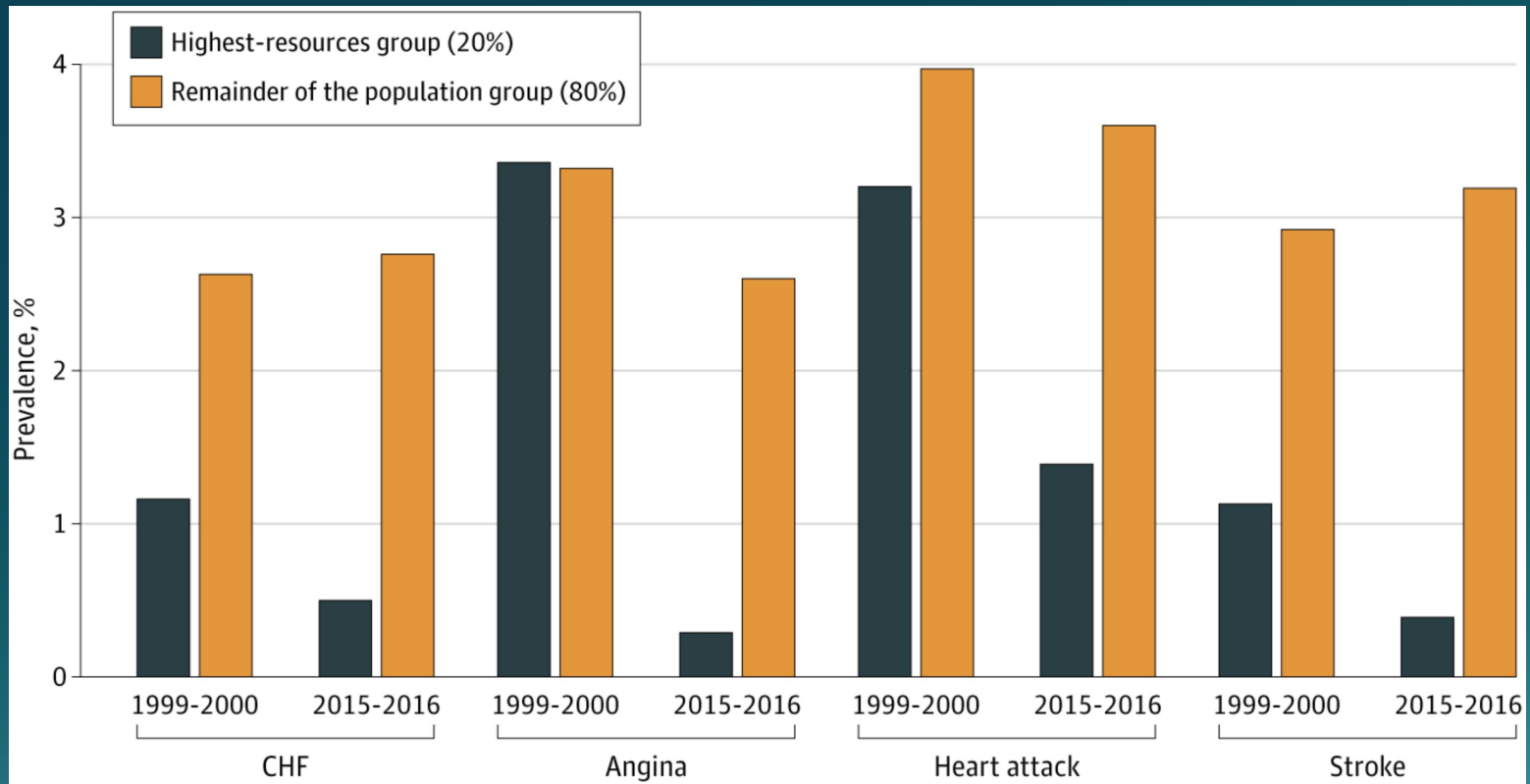
Heart Disease Death Rates among Adults >35 (2017-2019)



https://www.cdc.gov/dhdsp/maps/national_maps/hd_all.htm

<https://statecancerprofiles.cancer.gov/>

CVD Prevalence and Poverty in the US



Revised Conceptual Framework?



HIV Infection

Inflammation

Timing of Treatment Initiation

Toxicity

ART

Atherosclerosis

Cancer

Ageing-Related Syndromes

Longevity, Health and Wellbeing

Socioeconomic Status & other Social Determinants of Health

Healthcare Access
Environment
Quality of Care
Social Support



Summary

- Chronic inflammation, despite ART use, predisposes PWH to increased risk of multiple co-morbidities
 - Early ART mitigates some, but not all, risk
 - Risk of accelerated aging, liver and lung disease, and cancer persist
- Early data from sub-Saharan Africa seems to support a role for access to primary care as a mitigating factor against co-morbidity risk
- Social determinants of health are poorly measured and absent from much of the literature on co-morbidity risk in global north
 - Associated with HIV acquisition risk, HIV care delivery, HIV mortality
 - Also associated with poor outcomes for most “HIV related” co-morbidities
 - Degree of confounding unknown
 - Critical to determine its role in explaining HIV related co-morbidities to enable effective interventions to improve health

Research priorities for epi of HIV and aging

- Determine role of anti-inflammatories in prevention of HIV-related chronic co-morbidities
- Better elucidate contributions of social determinants of health in determining HIV-related co-morbidity risk
- Evaluation of interventions that promote health equity, increase healthcare access, and improve quality of care delivery on HIV risk, health outcomes and quality of life