Developing Sex and Gender-tailored Strategies for Healthy Aging with HIV: The Effect of Low-level Viremia and Non-AIDS Comorbidity Burden

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Disclosures

- None

Learning objectives

1) To describe the burden of non-AIDS comorbidities across the adult lifespan of persons with HIV with an emphasis on sex and gender differences including women's health transitions

2) To assess the prevalence of low-level viremia among women and men with HIV in the modern treatment era and consider downstream clinical sequelae

3) To evaluate sex and gender-specific and HIV-related factors contributing to comorbidity burden and implications for refined multimorbidity screening and prevention in this population

Outline

I. Importance of sex and gender health in HIV-aging science

II. A series of analyses on non-AIDS comorbidity prevalence and burden among U.S. women (and men) with and without HIV

III. Low-level viremia prevalence and consequences in modern treatment era

IV. Multimorbidity impact and implications for screening and prevention in persons with HIV

Importance of sex and gender health in HIV-aging science

Brief background

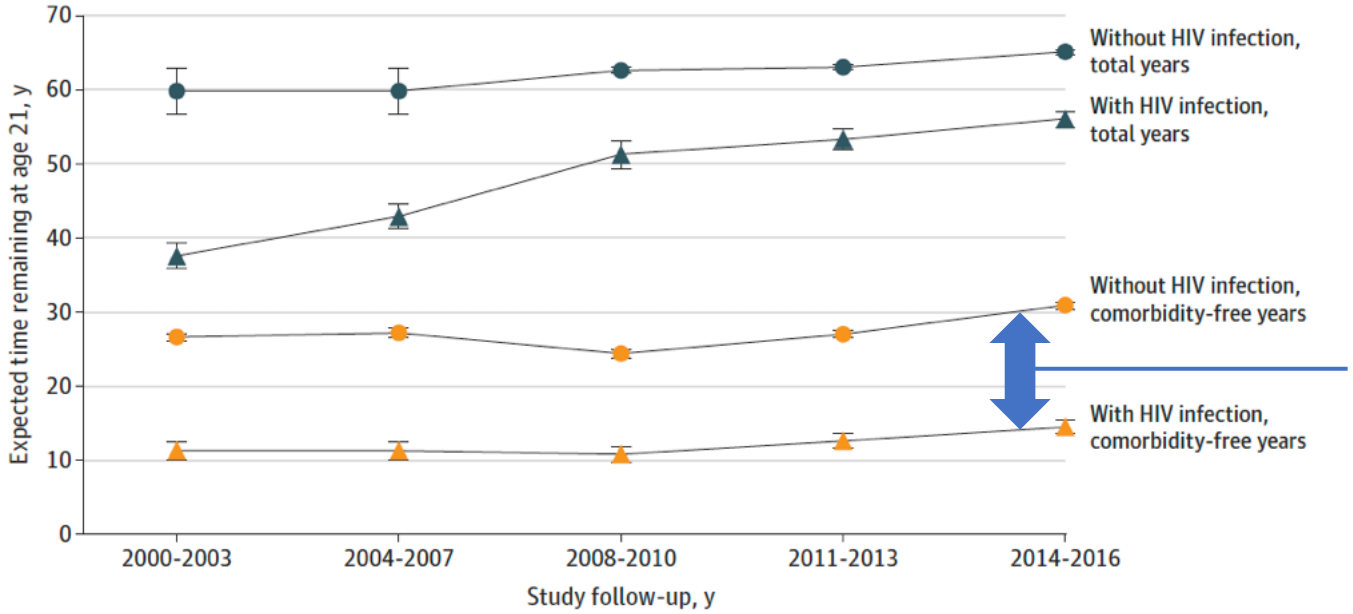
Persons with HIV (PWH) are living longer *and* aging

- In the U.S., >½ of PWH are aged ≥50 years old
- Increasingly, PWH are at risk of aging-related conditions

CDC. *HIV Surveillance Report, 2021*; vol 34. https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published May 2023. Accessed 01/22/2024.

Despite increasing life expectancy, years gained are *not* comorbidity-free

Figure 1. Overall and Comorbidity-Free Life Expectancy at Age 21 Years for Individuals With and Without HIV Infection, Kaiser Permanente, 2000-2016



PWH live ~16 fewer healthy years than persons without HIV

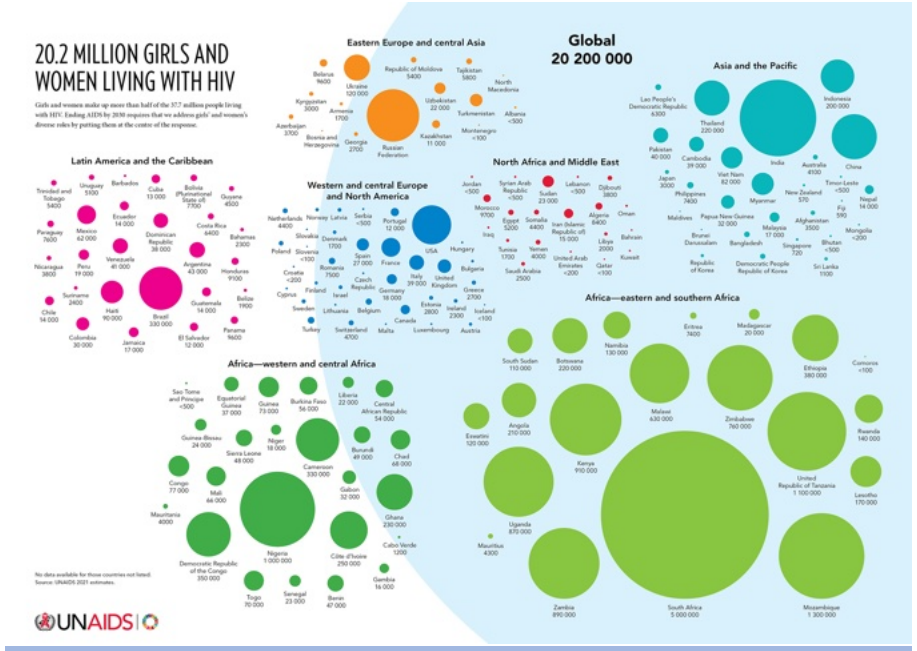
How do *sex and gender* affect aging-related comorbidity development among persons with and without *HIV*?

Marcus JL et al. JAMA Network Open. 2020;3(6):e207954

Sex = a biologic trait that is determined by anatomy, which is produced by chromosomes, hormones, and their interactions (male/female)

Gender = a social construct related to behaviors and attributes based on labels of masculinity-femininity (man-*spectrum*-woman)

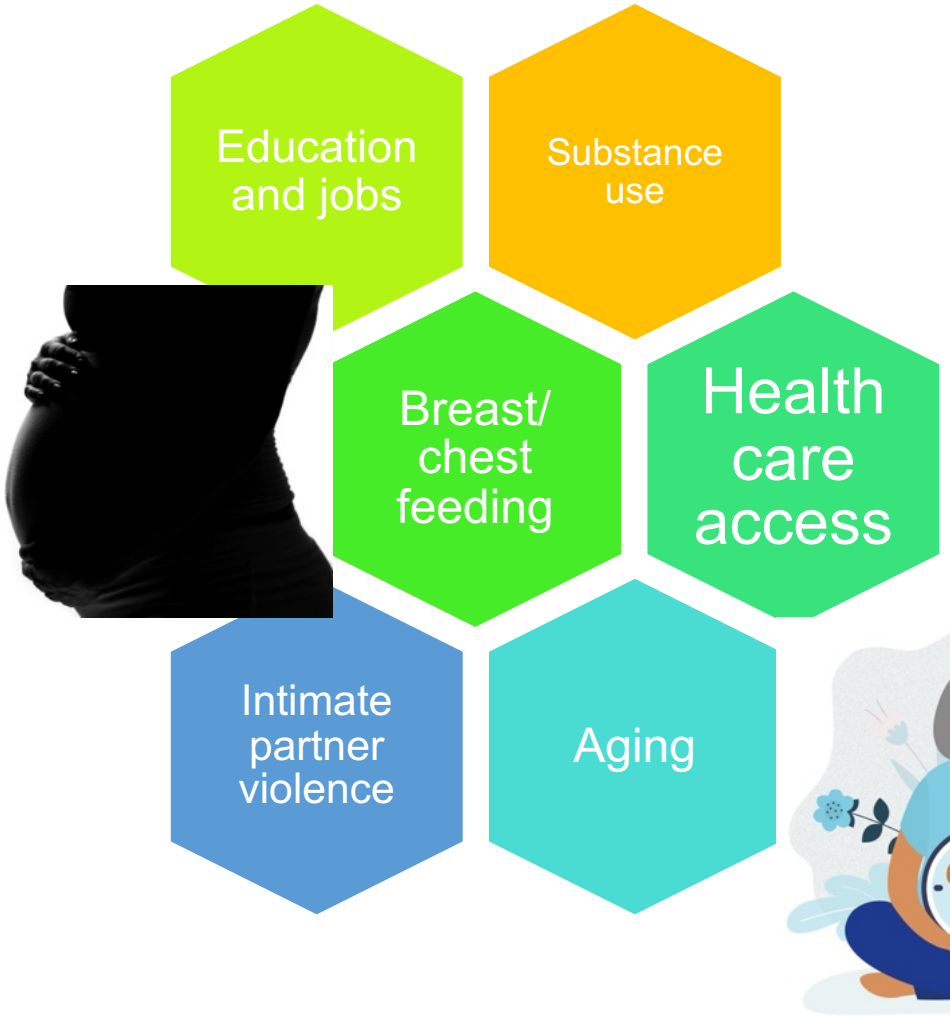
Why focus on *women's* health?

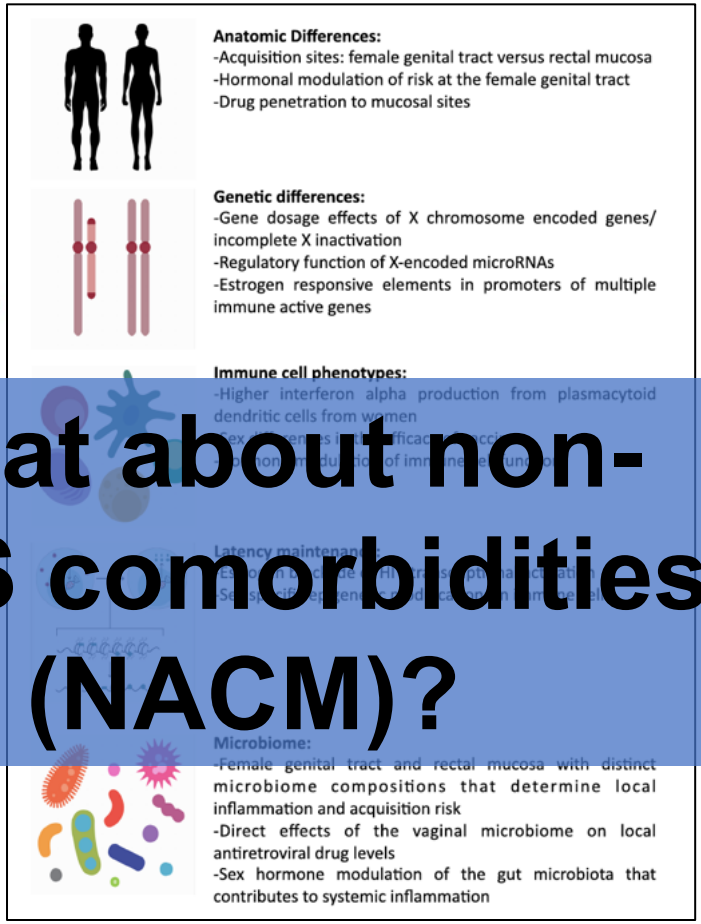


Despite representing **53% of PWH globally**, women and girls represent ~10-20% of population in HIV research

Women vs men have **unique sociobiologic considerations across the lifespan**, especially important in the context of HIV

Sex and gender—a complex interplay of sociobiologic factors with health implications



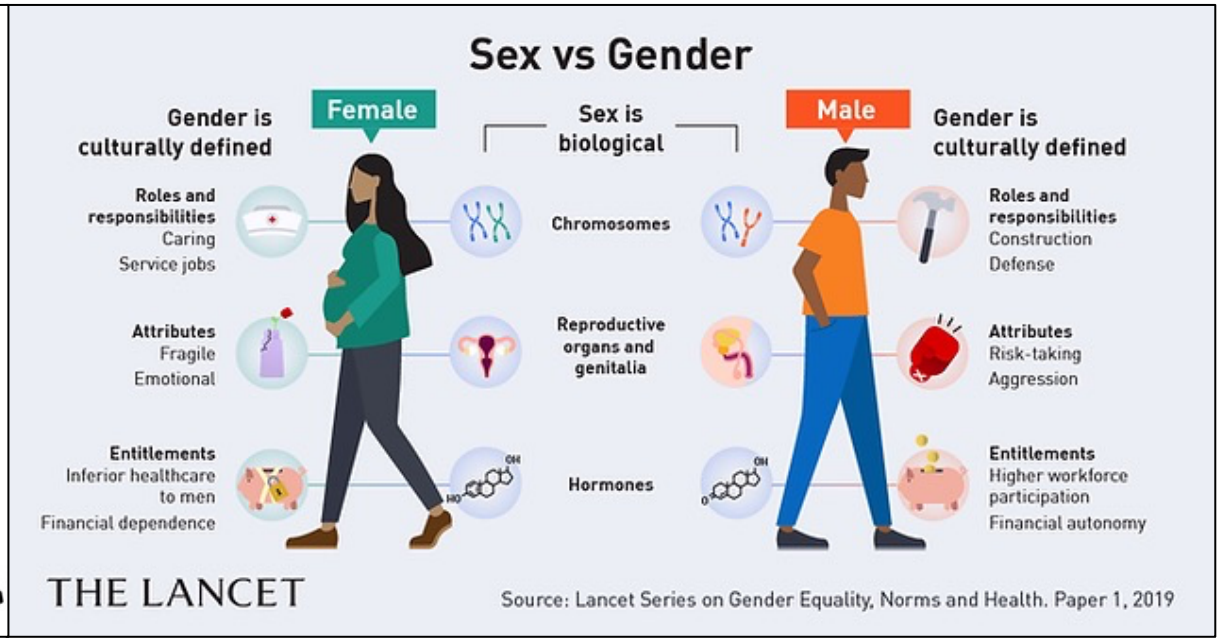


What about non-AIDS comorbidities (NACM)?

Scully EP. Curr HIV/AIDS Rep. 2018 Apr;15(2):136-146.

NACM prevalence and burden among U.S. women

A series of clinical epidemiologic analyses



1) How does *HIV* affect the development of aging-related comorbidities among cis-gender women?

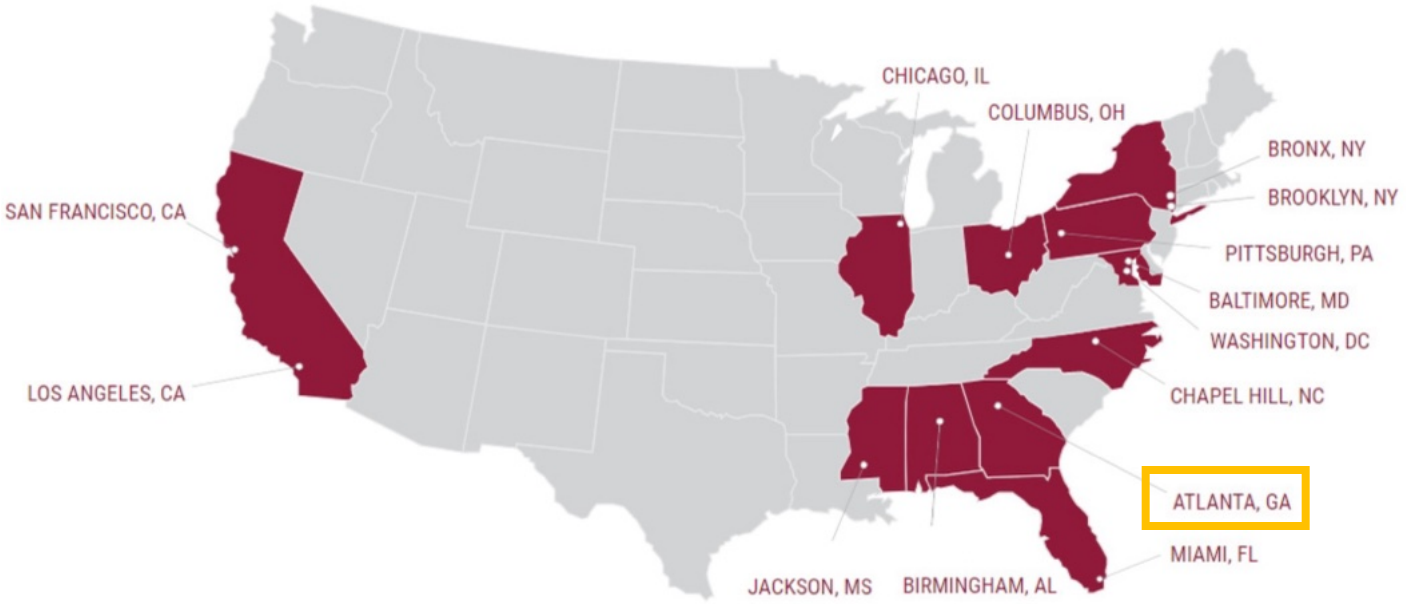
2) Do findings differ by sex and gender? What are the potential etiologies and implications for screening and prevention?

MWCCS

MACS/WIHS COMBINED COHORT STUDY

The largest and longest U.S. observational cohort study of men and women living with and without HIV

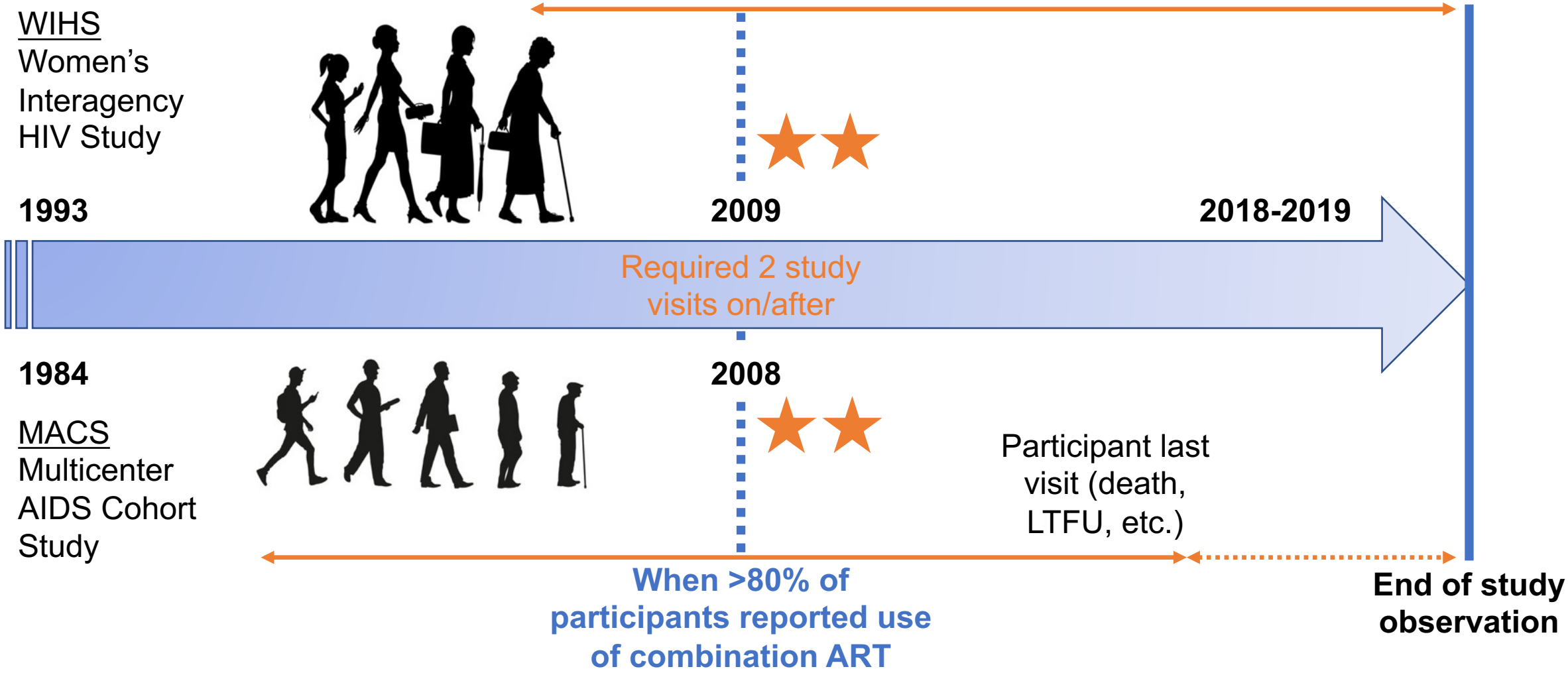
- Established 1984 (men) and 1993 (women)
- 13 active clinical research sites
- Data from ≥12,000 participants
- Semiannual study visits including detailed medical and behavioral history assessment, physical examination, and biospecimen banking



Igho Ofotokun MD / Anandi Sheth MD / Gina Wingwood ScD
MPIs of Atlanta MWCCS

https://statepi.jhsph.edu/mwccs/

General methodology used in the following series of analyses



Outcome: aging-related non-AIDS comorbidities (NACM)

PRIMARY: NACM burden

= the number of comorbidities per participant out of 10 total assessed:

- Hypertension
- Dyslipidemia
- Diabetes
- Cardiovascular disease
- Kidney disease
- Lung disease
- Liver disease
- Bone disease
- Non-AIDS cancer
- Psychiatric illness

Shared risk factors and/or pathophysiology

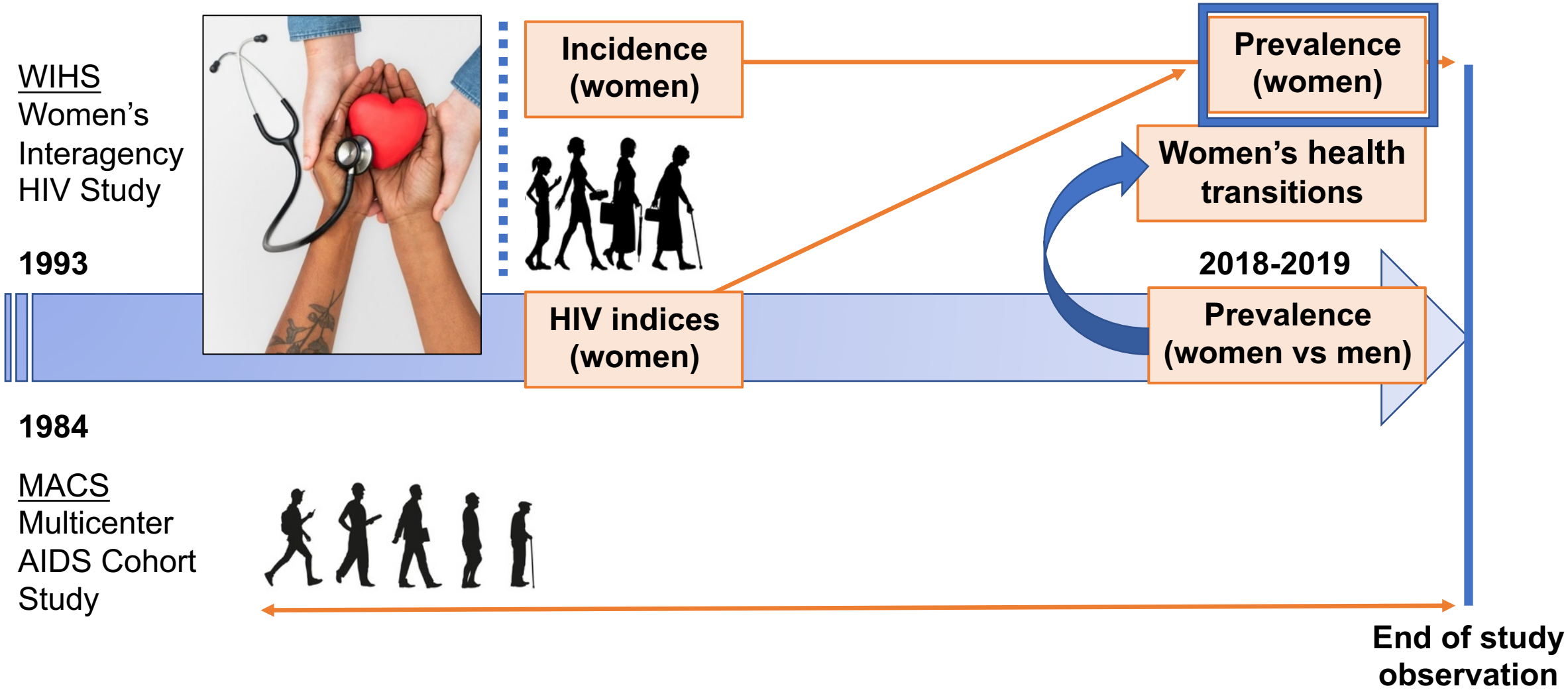
SECONDARY: Individual prevalence of each NACM

Multimorbidity = ≥2 of 5 vascular-related NACM assessed per participant

NACM were defined by using up to 3 data sources:

1) Clinical measurement
2) Laboratory value
3) Self-reported diagnosis or medication use

Series of analyses on NACM in MWCCS



CHARACTERISTICS AT END OF OBSERVATION

HIV indices among Women with HIV (WWH)

- CD4 count:
  - current: 615 cells/mm^3
  - nadir: 280 cells/mm^3
- 81% HIV-1 RNA <200 cp/ml
- Median 12.5yrs on ART

Characteristic, *median (Q1-Q3) or n (%)*	WWH (n=2309)	Women w/o HIV (n=923)	*p* value
Age, *yrs*	51 (44-57)	49 (41-55)	<0.0001
Observation time, *yrs*	15.3 (4-18)	15.3 (4-18)	0.6365
Black race	1486 (64)	622 (67)	0.0478
Annual income* <$12K	1091 (50)	424 (49)	0.0198
Current use			
tobacco	820 (36)	410 (45)	<0.0001
alcohol	954 (41)	526 (57)	<0.0001
crack/cocaine	133 (6)	85 (9)	<0.0001
Body mass index, *kg/m^2*	29 (25-35)	31 (26-37)	<0.0001
Systolic BP, *mmHg*	122 (110-136)	126 (115-141)	<0.0001
eGFR, *ml/min/1.73 m^2*	92 (73-108)	100 (84-114)	<0.0001
Chronic HCV	306 (13)	87 (9)	0.0026
Chronic HBV	56 (2)	10 (1)	0.0148

*Household income; *Abbreviations: BP: blood pressure; eGFR: estimated glomerular filtration rate; HBV/HCV: hepatitis B/C virus*

NACM prevalence among women

- **Prevalence of each NACM increased successively by age group** (<40, 40-49, 50-59, ≥60 yrs) overall and by HIV serostatus (all $p<0.001$)

- **Women with vs without HIV had a higher prevalence of most NACM** (all $p<0.01$) ★

Individual NACM	Women with HIV (N=2309)	Women without HIV (N=923)	
Hypertension	66%	64%	
Psychiatric illness	57%	48%	★
Lung disease	41%	42%	
Liver disease	45%	26%	★
Dyslipidemia	40%	35%	★
Bone disease	40%	33%	★
Diabetes	22%	24%	
CVD	19%	19%	
Kidney disease	15%	7%	★
Non-AIDS cancer	11%	7%	★

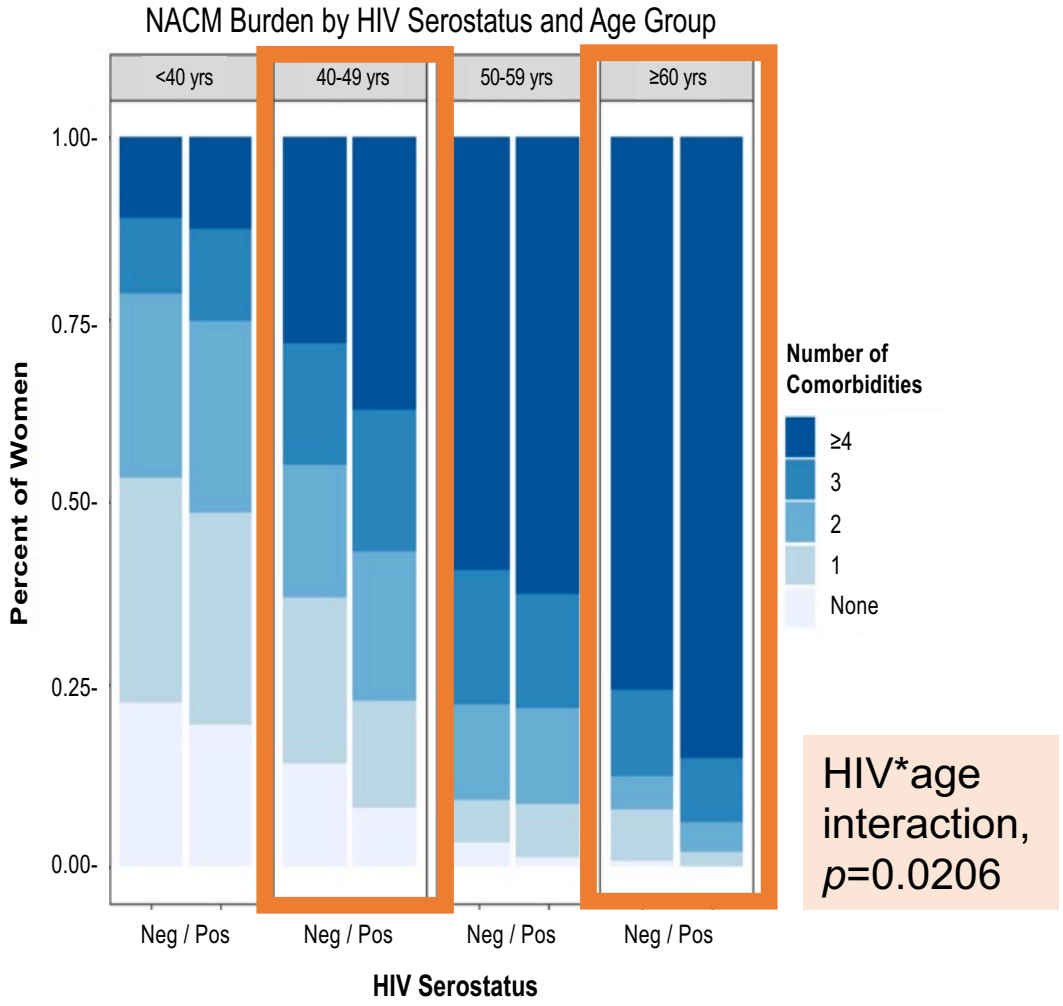
NACM burden among women

- **Mean NACM burden increased with older age (*p*<0.0001):**

Age, *yrs*	Mean NACM
<40	1.7
40-49	2.7
50-59	4.0
≥60	5.2

- **Overall, women with vs without HIV had a higher mean NACM burden:**

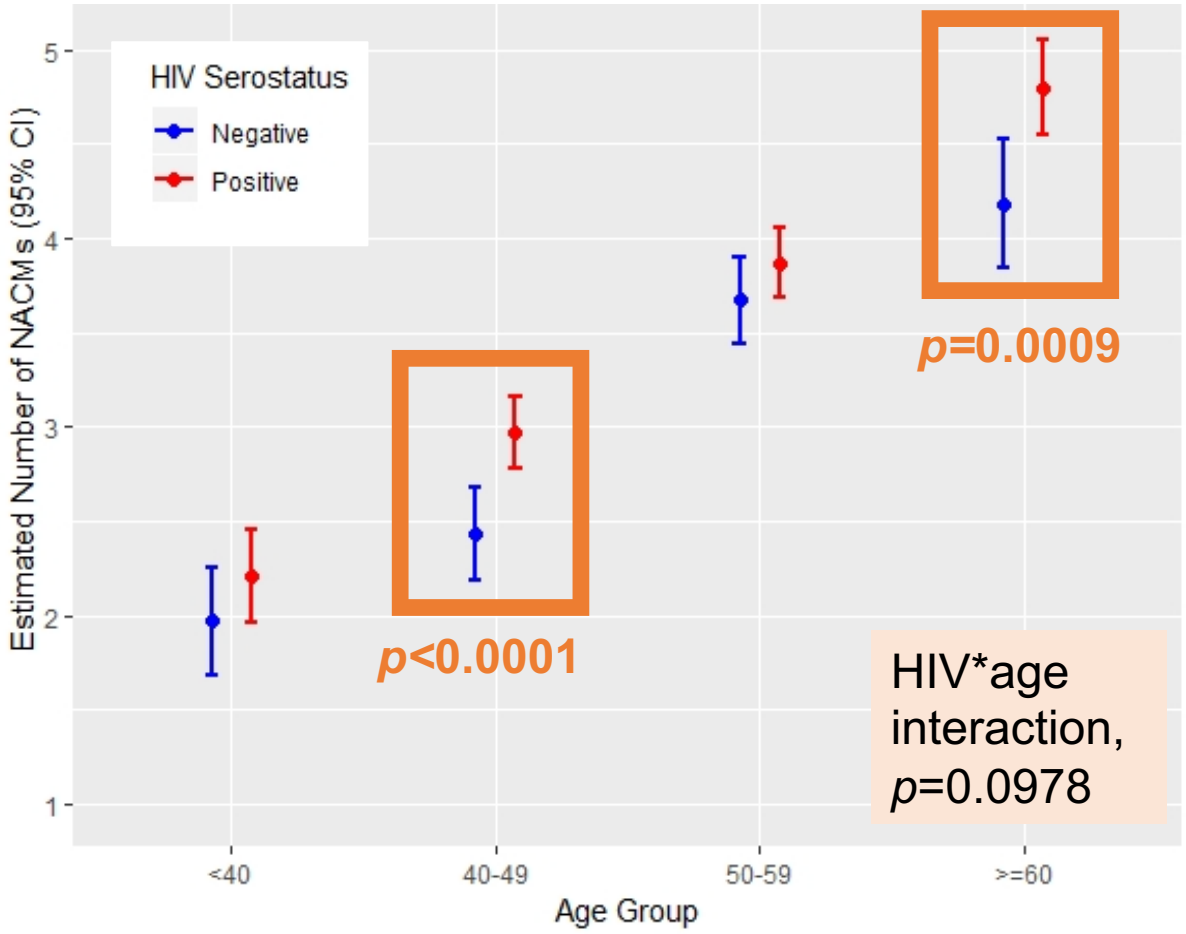
3.6 vs 3.0 (*p*<0.0001)



HIV*age interaction, *p*=0.0206

Collins LF et al. Clin Infect Dis. 2021 Apr 26;72(8):1301-1311.

Covariate-adjusted estimated **NACM burden** in women by HIV and age



Statistically significant

Adjusted for:

- HIV, age, HIV*age ★
- Race ★
- Body mass index ★
- Education
- Income ★
- Marital Status
- Residence
- Current tobacco ★
- Current alcohol ★
- Current crack/cocaine ★

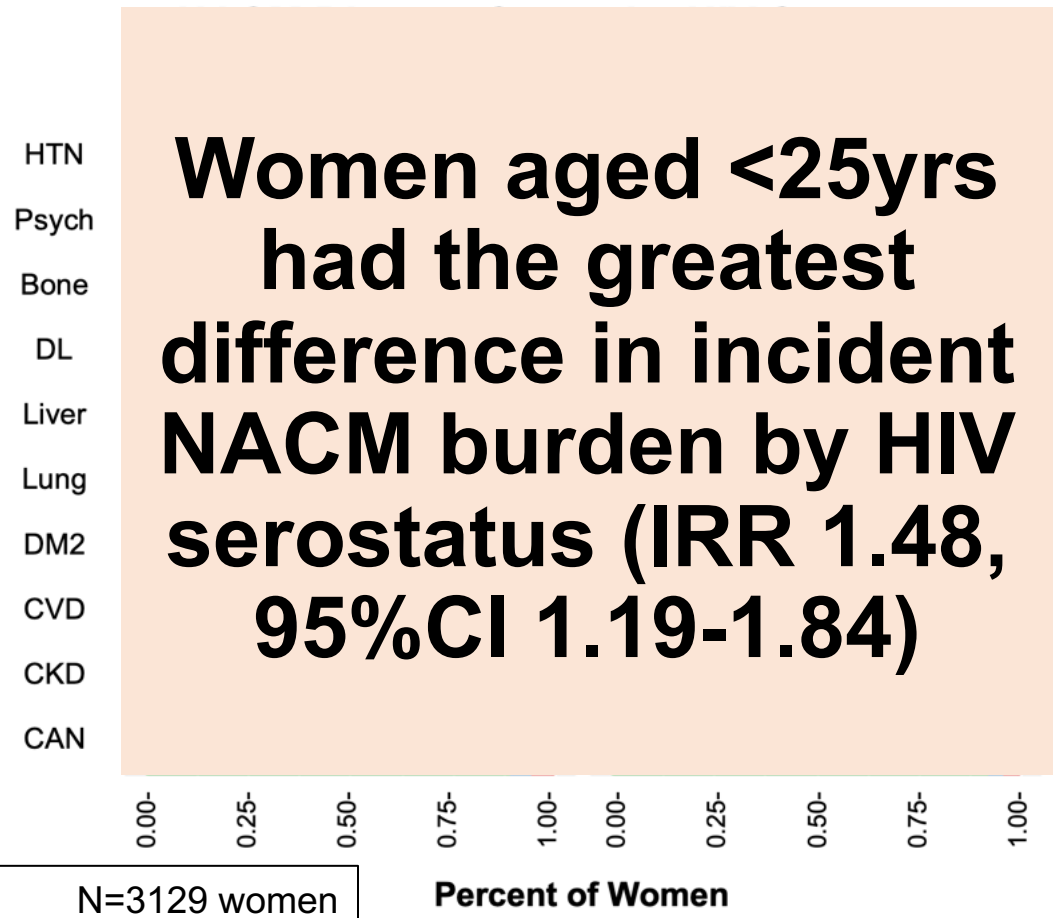
In a model including WWH only:
Higher NACM burden was associated with covariates + recent abacavir use (but not CD4, viral suppression, PI use, etc.)

Collins LF et al. Clin Infect Dis. 2021 Apr 26;72(8):1301-1311.

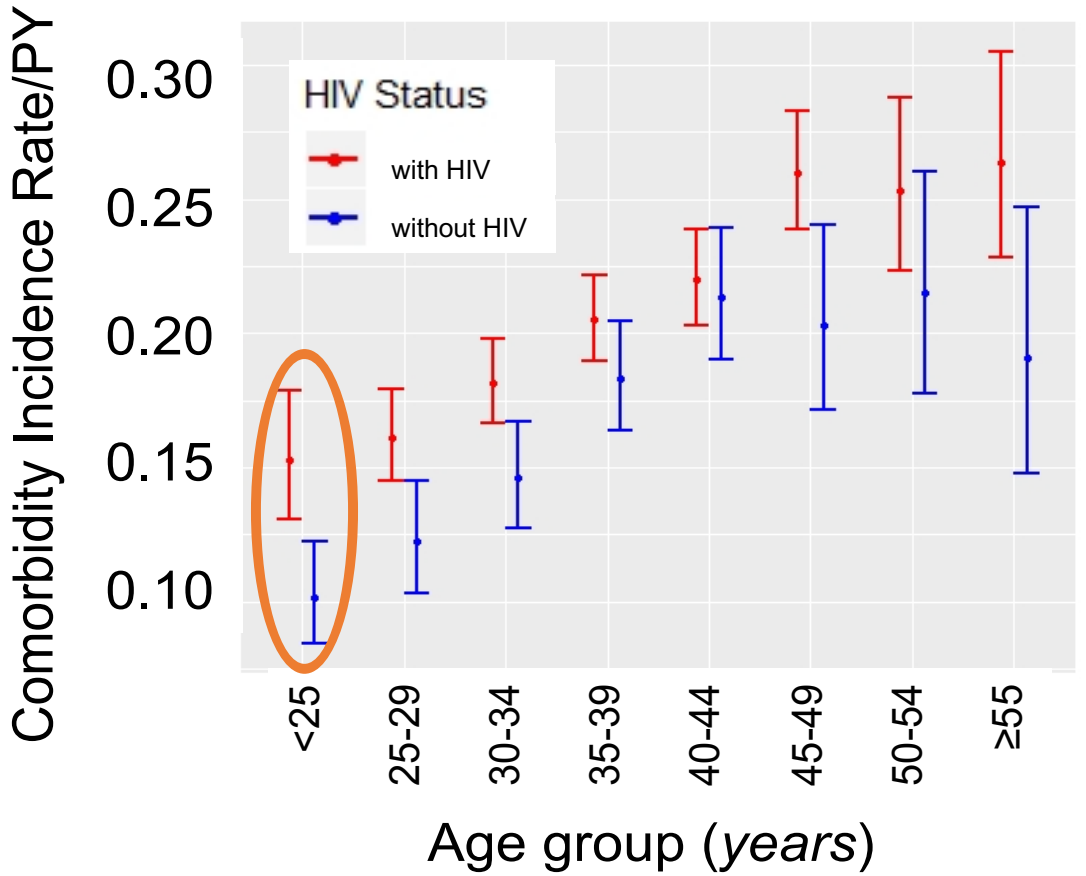
PI=protease inhibitor

Incident NACM burden was higher among women with vs without HIV in most age strata

Women aged <25yrs had the greatest difference in incident NACM burden by HIV serostatus (IRR 1.48, 95%CI 1.19-1.84)



N=3129 women
36,589 PY of follow-up
Median age 37yrs at baseline



Model adjusted for race, BMI, education, income, marital status, own residence, current use of cigarettes, alcohol, crack/cocaine, age, HIV; age*HIV (p=0.0438)

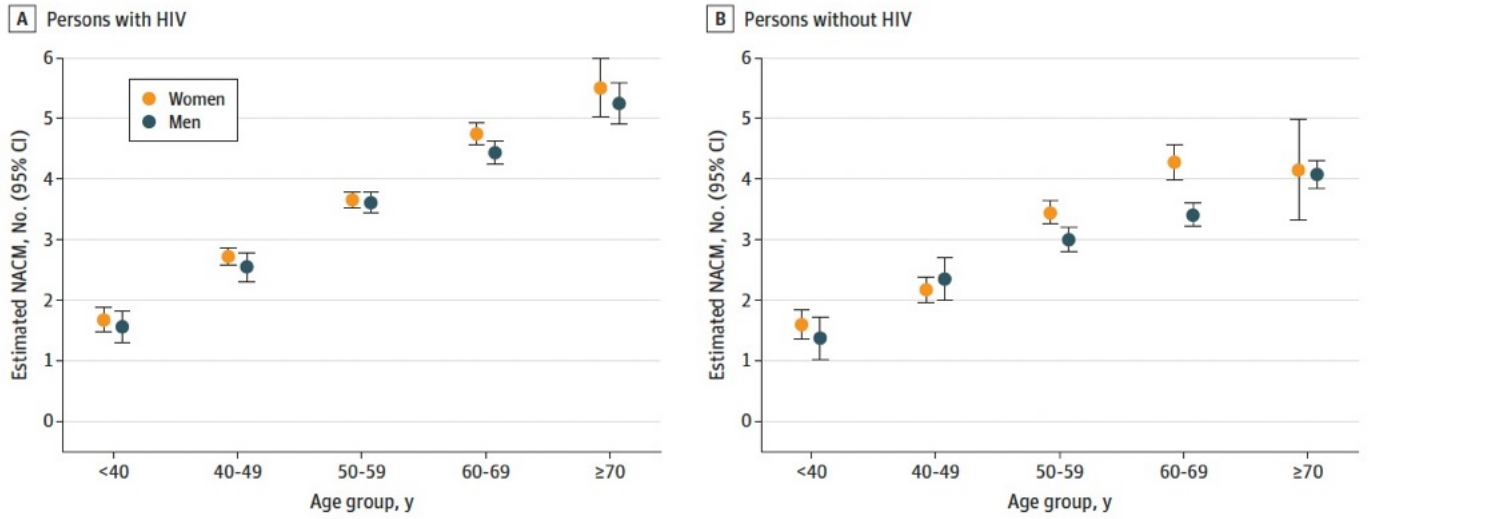
Collins LF et al. Clin Infect Dis. 2021 Oct 5;73(7):e2059-e2069.

NACM burden was higher among women vs men, particularly among PWH, and varied by age category

Median NACM burden, women vs men: 3.4 vs 3.2, *p*=0.02

NACM prevalence	Women n=3238	Men n=2691
Hypertension	68%	75%
Psych illness	55%	58%
Dyslipidemia	41%	64%
Liver disease	34%	38%
Bone disease	42%	19%
Lung disease	38%	10%
Diabetes	24%	17%
CVD	15%	15%
Kidney disease	14%	15%
Cancer	7%	12%

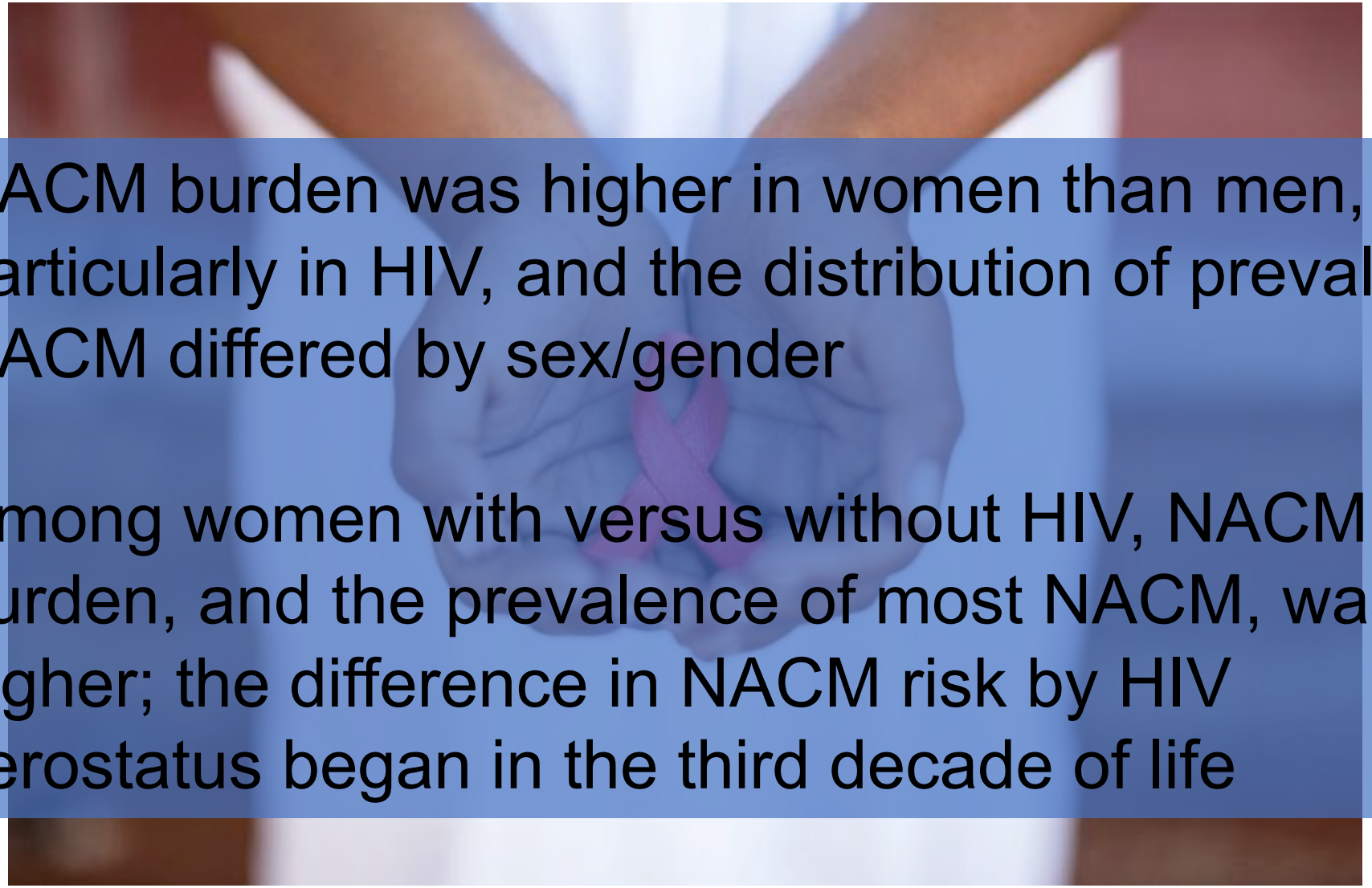
Figure 2. Estimated Mean Number of Non-AIDS Comorbidities (NACM) Among Persons With and Without HIV Stratified by Sex and Age Group



Participants were enrolled in the Women's Interagency HIV Study (for women) or the Multicenter AIDS Cohort Study (men), stratified by sex and age group. Adjusted linear regression (model 2) was performed with the following covariates included: race and ethnicity, body mass index, socioeconomic status, cigarette use, alcohol use, crack or cocaine use, in addition to HIV serostatus, age, sex, and all interaction terms (HIV × age × sex, *P* for interaction = .04).

Effect modification was attenuated when adjusting for traditional comorbidity risk factors (HIV*age*sex, *p*=0.001 [data not shown] → *p*=0.04 [shown above])

Collins LF et al. JAMA Netw Open. 2023 Aug 1;6(8):e2327584



- NACM burden was higher in women than men, particularly in HIV, and the distribution of prevalent NACM differed by sex/gender
- Among women with versus without HIV, NACM burden, and the prevalence of most NACM, was higher; the difference in NACM risk by HIV serostatus began in the third decade of life

Investigating sex and gender and HIV factors associated with multimorbidity

How to incorporated into refined NACM risk-assessment and modification?

What are the drivers of *sex and gender differences* in aging-related NACM burden?

Psycho-social effects

- The majority of WIHS participants were women of color living in poverty, whereas the MACS participants were predominantly White men with higher levels of education, income, employment
- Internalized HIV stigma
- Access to healthcare

Biologic factors

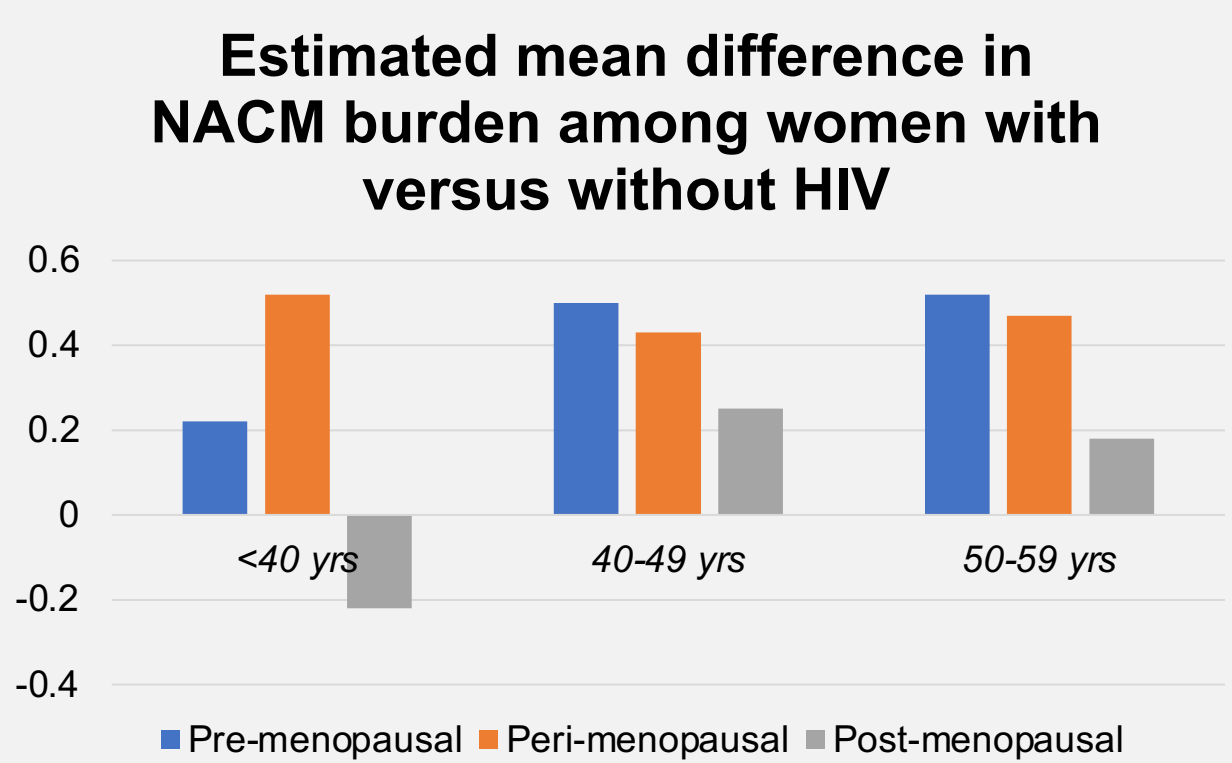
- Even after achieving HIV suppression on ART, women vs men have higher levels of inflammatory markers
- Gut permeability > bacterial translocation > inflammation
- Sex hormone effects
  - Menopausal transition
  - Pregnancy history
- Microvascular abnormalities

Pond RA, Collins LF, Lahiri CD. Open Forum Infect Dis. 2021 Nov 3;8(12):ofab558.

HIV, age, and menopausal status were independently associated with higher NACM burden

- N=2716 women
- Median age 48yrs
- STRAW +10

HIV serostatus impacted comorbidity burden most in the pre- and peri-menopausal phases

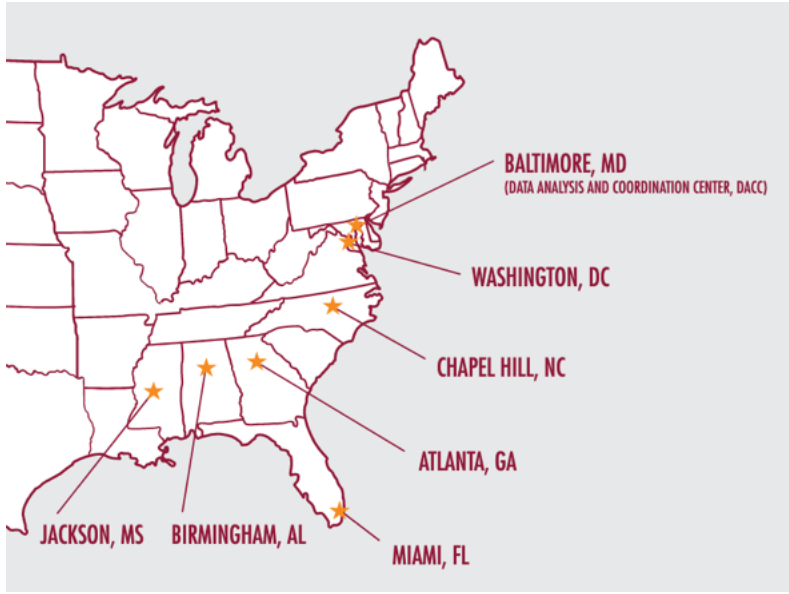


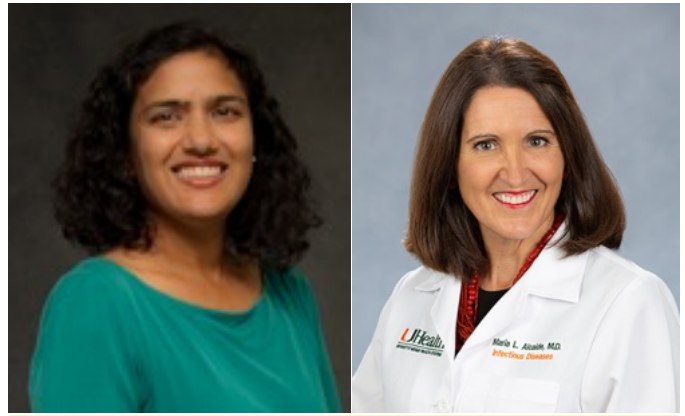
Model adjusted for HIV serostatus, categorized age, menopausal status, all interaction terms, in addition to race, body mass index, smoking status; HIV*age*menopausal status interaction, *p*=0.9580

Collins LF et al. Clin Infect Dis. 2022 Jun 10;ciac465.

STAR

Study of Treatment And Reproductive Outcomes





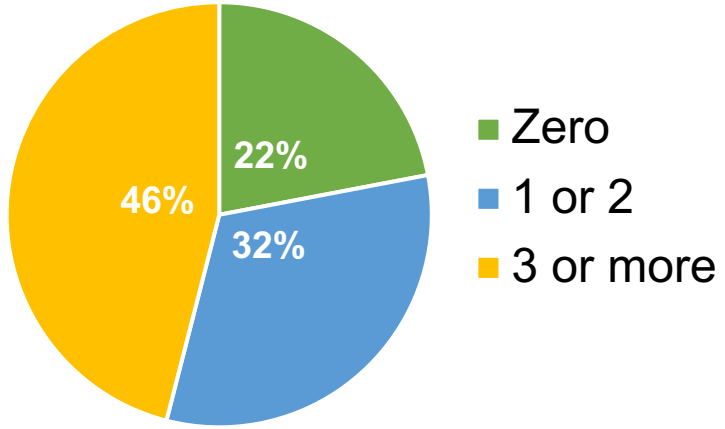
Anandi Sheth MD / Maria Alcaide MD
MPIs of Atlanta STAR

- Established 2019
- 6 sites, U.S. South
- Enrolling cis- and trans-women, aged 18-45 years (n>800 to date)

Does pregnancy history affect NACM burden? Differently by HIV serostatus?

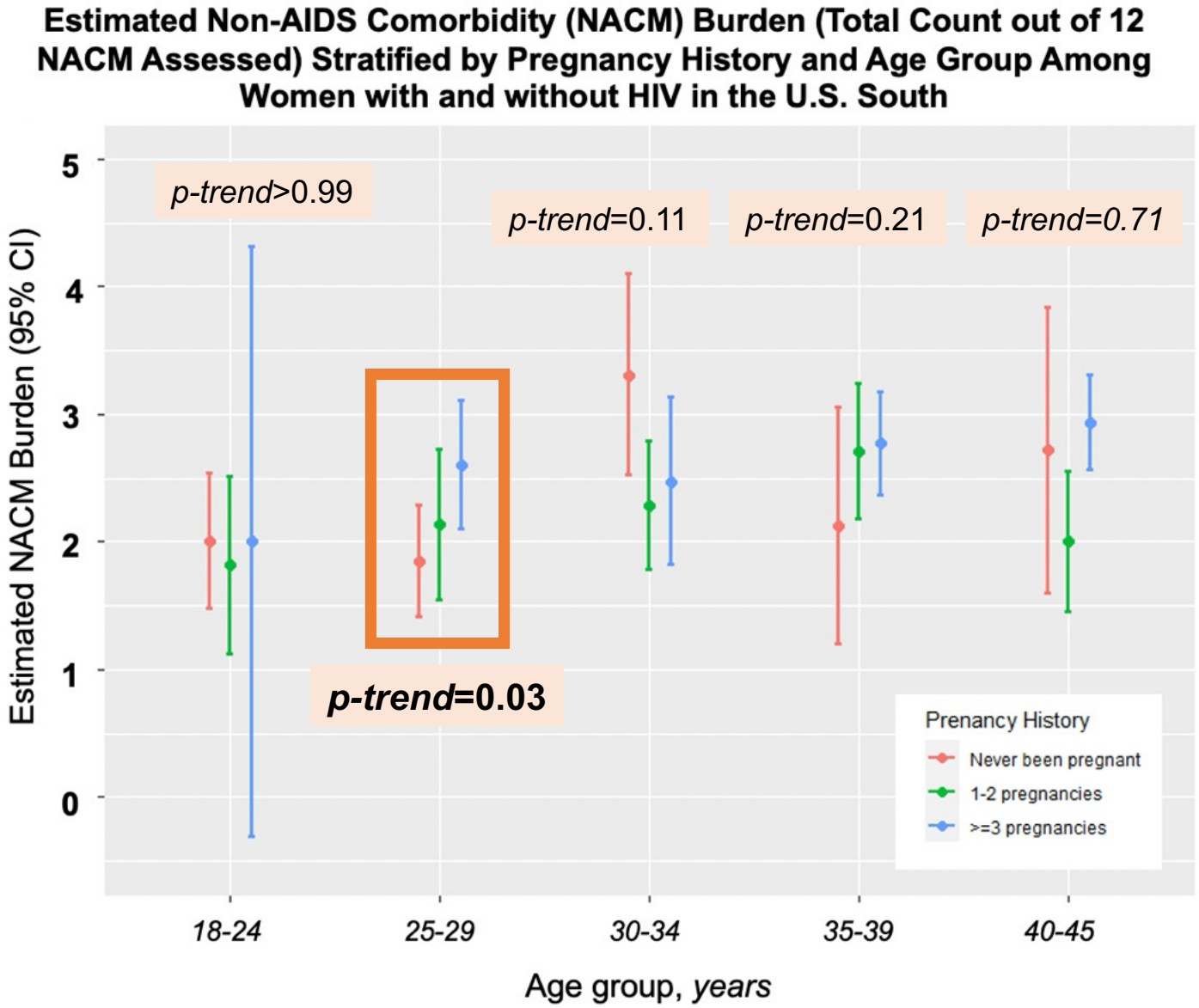
Prior pregnancies

N=519
Median age 36yrs



https://statepi.jhsph.edu/star/

Among women across HIV serostatus, pregnancy history was associated with estimated NACM burden only in certain age groups

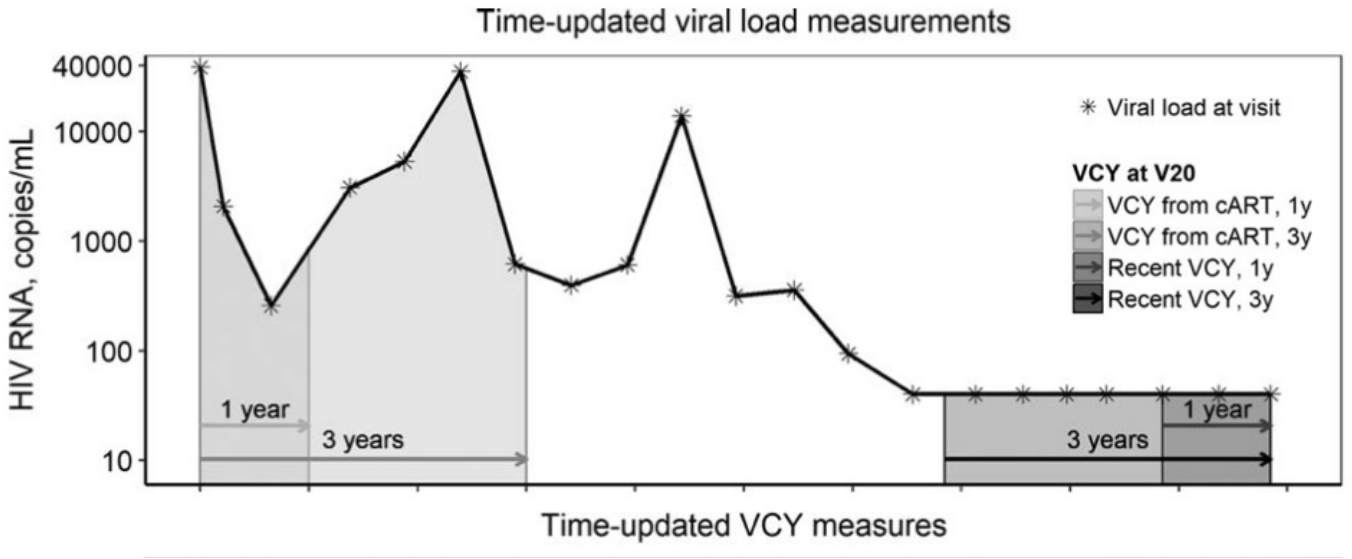


Collins LF et al…Sheth AN; CROI 2024

How do *HIV-related* factors contribute to development of NACM?

- In prior analyses, NACM burden was associated with:
  - ***traditional*** risk factors (e.g., race, body mass index, substance use, social contributors to health)
  - but not with ***HIV-related*** factors (e.g. CD4 count, viral load, certain ART use, etc.)

Viremia copy-years (VCY): a longitudinal measure of cumulative HIV-1 viral exposure calculated using the trapezoidal rule as the area-under-the-viral-load-curve (akin to "pack-years" of smoking)

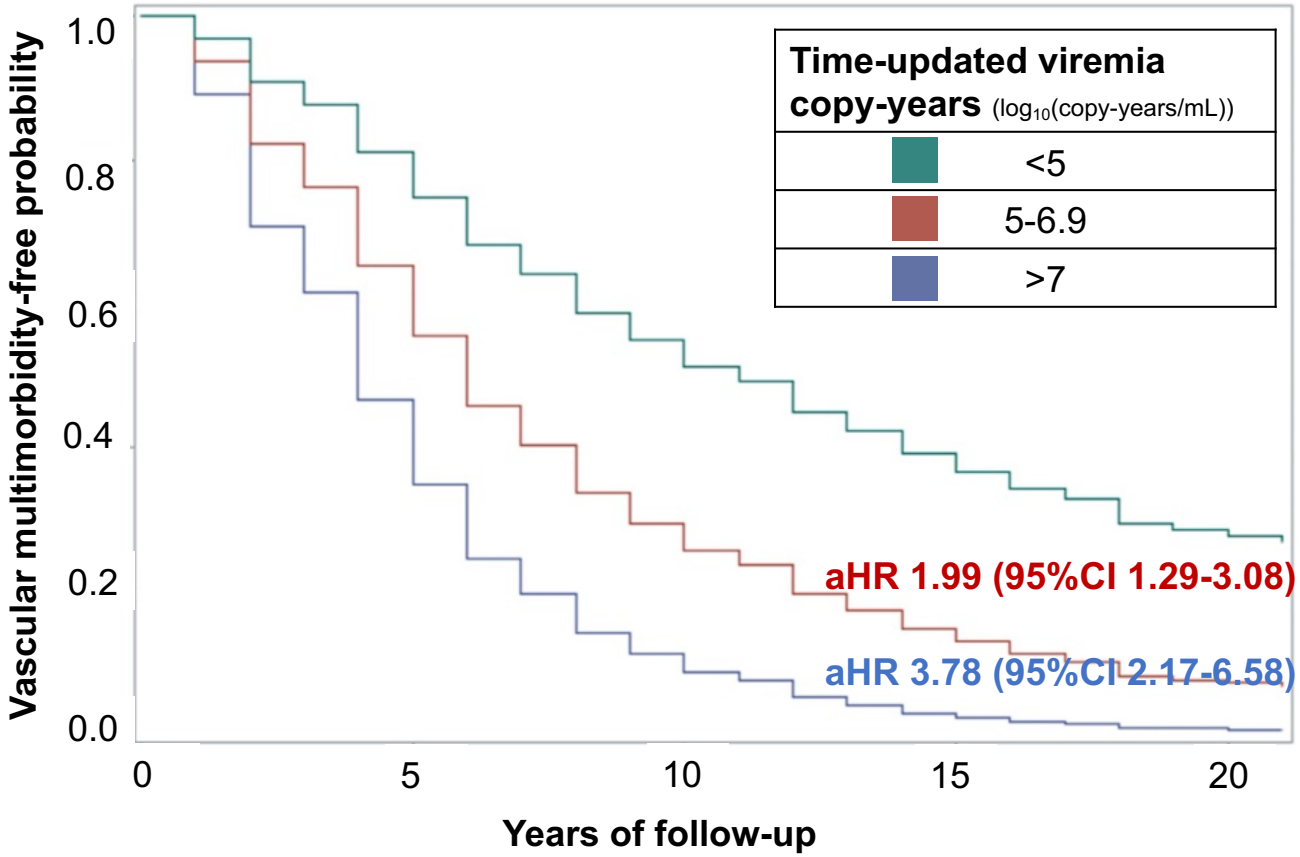


Wang R et al. AIDS. 2018 Nov 13;32(17):2547-2556.

Time-updated VCY was associated with incident multimorbidity in a dose-dependent fashion

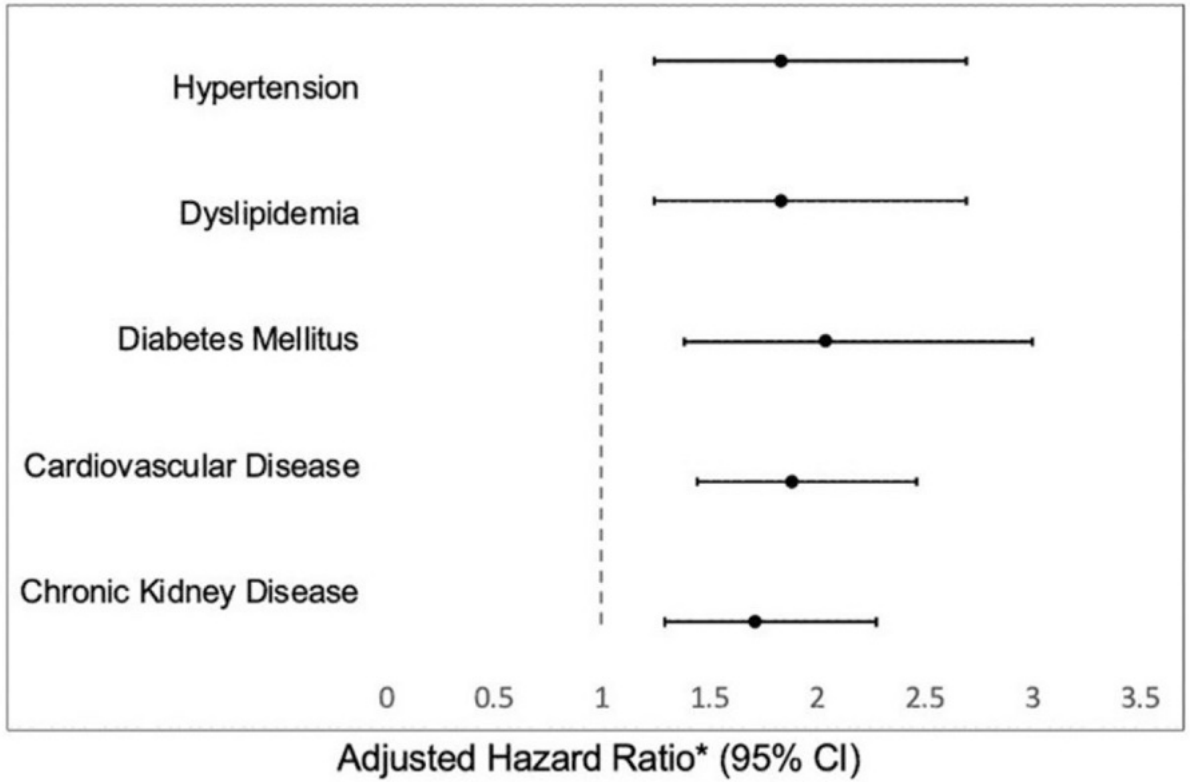
- N=806 women, after ART initiation
- NACM-free at baseline (out of 5)
- Primary outcome: time-to-multimorbidity
  - ≥2/5 vascular NACM
  - **211 (26%) developed multimorbidity**

Zoey Morton MD, PGY2
University of Chicago
(Emory Discovery project)



Morton ZP et al. Open Forum Infect Dis. 2022 Dec 28;10(2):ofac702.

Time-updated VCY was associated with incidence of each of five vascular comorbidities assessed



Model included those comorbidity-free at baseline and compared women with HIV with VCY ≥5 vs <5 $\log_{10}$ copy-years/ml and adjusted for demographic and clinical characteristics.

Morton ZP et al. Open Forum Infect Dis. 2022 Dec 28;10(2):ofac702.

- Reproductive health transitions may serve as windows of opportunity to integrate comorbidity screening and prevention interventions into a broader women's health agenda

WHAT ABOUT LOW-LEVEL VIREMIA?

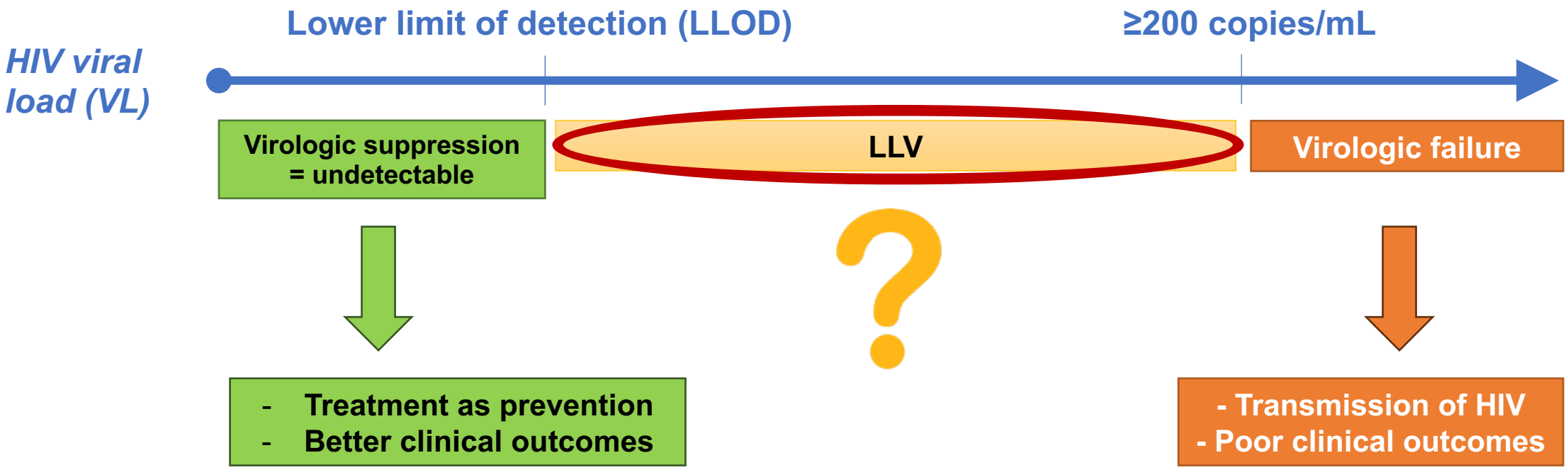
- Viremia copy-years may be a prognostically useful biomarker of multimorbidity in this population

- Both traditional and HIV-related factors impact NACM development and should be prioritized in multimorbidity risk-assessment and mitigation

Low-level viremia prevalence and consequences in the modern treatment era

A balance of science and ART

What is low-level viremia (LLV)?

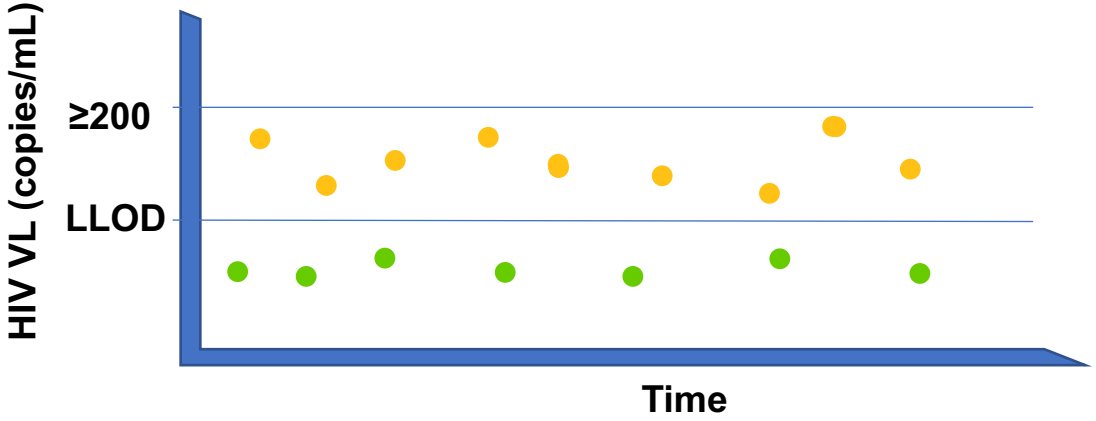


In the modern treatment era: one third of PWH on ART experience LLV

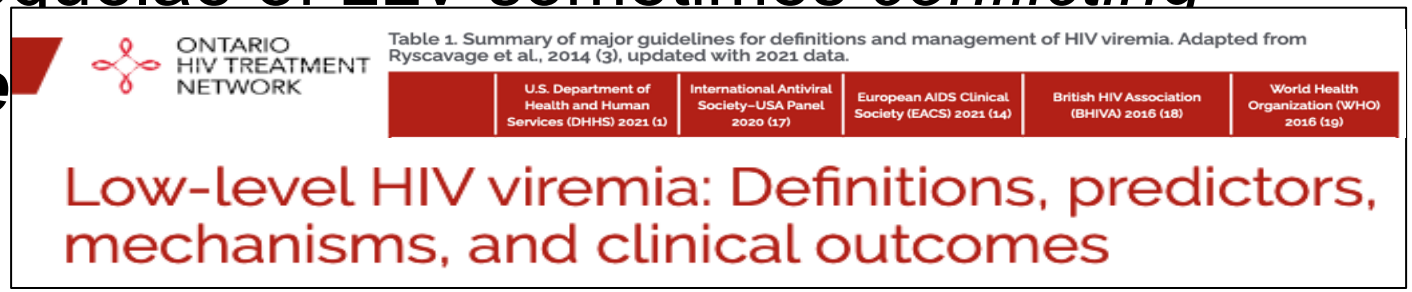
Elvstrom, 2023

Evolving landscape of LLV

- There are *varying definitions* of LLV
- There are *different patterns* of LLV
  - **Intermittent (iLLV)**
    - i.e. “blips”
  - **Persistent (pLLV)**

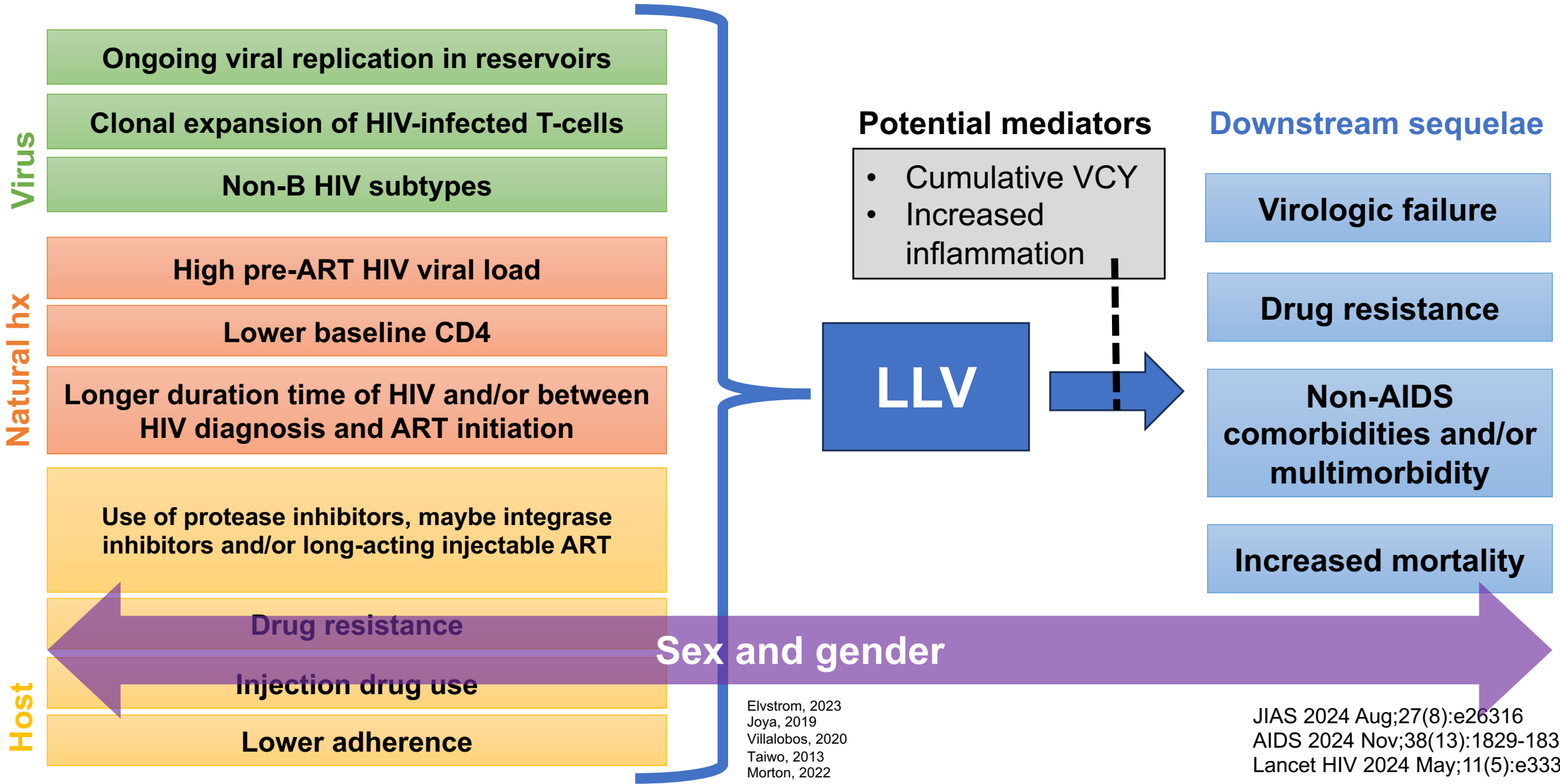


- Data on risk factors and sequelae of LLV sometimes *conflicting*
- ***Limited clinical guidance for people with LLV***



https://www.ohtn.on.ca/wp-content/uploads/2022/01/RR166_Low-level-viremia_version2.pdf

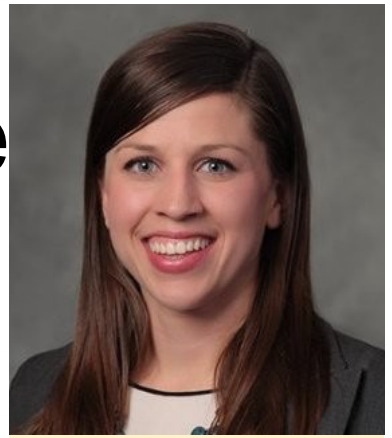
What we (may) know (now) about LLV



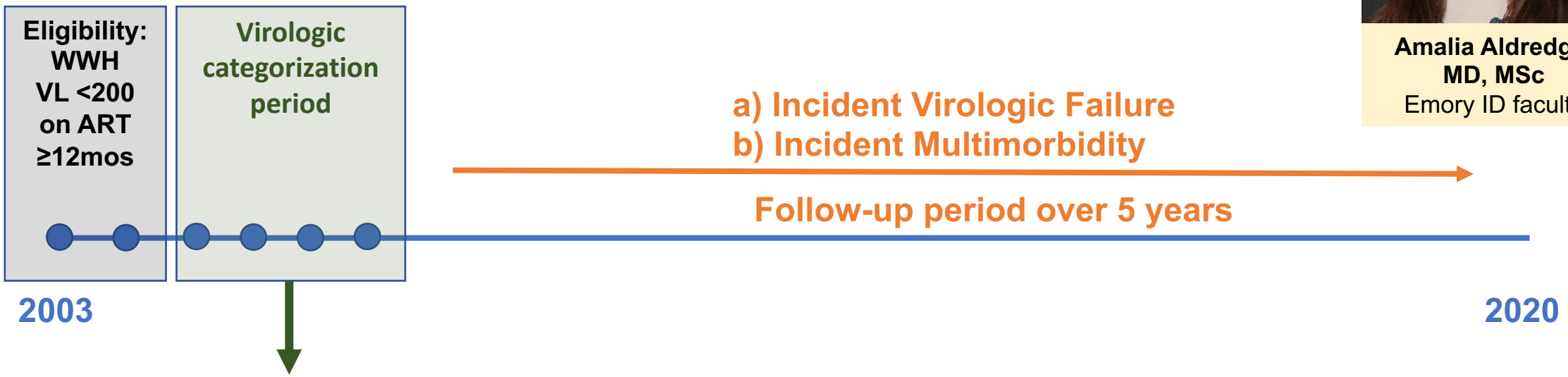
Elvstrom, 2023
Joya, 2019
Villalobos, 2020
Taiwo, 2013
Morton, 2022

JIAS 2024 Aug;27(8):e26316
AIDS 2024 Nov;38(13):1829-1838
Lancet HIV 2024 May;11(5):e333-e340

Impact of LLV on incident virologic failure and multimorbidity in women with HIV

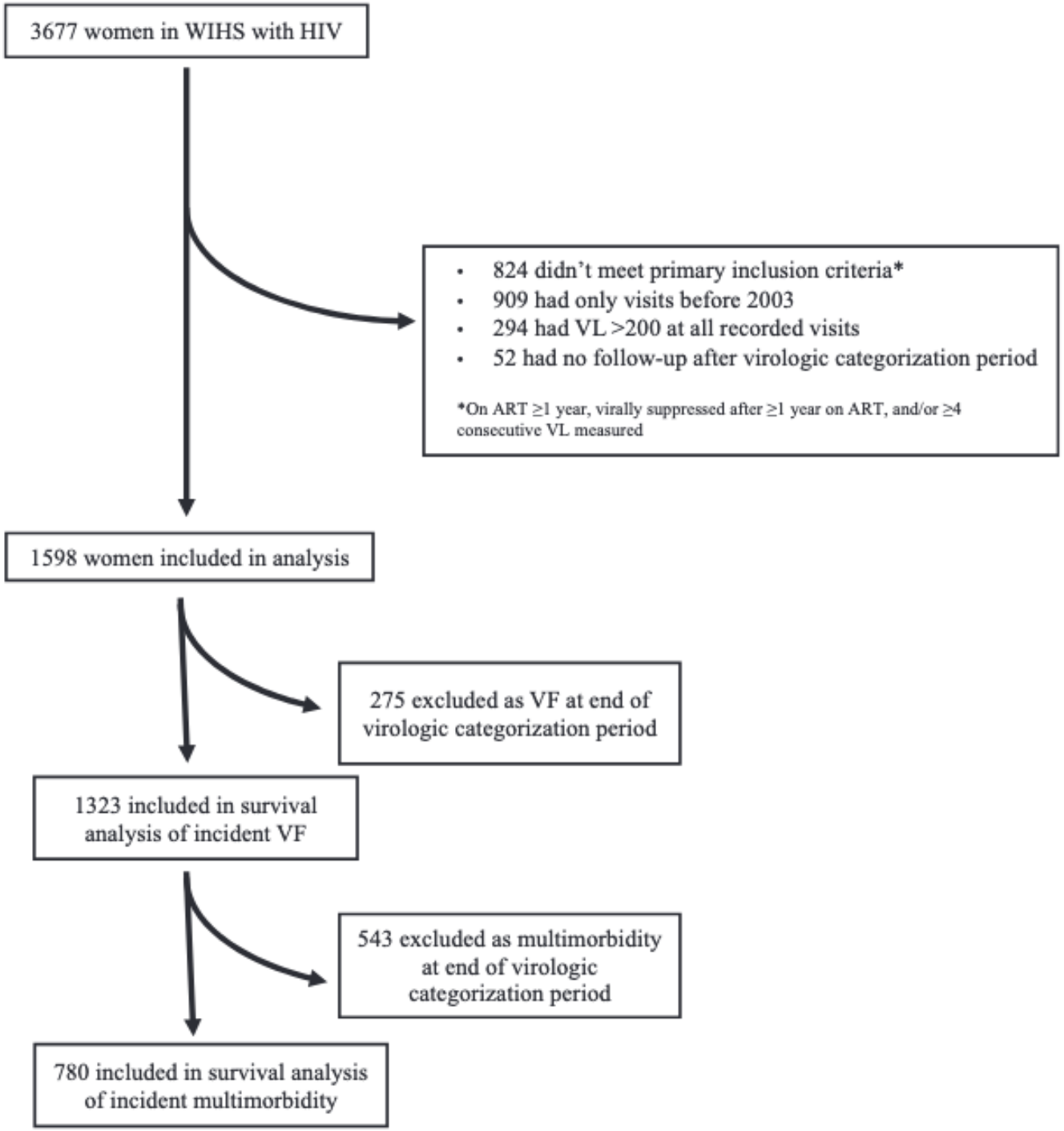


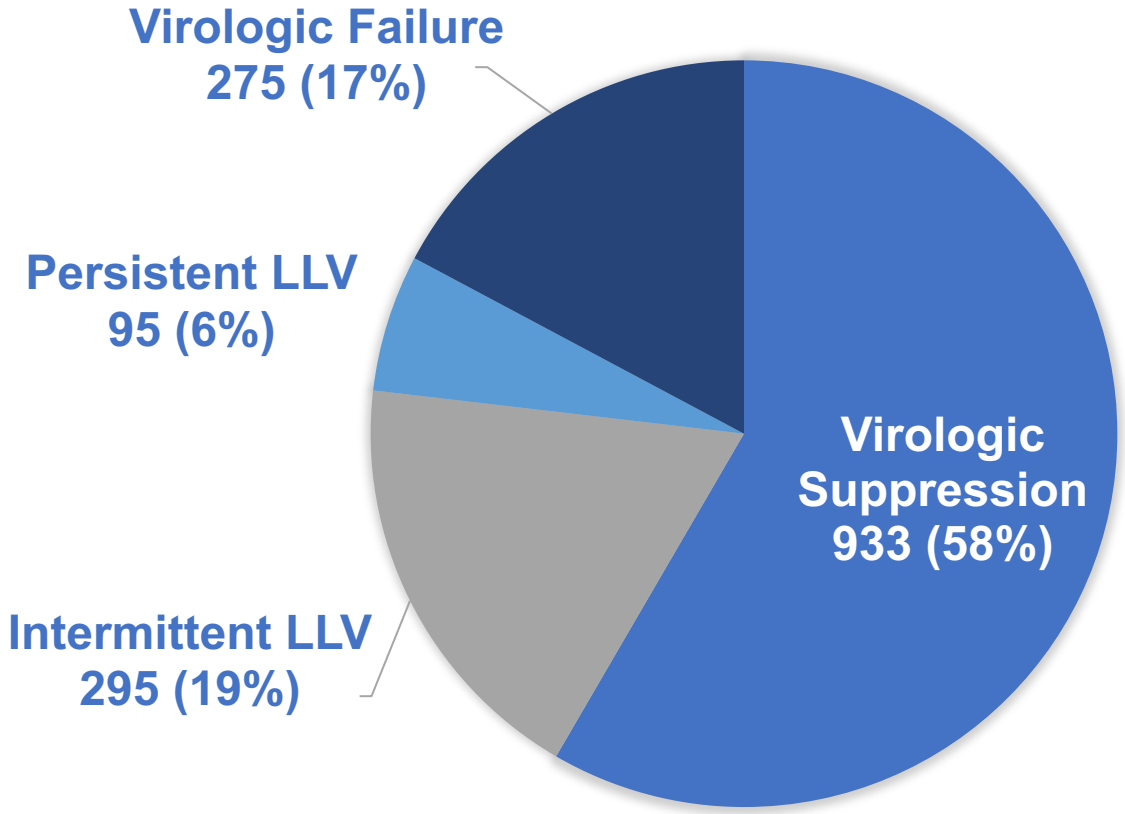
Amalia Aldredge, MD, MSc
Emory ID faculty



Study Definition	HIV-1 RNA (copies/mL)	Number of Visits
Sustained Virologic Suppression	Below lower limit of detection	All visits
Intermittent Low-Level Viremia (iLLV)	Detectable-199 c/mL	Non-consecutive visits
Persistent Low-Level Viremia (pLLV)	Detectable-199 c/mL	≥2 consecutive visits
Virologic Failure (VF)	≥200 c/mL	Any visit

1/4 of WWH developed LLV





Aldredge A et al. AIDS. 2024; 38:1829-1838.

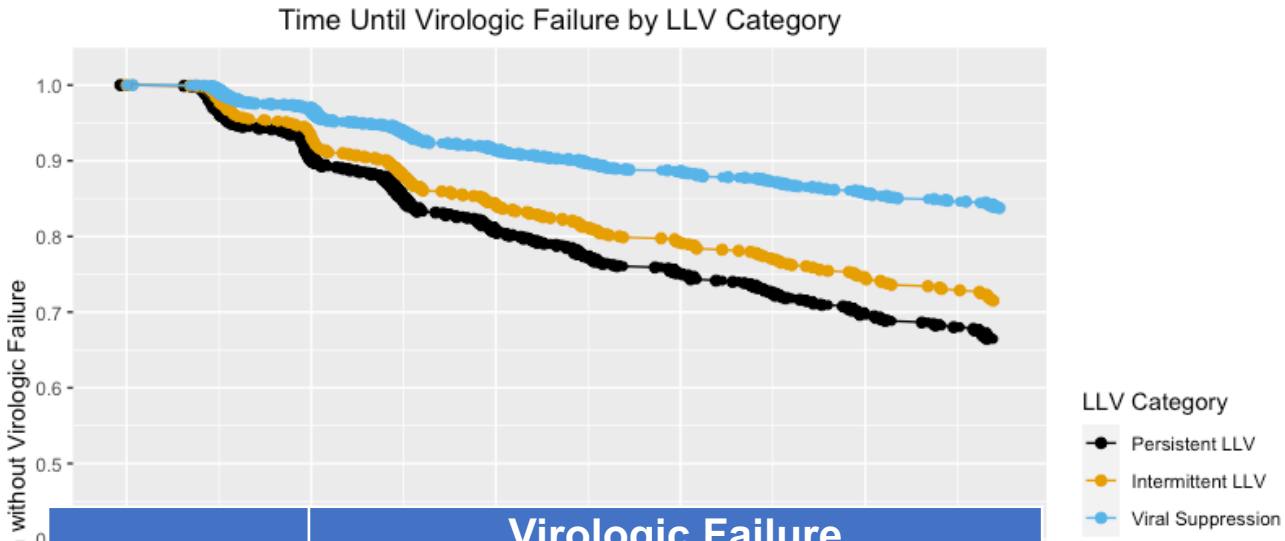
Baseline HIV-related characteristics among WWH stratified by virologic status

Participant Characteristics, *Median (Q1, Q3) or n (%)*	Total WWH N=1598	Virologic Category			
		Virologic Suppression n=933	Intermittent Low-level Viremia n=295	Persistent Low-level Viremia n=95	Virologic Failure n=275
CD4, cells/μL	621 (453, 820)	642 (486, 847)	685 (492, 885)	667 (457, 830)	471 (276, 629)
Adherence ≥95%	1384 (87)	837 (90)	255 (86)	82 (86)	210 (76)
ART Anchor Drug					
INSTI	454 (28)	258 (28)	93 (32)	37 (39)	66 (24)
PI	587 (37)	293 (31)	115 (39)	38 (40)	141 (51)
NNRTI	516 (32)	357 (38)	80 (27)	19 (20)	60 (22)

INSTI – integrase strand transfer inhibitor
PI – protease inhibitor
NNRTI – non-nucleoside reverse transcriptase inhibitor

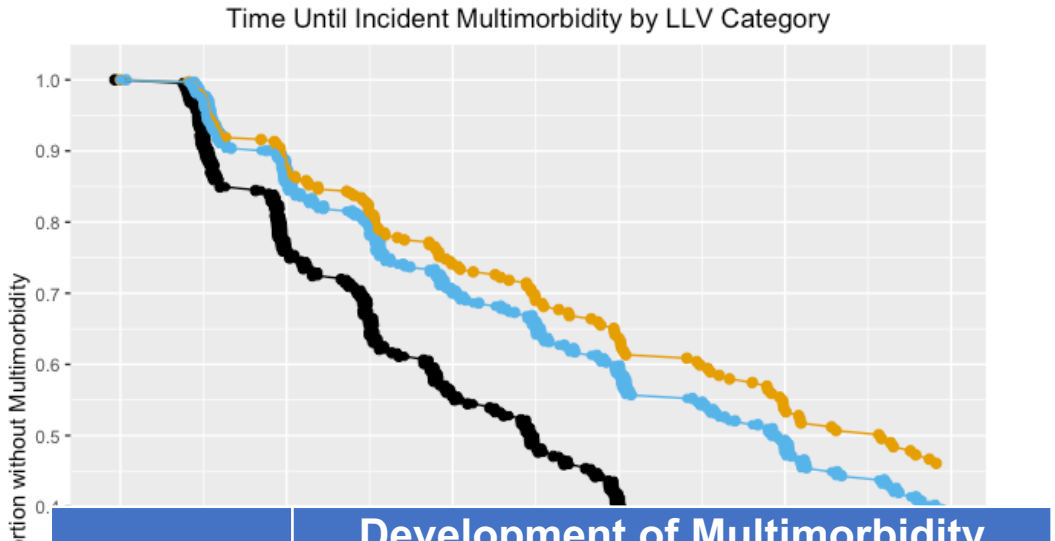
Aldredge A et al. AIDS. 2024; 38:1829-1838.

WWH with any LLV had higher risk of VF, those with pLLV had a trend toward increased incidence of multimorbidity



Virologic Outcome	Virologic Failure n=1323 Unadjusted HR (95% CI)	Virologic Failure n=1323 Adjusted HR (95% CI)*
VS	REF	REF
iLLV	2.08 (1.60, 2.71)	1.89 (1.45, 2.47)
pLLV	2.52 (1.70, 3.74)	2.31 (1.53, 3.47)

*Adjusted for age, race/ethnicity, CD4 count, adherence, and ART regimen



Virologic Outcome	Development of Multimorbidity n=780 Unadjusted HR (95% CI)	Development of Multimorbidity n=780 Adjusted HR (95% CI)**
VS	REF	REF
iLLV	0.94 (0.63, 1.40)	0.84 (0.56, 1.26)
pLLV	1.74 (1.01, 2.98)	1.61 (0.93, 2.82)

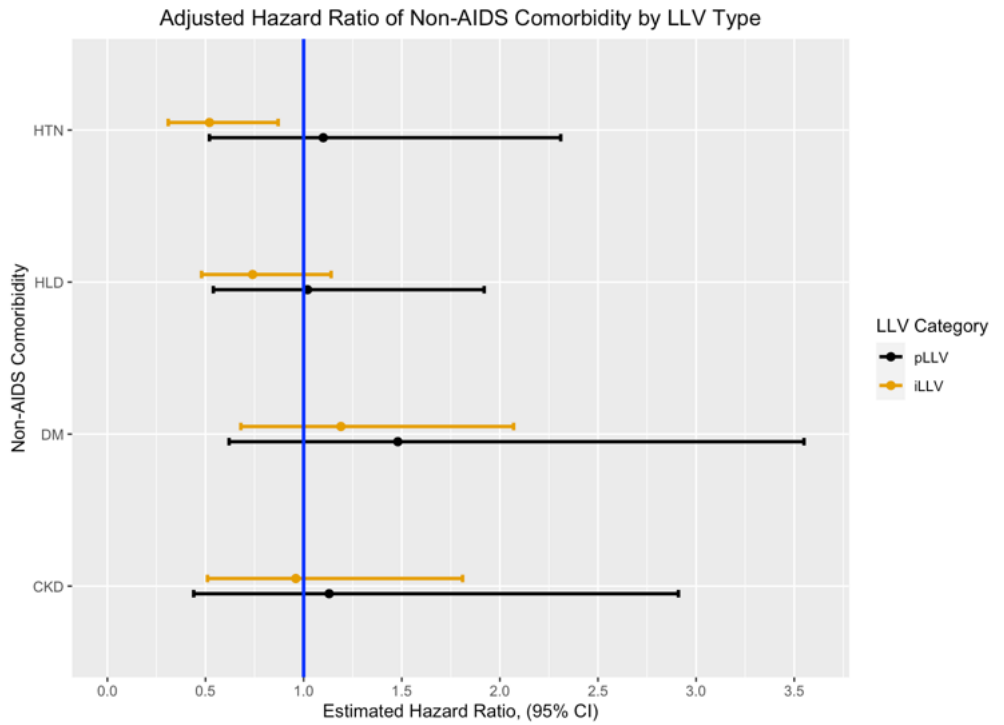
**Adjusted for age, race/ethnicity, obesity, smoking status, adherence, CD4 count, and INSTI use

Aldredge A et al. AIDS. 2024; 38:1829-1838.

WWH and LLV summary

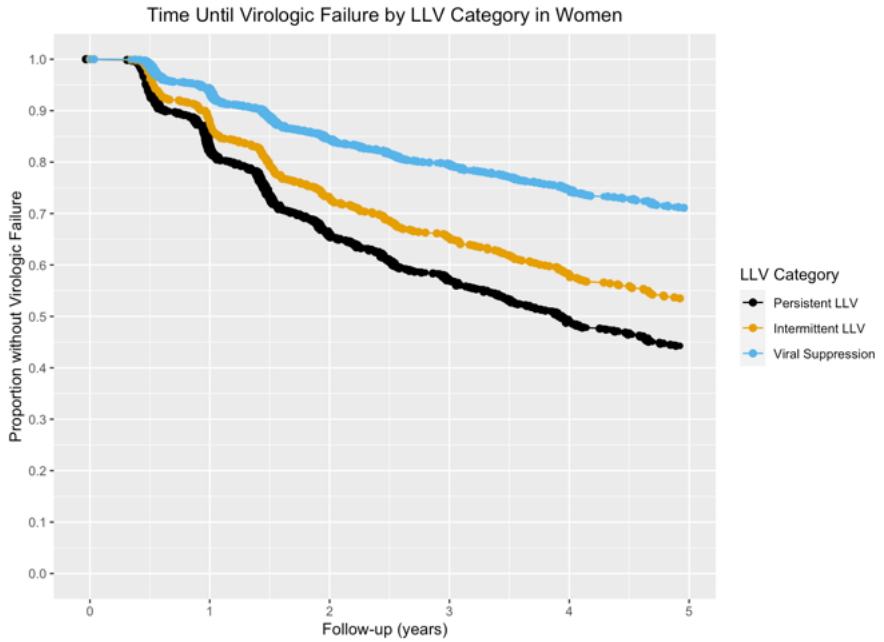
- Using a viral load threshold of ≥500 cp/ml for VF resulted in similar findings

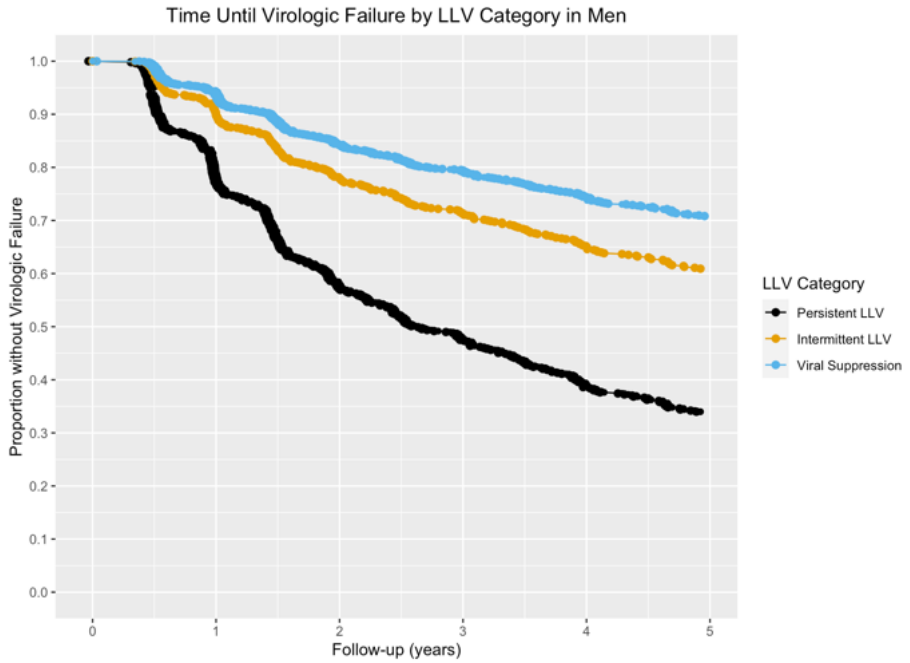
- No individual comorbidity appeared to drive incident multimorbidity (Too few CVD cases to analyze)



HOW DO THESE FINDINGS COMPARE TO MEN WITH HIV?

Aldredge A et al. AIDS. 2024; 38:1829-1838.





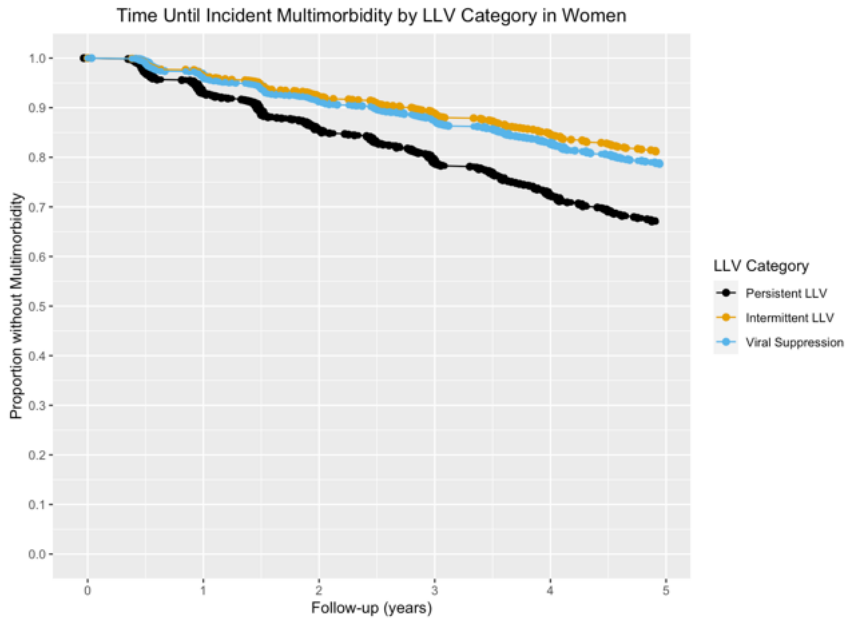
Any LLV was associated with increased risk of VF for women and men

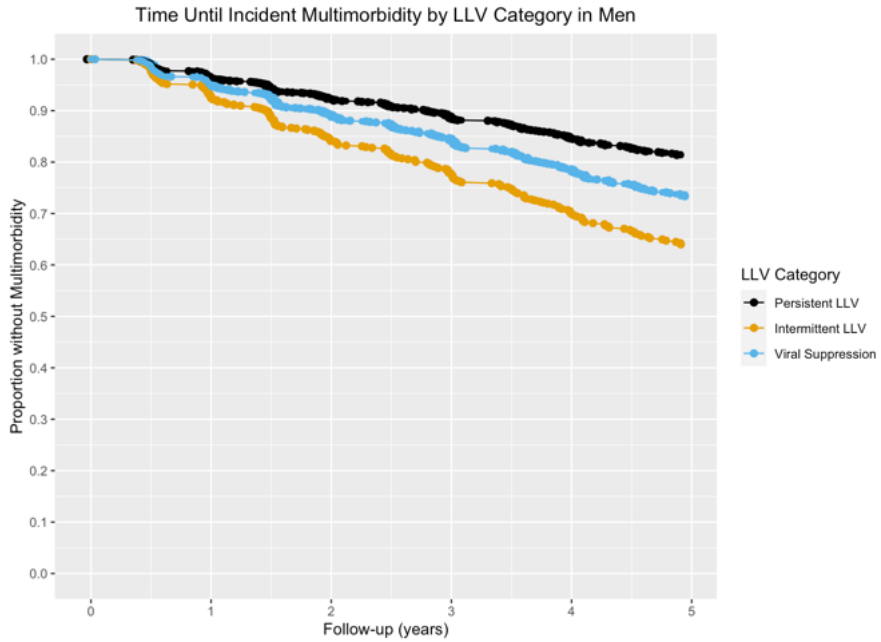
	Incident Virologic Failure Adjusted Hazard Ratio (95% Confidence Interval)*		
Virologic Category	**All n=1968**	**Women n=1304**	**Men n=664**
Virologic Suppression	REFERENT	REFERENT	REFERENT
Intermittent LLV	**1.6 (1.2, 2.1)**	**1.8 (1.4, 2.4)**	**1.4 (0.9, 2.3)**
Persistent LLV	**2.7 (1.9, 3.9)**	**2.4 (1.6, 3.6)**	**3.1 (1.7, 5.6)**

*Adjusted for age, ±sex (overall), ±LLV*sex (overall), race, socioeconomic status (SES), CD4, adherence, antiretroviral anchor

LLV*sex interaction p=0.4

Aldredge A et al. CROI 2024.





Persistent LLV was associated with trend in increased risk of multimorbidity in women

	Incident Multimorbidity Adjusted Hazard Ratio (95% Confidence Interval)**		
Virologic Category	**All n=1123**	**Women n=773**	**Men n=350**
Virologic Suppression	REFERENT	REFERENT	REFERENT
Intermittent LLV	**1.1 (0.8, 1.6)**	**0.9 (0.6, 1.3)**	**1.4 (0.9, 2.4)**
Persistent LLV	**1.1 (0.6, 1.9)**	**1.7 (1.0, 2.9)**	**0.7 (0.2, 1.9)**

**Adjusted for age, ±sex (overall), ±LLV*sex (overall), race, SES, obesity, smoking, CD4, adherence, integrase inhibitor use

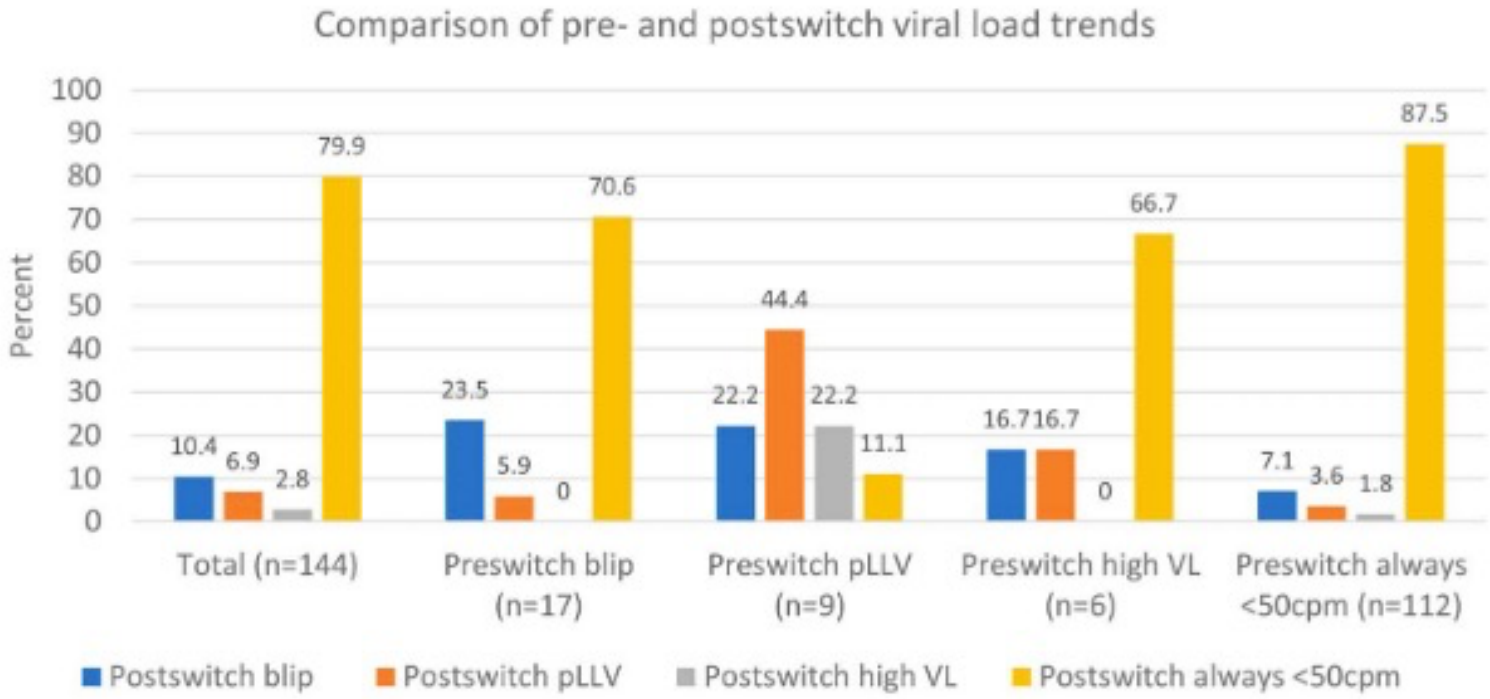
LLV*sex interaction p=0.1

Aldredge A et al. CROI 2024.

What about LLV in the era of long-acting (LA) ART?

***NOT* associated with post-switch viremia:**
- *BMI*
- *Late injection*
- *Q4wk vs Q8wk injections*

- Retrospective cohort* (04/2021-12/2022)
- N=144: median age 44yrs, 10% ciswomen, median follow-up of 287 days
- After switch, ≥1 HIV RNA ≥ 20/50/200 cp/ml occurred in 35%, 15%, and 3% of PWH, respectively



PWH with **persistent LLV (pLLV) pre-switch** were significantly more likely to have detectable HIV RNA after switch (HR 24.4, 95%CI 8.7-68.3); **44% of PWH with pLLV pre-switch continued pLLV post-switch**

*Inclusion: CAB/RPV-LA ≥3mo, availability of pre/post-switch HIV RNA values, VL <200 cp/ml at time of switch, ≥1 post-switch VL >21 days after CAB/RPV-LA start

Hill et al. JAIDS 2024;95(1):90-96

- Low-level viremia is common among ART-treated persons with HIV
- Women vs men with HIV who have persistent LLV may have an increased risk of multimorbidity
- The clinical landscape of LLV definitions, patterns, risk factors, and sequelae is evolving and continued research is needed including on use of long-acting ART to inform clinical guidance

Multimorbidity impact and implications for screening and prevention in persons with HIV

Developing strategies for healthy aging


PROFESSIONAL
AMBULANCE

How does NACM burden affect *Quality of Life* (**QoL**) index in aging women by HIV status?

MWCCS
MACS/WIHS COMBINED COHORT STUDY

N=3306 (72% HIV)
Median age 50yrs

- Mean QOL index did not differ in women with vs without HIV (68 vs 69, *p*=0.40), but decreased with older age (*p*<0.001)
- In unadjusted models, QOL index was negatively associated with each prevalent NACM (**Table**); and NACM burden was associated with all nine QOL domains*

Table. The association of 10 aging-related NACM on QOL index among women with and without HIV (unadjusted)

NACM	**Prevalence N (%) of 3,036**	**Estimated change in mean QOL index in women with vs without HIV (95% CI)**
Hypertension	2012 (66%)	-10.5 (-12.1, -8.9)
Psych. Illness	1647 (54%)	-19.8 (-21.2, -18.5)
Lung disease	1270 (42%)	-11.3 (-12.8, -9.7)
Dyslipidemia	1175 (39%)	-6.6 (-8.1, -5.0)
Liver disease	1179 (39%)	-7.1 (-8.7, -5.6)
Bone disease	1155 (38%)	-9.3 (-10.9, -7.8)
Diabetes	691 (23%)	-8.0 (-9.8, -6.2)
CVD	582 (19%)	-11.6 (-13.5, -9.7)
Kidney disease	386 (13%)	-9.8 (-12.1, -7.5)
Cancer, non-AIDS	300 (10%)	-8.7 (-11.3, -6.1)

*QOL domains: physical function, role function, energy/ fatigue, social function, cognitive function, emotional well-being, health perception, pain, and perceived health index

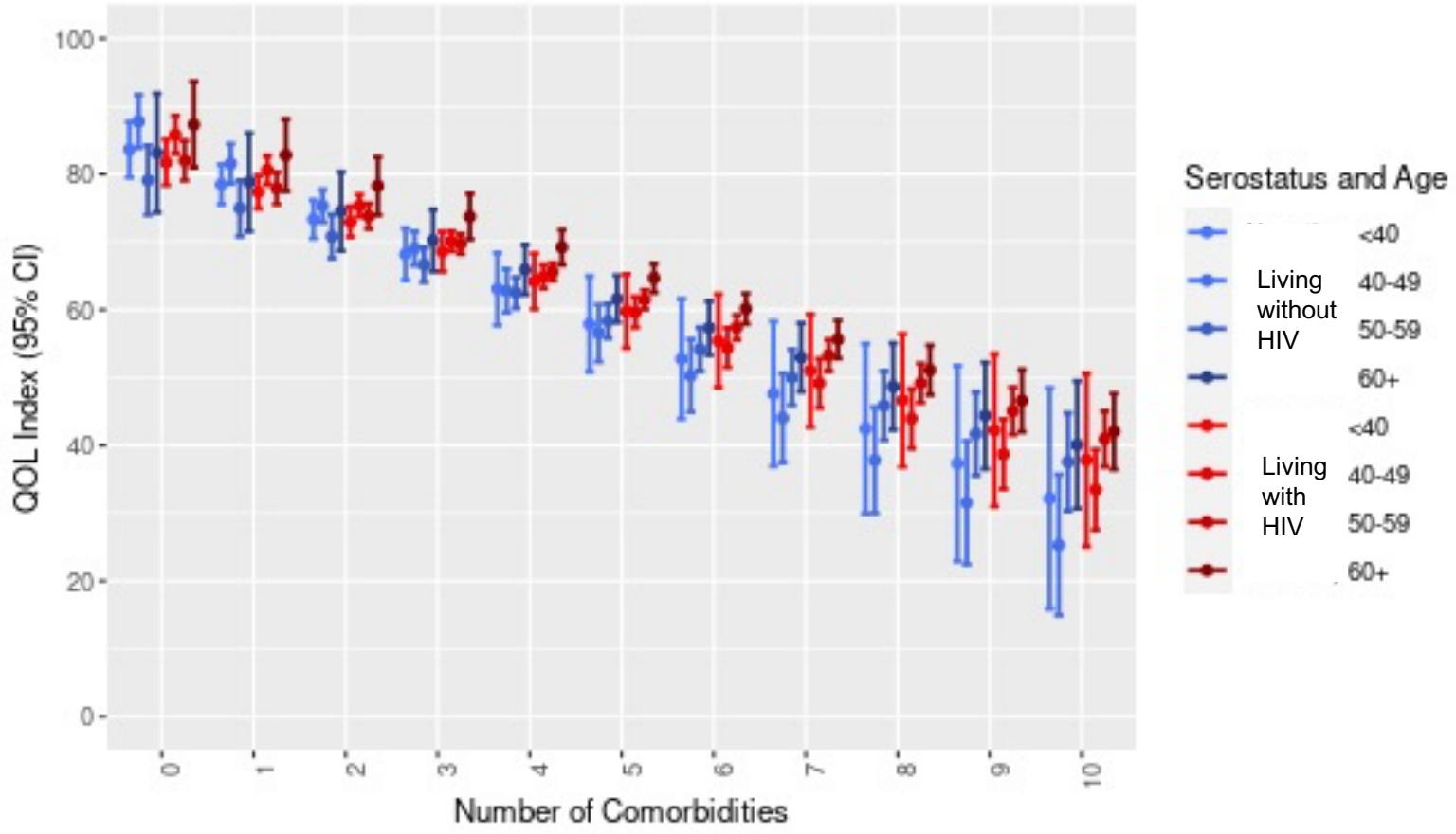
Collins LF et al… Mehta CC; IDWeek 2023

Among women with a high prevalence of multimorbidity, HIV, and health disparities, NACM burden was associated with overall quality of life (QoL), independent of age or HIV serostatus

MWCCS
MACS/WIHS COMBINED COHORT STUDY

- N=3,306 women
- Median age 50yrs

Each additional NACM decreased mean QoL by -4.4 (95% CI: -4.7, -4.1)



Collins LF et al… Mehta CC; IDWeek 2023

“Multimorbidity” among PWH is a health crisis

VIEWPOINT

Comorbidities in Persons With HIV
The Lingering Challenge

JAMA January 7, 2020 Volume 323, Number 1

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The United States recently announced an initiative for ending the HIV epidemic in the United States.[1] The initiative is a joint effort of agencies across the US Department of Health and Human Services that is designed to decrease HIV transmissions in the United States by 75% over 5 years and by 90% over the next 10 years. This initiative represents the first time a coordinated effort of resources, programs, and infrastructure will focus on geographic areas and demographic groups with the highest rates of new HIV diagnoses in the United States.[1] If successful, this effort would substantially decrease HIV transmission in the United States, thus ending the epidemic as an epidemiological phenomenon and could serve as a model for implementation of similar plans on a global scale.

Even if this aspirational goal is achieved and HIV transmissions no longer occur in epidemic proportions in the United States, it still would not be possible to declare an end to HIV. There will still be at least 1 million people in the United States living with HIV, and it will be important to attend to their special medical needs even

tion biomarkers that are associated with poor outcomes including increased mortality.[4] Increasing the understanding of the complex mechanisms behind the immune activation and dysfunction seen in chronic HIV disease could potentially lead to new therapies that could help improve the clinical management of many HIV-associated comorbidities.

Persons with HIV, including individuals receiving ART, show an increased risk of ischemic heart disease and other serious cardiovascular conditions.[4] Although this risk has been associated with immune activation, numerous other factors are likely involved, including the effects of some antiretroviral drugs and the overrepresentation of certain established cardiovascular disease risk factors, such as tobacco use, in persons with HIV. It is critical to elucidate these mechanisms and develop and implement treatments that mitigate this risk. In this regard, a large ongoing clinical study (Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults [REPRIEVE]; NCT02344290) is investigating whether

Healthcare expenditures of **$300-$5000 more per patient month** in PWH with than without comorbidities

Gallant J. CRMO. 2018 Jan; 34(1):13-23.

How can we optimally screen and prevent NACM in PWH?

Given HIV is associated with differential effects on comorbidities among women and men, HIV- and sex/gender-specific strategies for NACM screening and prevention are needed

Clinical Infectious Diseases

MAJOR ARTICLE

Primary Care Guidance for Persons With Human Immunodeficiency Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America

Melanie A. Thompson,[1,a] Michael A. Horberg,[2,a] Allison L. Agwu,[3] Jonathan A. Colasanti,[4] Mamta K. Jain,[5] William R. Short,[6] Tulika Singh,[7] and Judith A. Aberg[8]

- ✓ Who to screen?
- ✓ For which comorbidities?
- ✓ With which tools?
- ✓ When to initiate screening?
- ✓ Repeat at which intervals?

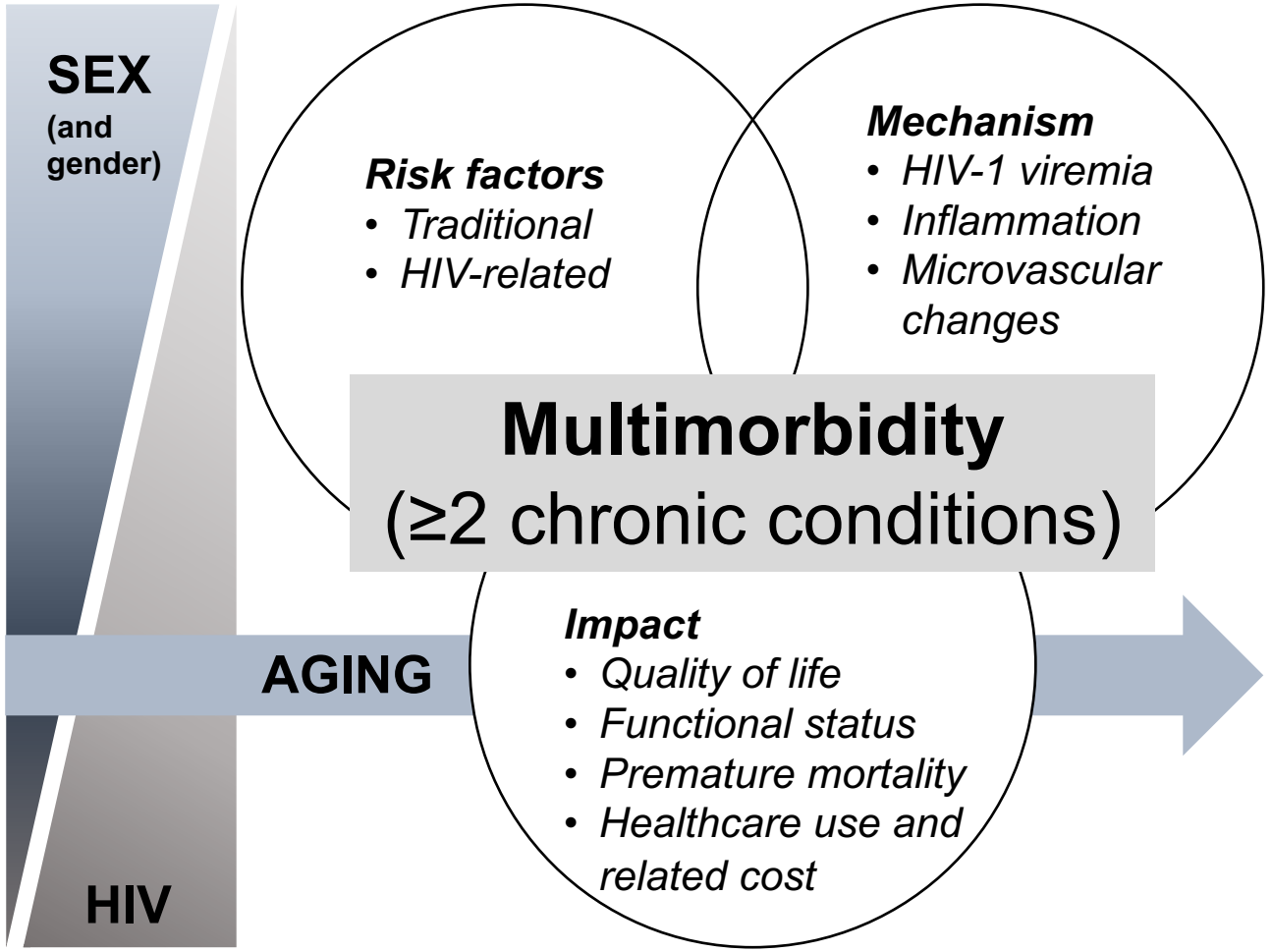
Innovate a multimorbidity screener?

Integrate into aging care?

Thompson MA et al. CID. 2021 Dec 6; 73(11):e3572-3605.

K23: Leveraging geroscience-guided principles to profile multimorbidity patterns

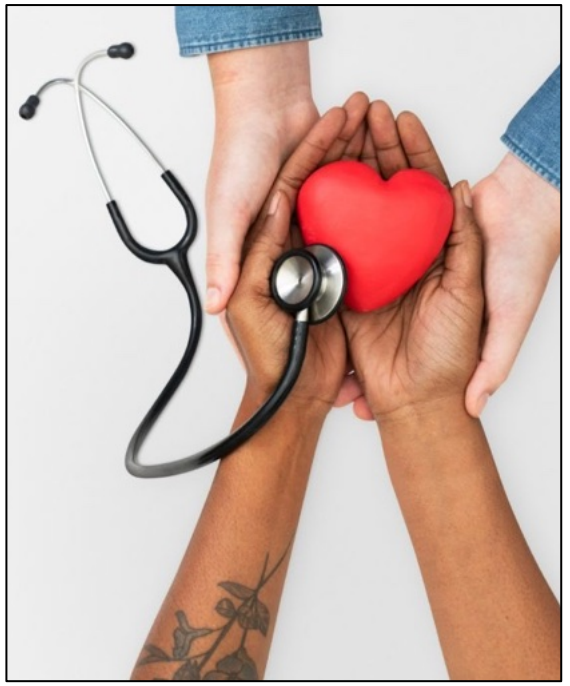
The ***geroscience hypothesis*** posits that by targeting fundamental aging processes one could alleviate multiple age-related diseases.



https://www.nia.nih.gov/gsig

Overall study goal:

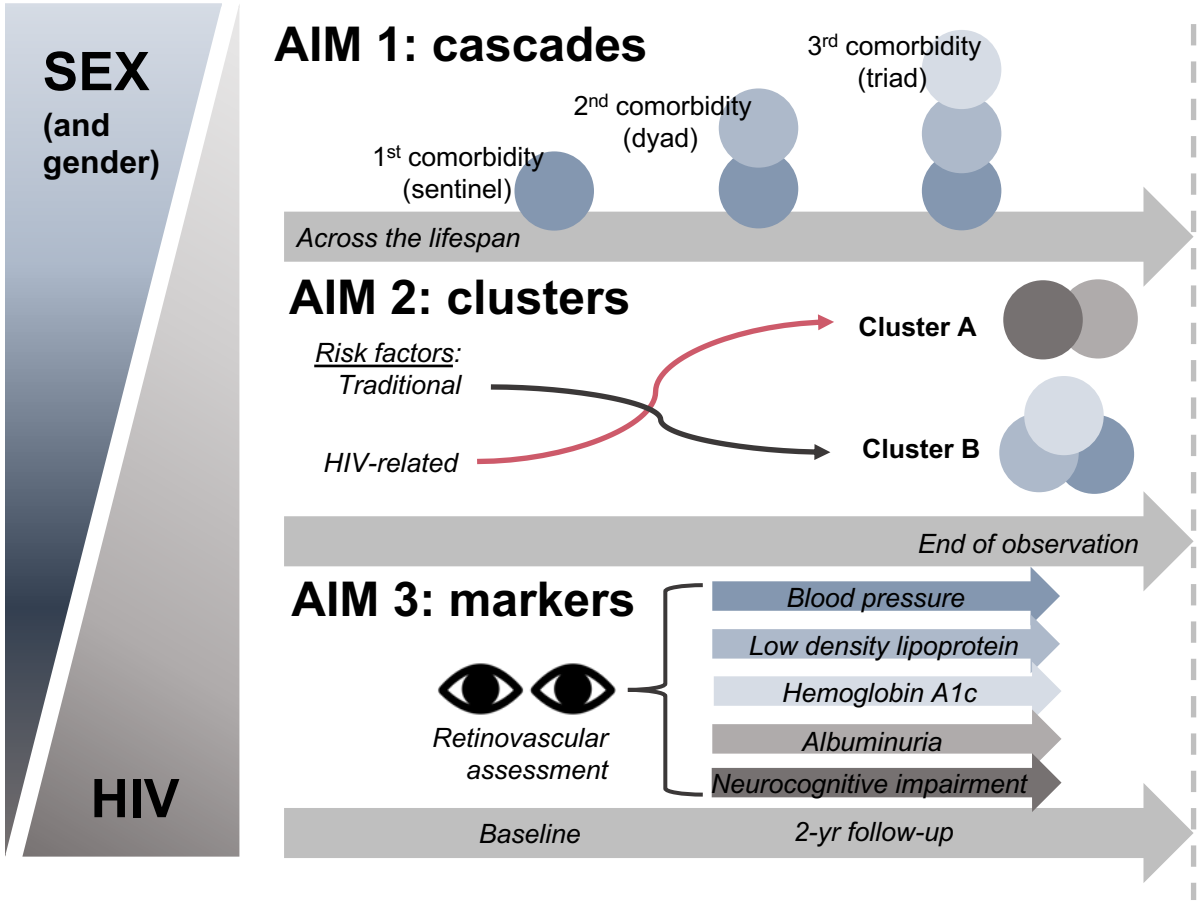
- To translate geroscience-guided multimorbidity profiling into sex and gender-tailored interventions that promote healthy aging in HIV.



Overarching hypothesis:

Aging-related multimorbidity onset and phenotypes vary by HIV serostatus and sex/gender, and common biologic byproducts of accelerated aging in PWH—namely, microvascular changes—may serve as a biomarker to guide HIV- and sex/gender-tailored multimorbidity screening and prevention.

Assessing comorbidity cascades, clusters, and progression markers



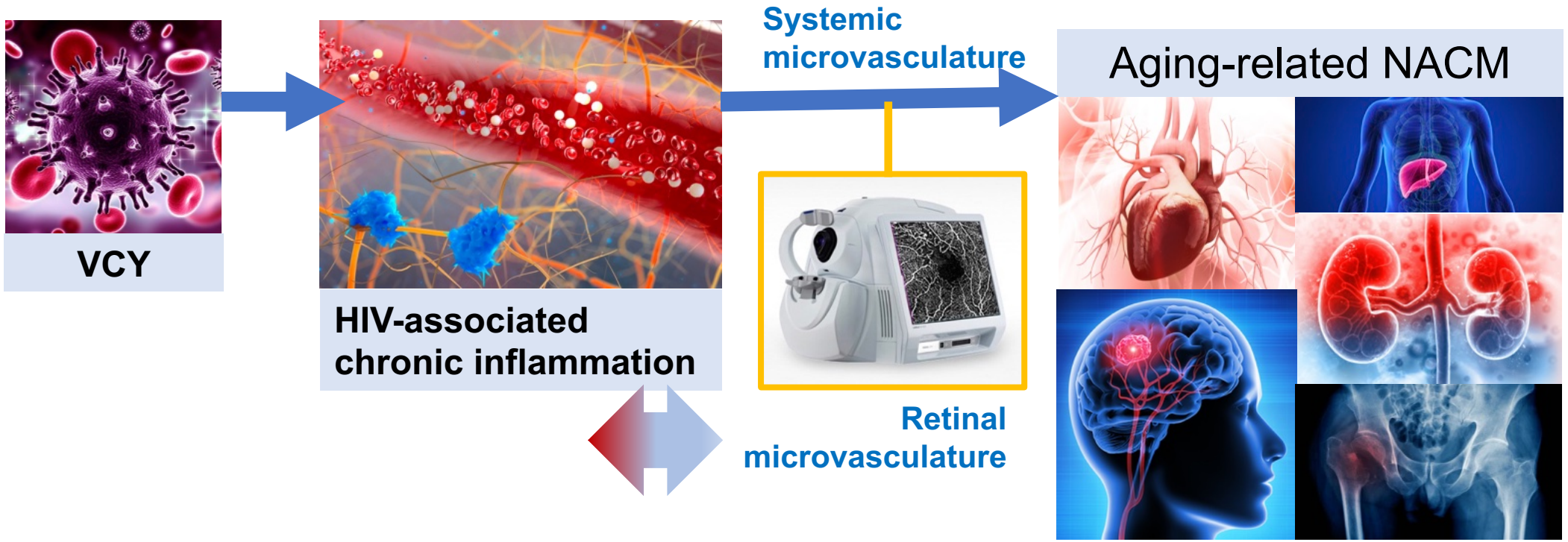
1) How do aging-related comorbidities develop and compound over time?

2) How do comorbidities cluster in subgroups and what are the shared risk factors?

3) Can the retina serve as an early and sensitive biomarker of comorbidity progression?

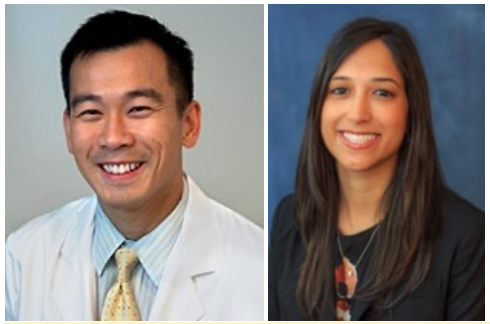
Building evidence for refining NACM – and possibly developing multimorbidity – risk-assessment in PWH

- Central hypothesis: microvascular abnormalities may link HIV-related chronic inflammation and premature multimorbidity, similar to diabetes and other conditions characterized by inflammatory end-organ damage.



Can the retina be employed as a convenient window into systemic vascular health in HIV?

- Proof-of-concept study
- Emory Eye Center
- N=12 PWH underwent retinovascular assessment by **optical coherence tomography angiography (OCTA)**:
  - Non-invasive
  - High-resolution
  - Automated imaging analytics
  - Multiple reproducible metrics
  - Broad applicability across disciplines of medicine



Steven Yeh MD / Jessica Shantha MD
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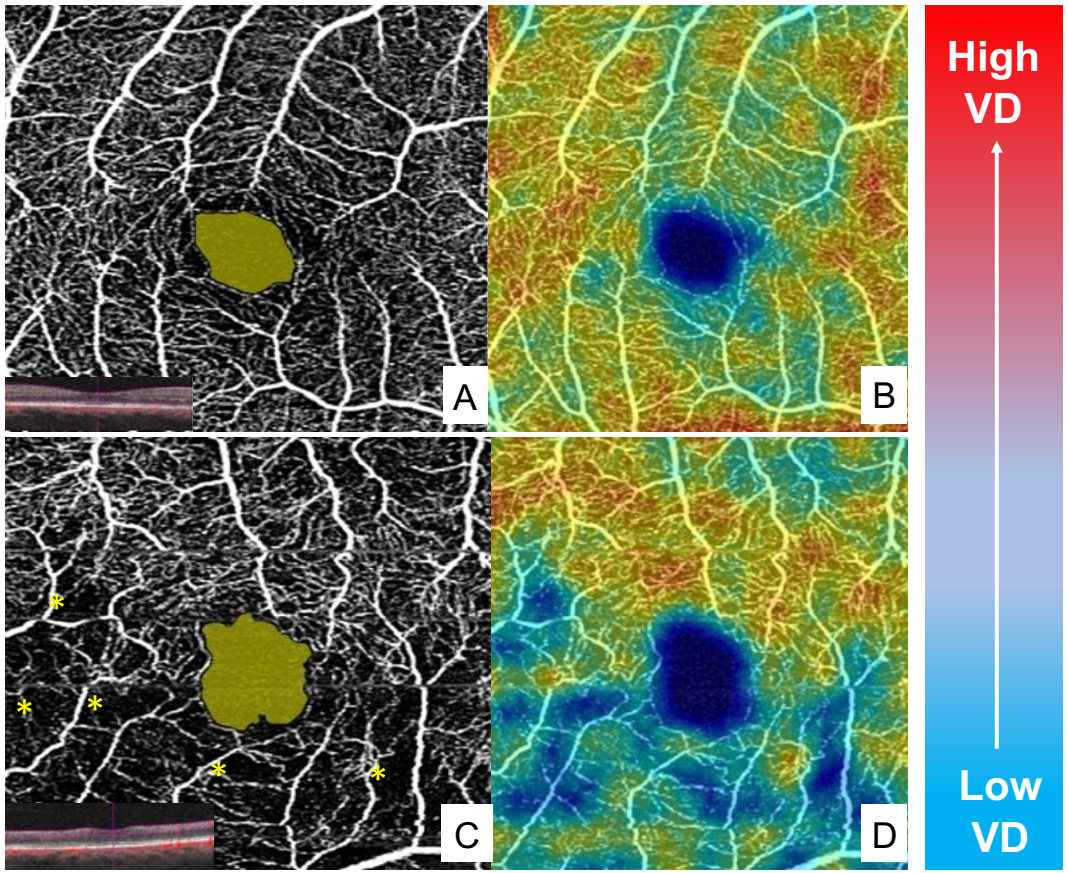
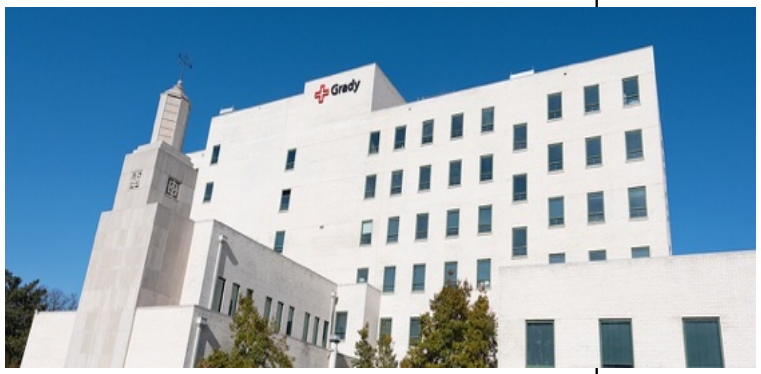
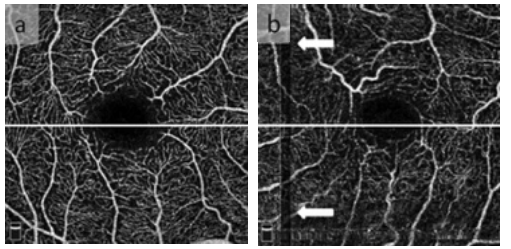
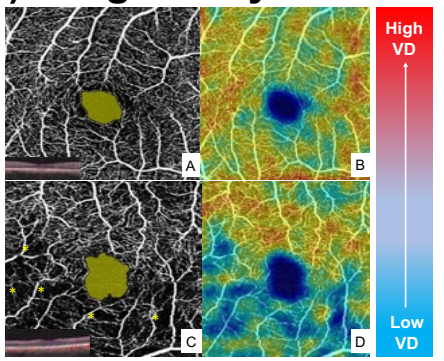


OCTA shows normal (A) foveal avascular zone area and (B) vessel density (VD) versus (C) **enlarged, irregular FAZ area** with flow voids (*) and (D) **abnormal vessel density** in eyes of persons with HIV

Collins LF et al. AIDS. 2021 Jul 1;35(8):1321-1324.

Retinovascular assessment by OCTA among women enrolled in Atlanta MWCCS



	A) Image acquisition	B) Image quality review	C) Image analysis
		 **Grade 1** (5/5 quality criteria satisfied) **Grade 2** (white arrows show motion artifact)	 **FAZ area** **Vessel density (VD)**
Personnel	Trained operator	Two independent reviewers; third adjudicates	Automated software algorithm
Time	1-2 min/participant	50 images/hr per reviewer	Seconds
Output	Two 3x3 angiography images of each eye	Grade 1 = sufficient (a) Grade 2 = insufficient (b)	• FAZ area (A,C) • Vessel density (B,D)

* Quality criteria:
1) Image truncation
2) Motion artifact
3) Fovea centration
4) Segmentation error
5) Capillary visibility

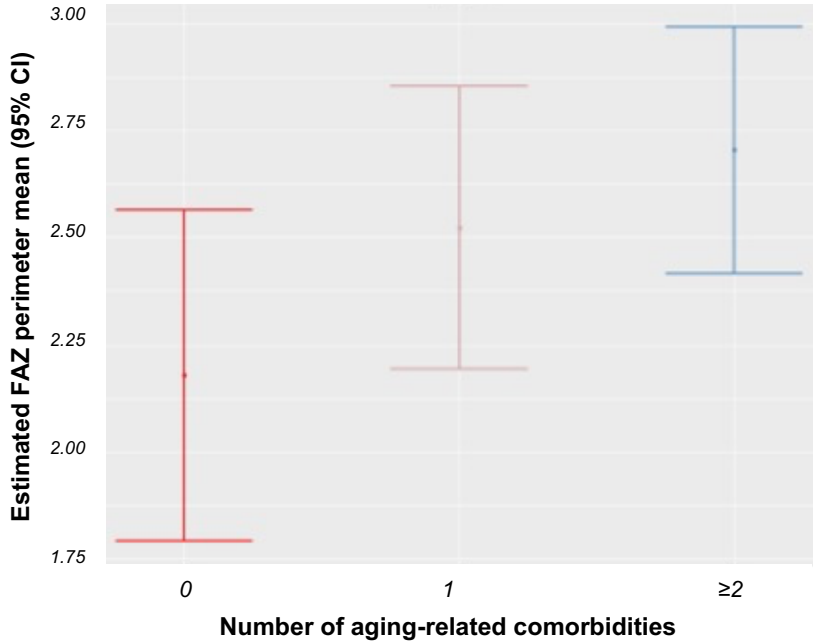
115 women successfully imaged → 96/115 (83%) had quality images → 84/96 (88%) had available clinical data →

Preliminary data *among women* suggest that retinovascular changes may be associated with increasing NACM burden

Characteristic, n (%)	**Women (N=84)**
Median age (Q1-Q3), yrs	49.5 (41-57)
Living with HIV	52 (62)
Black race	77 (92)
Current/former cigarette use	59 (70)
Multimorbidity (≥2 of 10 NACM)	59 (70)
OCTA metrics	
Mean FAZ area (sd), mm^2	0.36 (0.13)
Mean vessel density (sd), mm^{-1}	19.6 (2.0)

Findings comparable to cohorts of PWH without clinical retinopathy

In a model adjusted for age and race, estimated mean **FAZ perimeter** was significantly associated with increasing comorbidity burden (*p-trend*=0.02)



Agarwal A et al. Ophthalmol Retina. 2017 Dec;1(6):545–554
Akmaz B et al. Graefes Arch Clin Exp Ophthalmol. 2020 Aug;258(8):1671–1676.

How to optimally prevent multimorbidity among PWH to promote healthy aging?

35% reduction in risk of incident *major adverse cardiac events* with **statin use** (*ACTG REPRIEVE*)

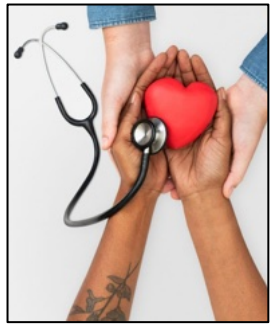
43% lower prevalence of *carotid plaque* among women who ever used **hormone replacement therapy** (*WIHS observational data*)

29% of PWH had complete resolution of *metabolic liver disease* with **semaglutide use** (*ACTG SLIM LIVER*)

2-4x risk of *multimorbidity* with higher cumulative viremia copy-years among ART-treated women (*WIHS observational data*)

NEJM 2023 Aug;389(8):687-699
CID 2023 Feb;76(3):e661-e670
Ann Intern Med 2024 Jun;177(6):835-838
OFID 2022 Dec;10(2):ofac702

Future directions: developing strategies for healthy aging across the lifespan considering *HIV and sex and gender*



- Further characterize multimorbidity phenotypes, including NACM clusters and associated factors (who, what, where, when, why)

- Develop novel tools and strategies for comorbidity screening and prevention that may be deployed across the reproductive life course
  - Viremia copy-years or LLV and non-invasive microvascular assessments may be promising clinical targets for screening
  - Preventive interventions should be evaluated using geroscience framework

- Integrate multimorbidity care into HIV clinics as part of a broader aging health agenda and infrastructure for persons with HIV

Next frontier of HIV care in the U.S. South: integrating healthy aging approaches

https://www.hivguidelines.org/guideline/hiv-aging/

American Geriatrics Society

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RHYTHM

RESEARCH IN HIV AND WOMEN'S HEALTH AND Y THIS HARMONY MATTERS

Mission

Our core mission is to engage in community-informed science and advocacy related to human immunodeficiency virus (HIV), emerging infections, and sex and gender science with an emphasis on women's health with the overarching goal of improving the health of our community, locally and globally.

/ˈriTH̲əm/
the aspect of music comprising all the elements (such as accent, meter, and tempo) that relate to forward movement.

https://med.emory.edu/departments/medicine/divisions/infectious-diseases/research/rhythm/index.html

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MWCCS
MACS/WIHS COMBINED COHORT STUDY

SCORE
SPECIALIZED CENTER OF RESEARCH EXCELLENCE ON SEX DIFFERENCES

STAR
Study of Treatment And Reproductive Outcomes

CFAR
EMORY CENTER FOR AIDS RESEARCH

EMORY UNIVERSITY SCHOOL OF MEDICINE
Division of Infectious Diseases

Grady

Georgia CTSA
Georgia Clinical & Translational Science Alliance

DORIS DUKE CHARITABLE FOUNDATION

NIH NICHD

NIH National Heart, Lung, and Blood Institute

NIH National Institute on Aging

Questions?

Thank you for your attention and interest

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