

The HIV Pandemic- Aging into Geriatrics



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Galkin Lecture
February 26th, 2025

Disclosures

- **No personal disclosures**
- **I will be discussing the use of medications/products outside of FDA-approved indications**





Epidemiology



Biology of Aging



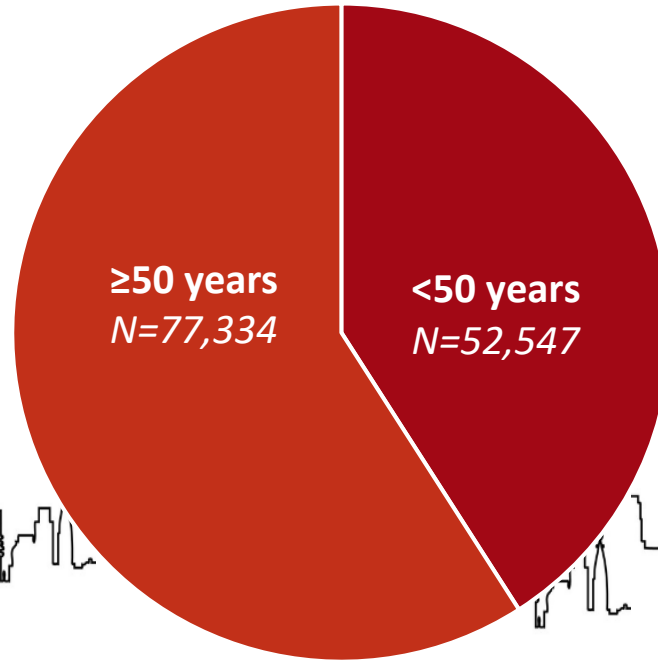
Advances in HIV
Geroscience



Care and Research for
Older Adults with HIV

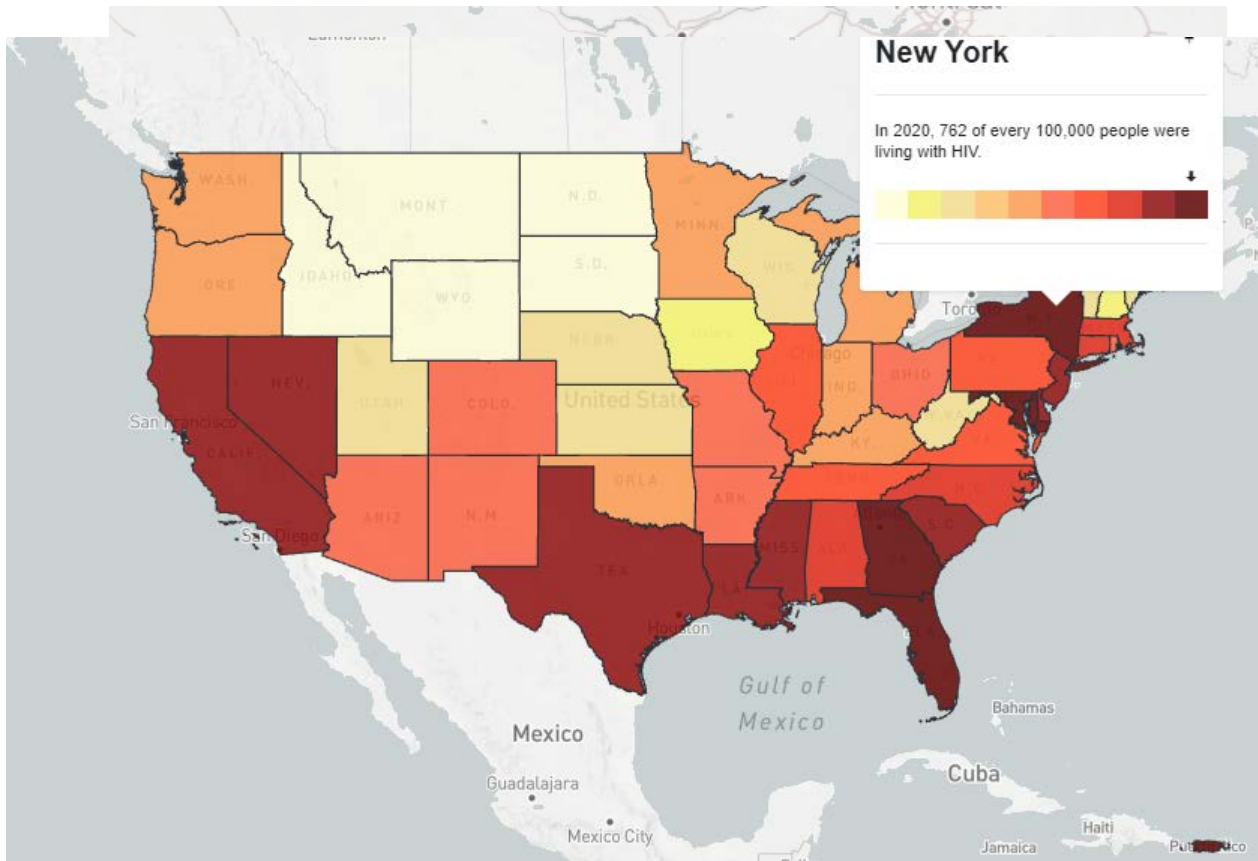


Over Half of People Living with HIV in NYC are ≥ 50 years old



*Of those ≥ 50 , nearly half are ≥ 60





Nearly 1% of people 55+ in NYS have HIV

Age group with HIV	% of HIV NYS
50+	54.9% (59,688)
60+	23.3% (25,314)

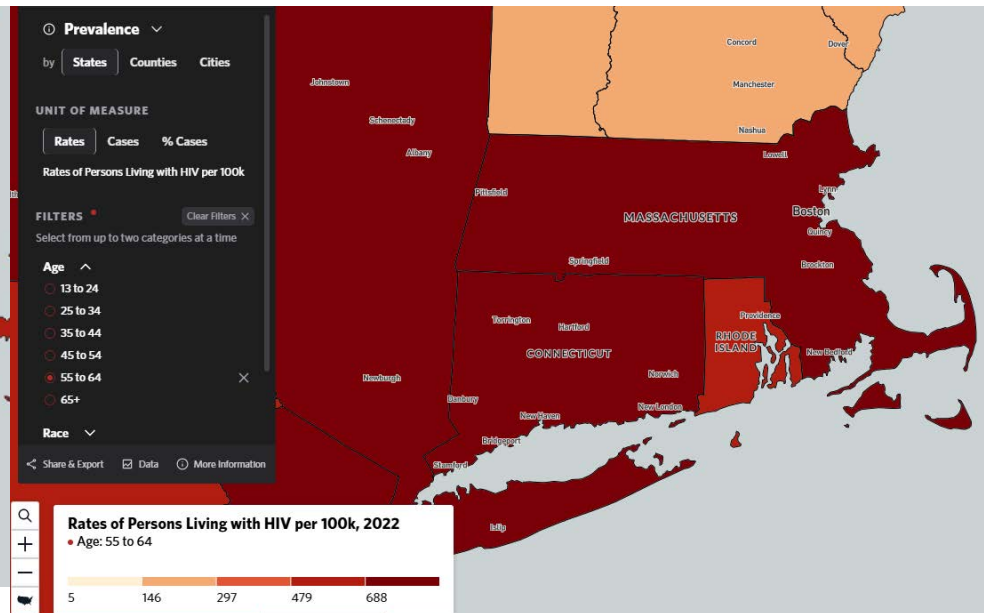
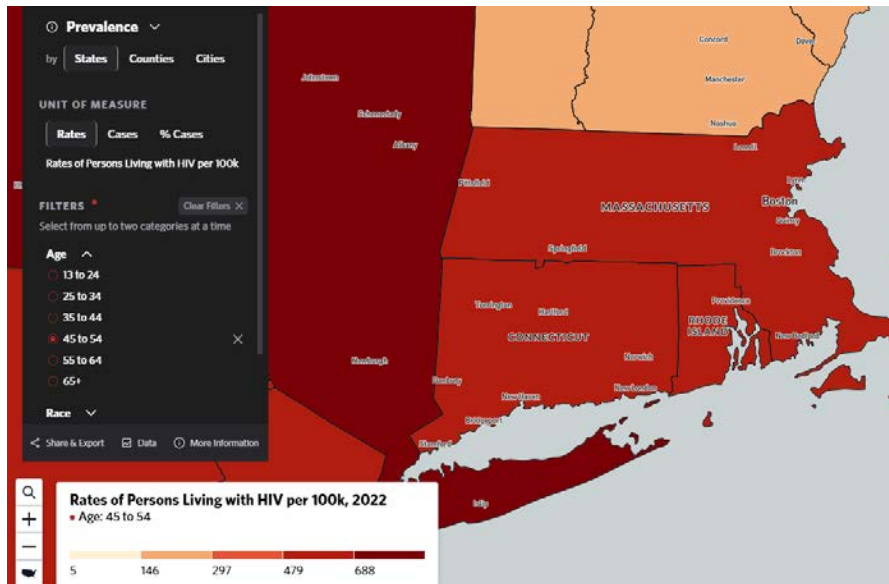
https://www.health.ny.gov/diseases/aids/general/statistics/annual/2018/2018_annual_surveillance_report.pdf



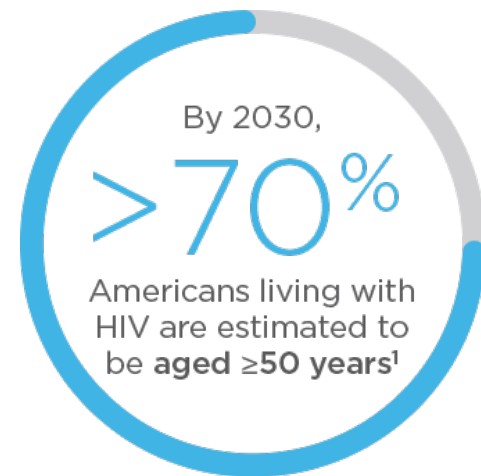
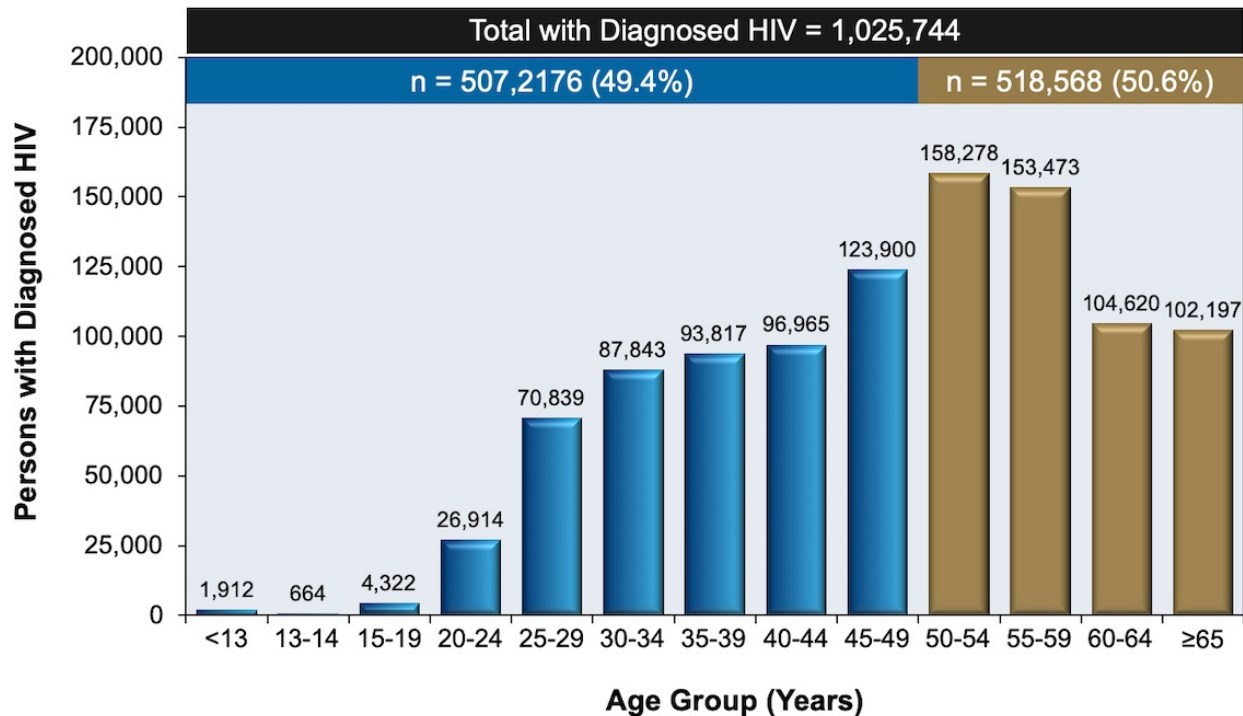
Rhode Island Data

Age 45-54 (approx. 500/100k)

Age 55+



In the US, over half of PWH are ≥ 50 years old



Persons Living with Diagnosed HIV Infection in United States, by Age Group, Year-End 2018

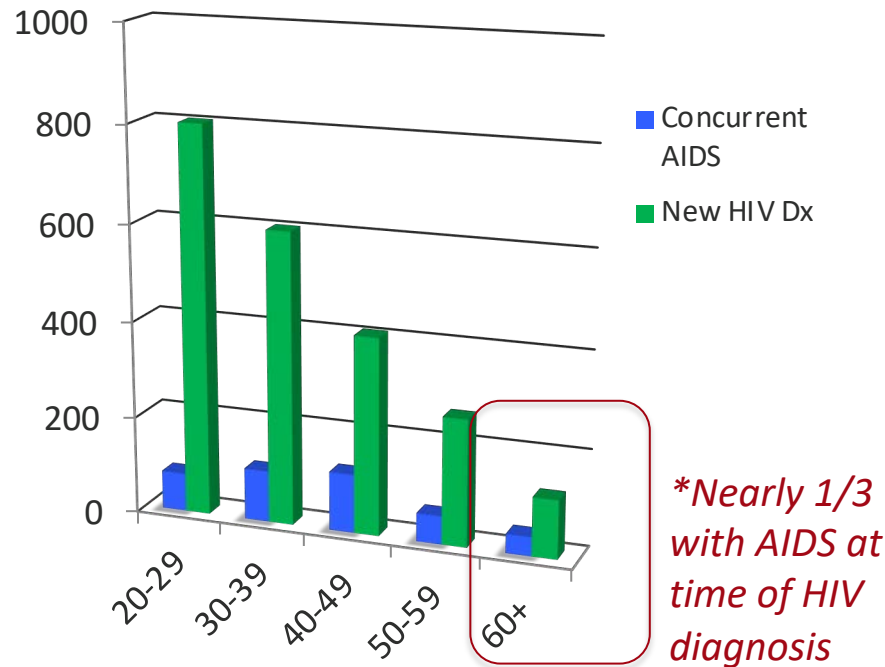
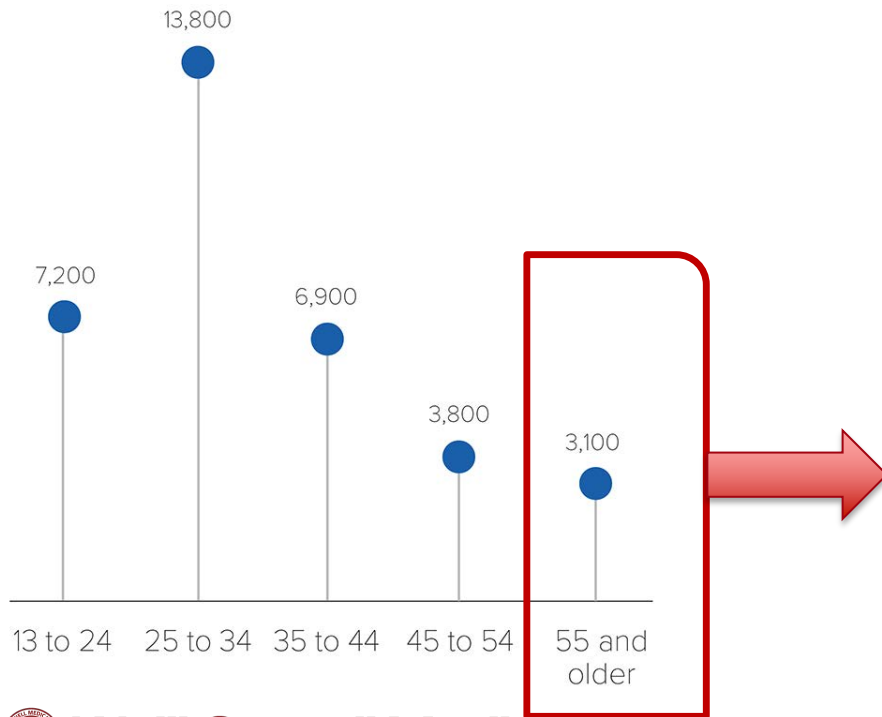
Centers for Disease Control and Prevention, 2018 (Updated). HIV Surveillance Report, 2020; vol. 31:1-119. Published May 2020



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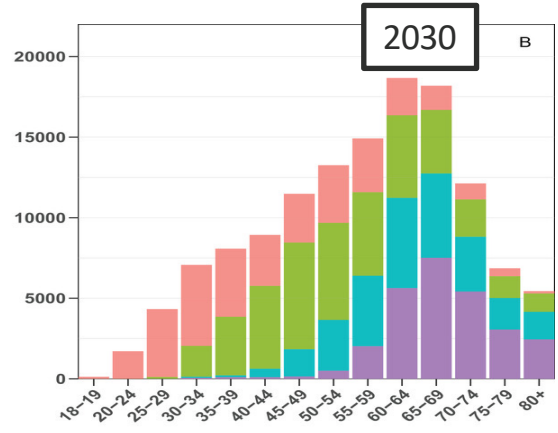
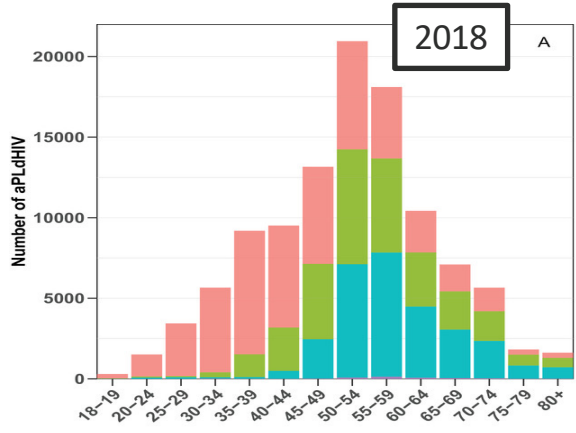
1. Wing EJ. The aging population with HIV infection. Trans AM Clin Climatol Assoc. 2017;128:131-144.

Of new HIV infections diagnosed, ~10% in adults ≥ 55

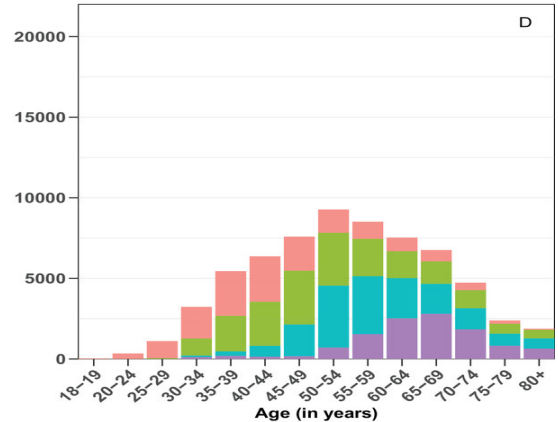
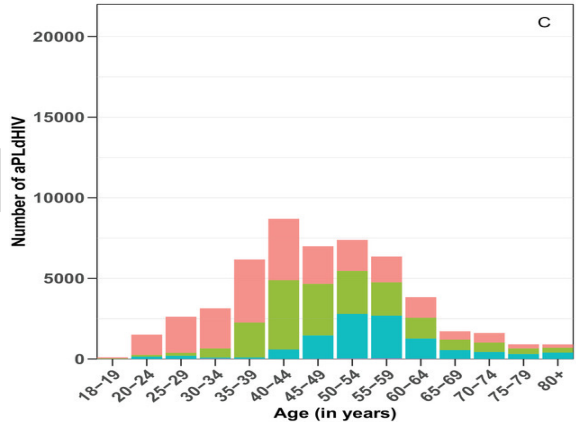


By 2030, large numbers of people with HIV will be over 60 and will have been on ART for 30+ years

Men



Women



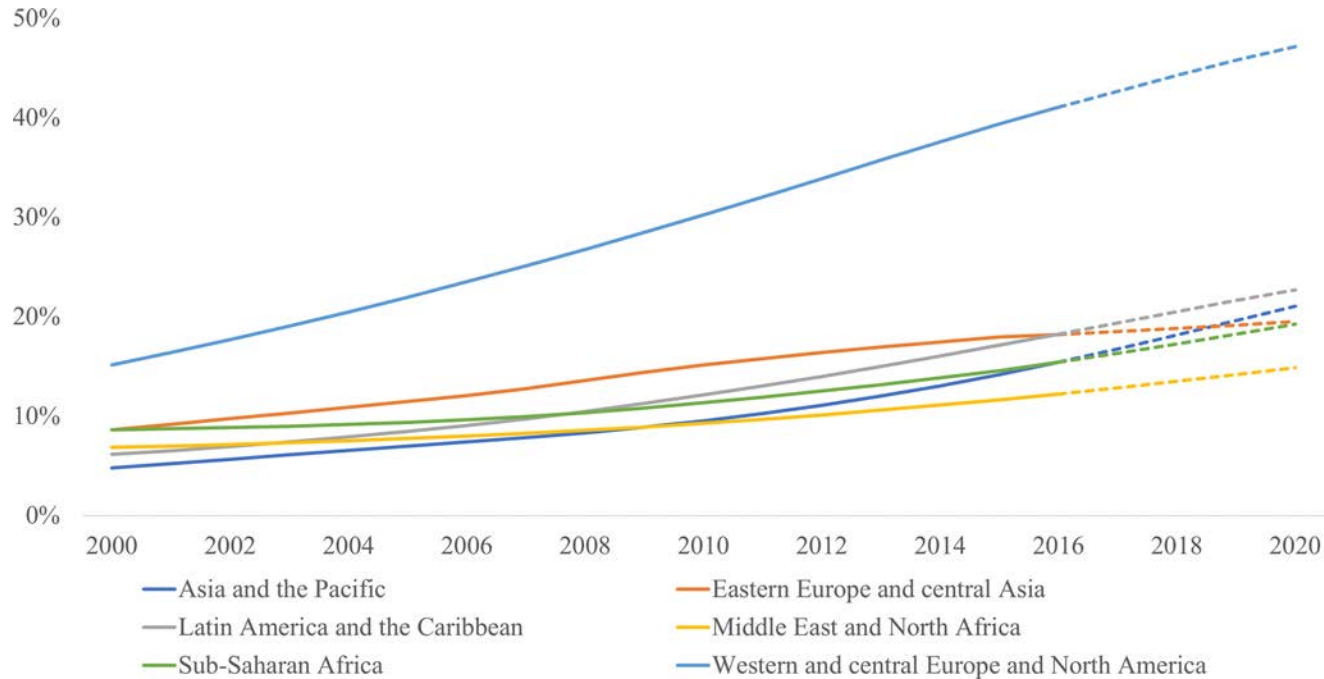
Time since ART initiation (years): 0-9 10-19 20-29 30+



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Journal of the International AIDS Society, Volume: 25, Issue: S4, First published: 29 September 2022, DOI: (10.1002/jia2.25986)

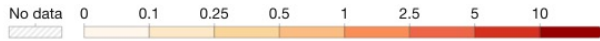
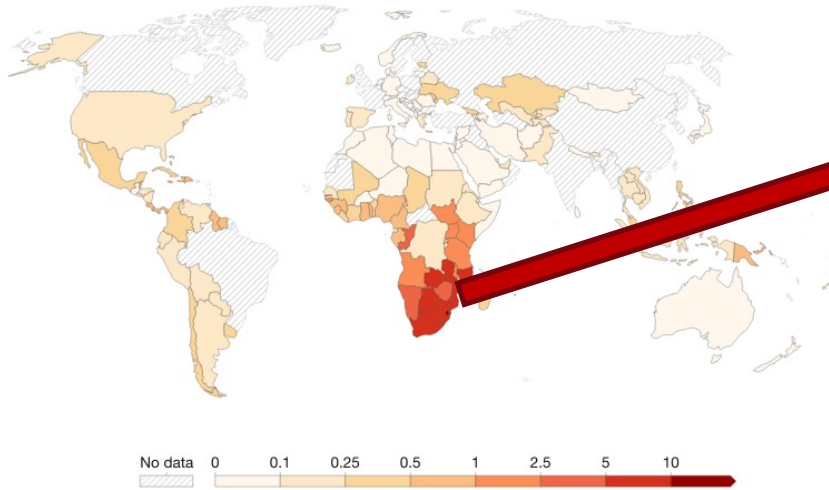
The proportion of PWH ≥ 50 years old is increasing globally



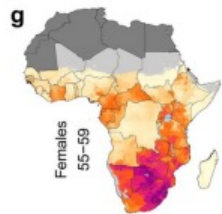
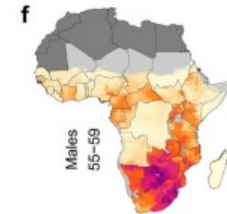
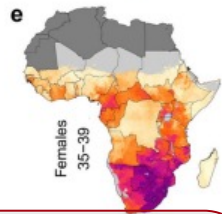
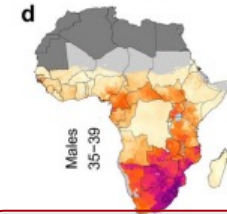
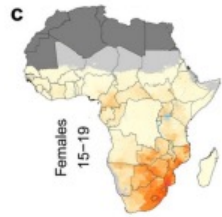
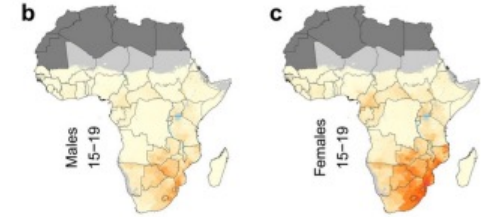
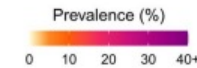
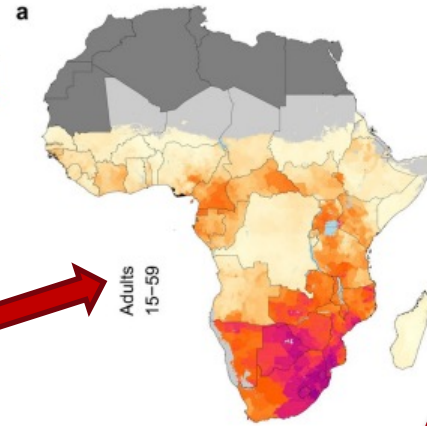
Growing prevalence of older adults with HIV in Sub-Saharan Africa

Incidence of HIV, 2020

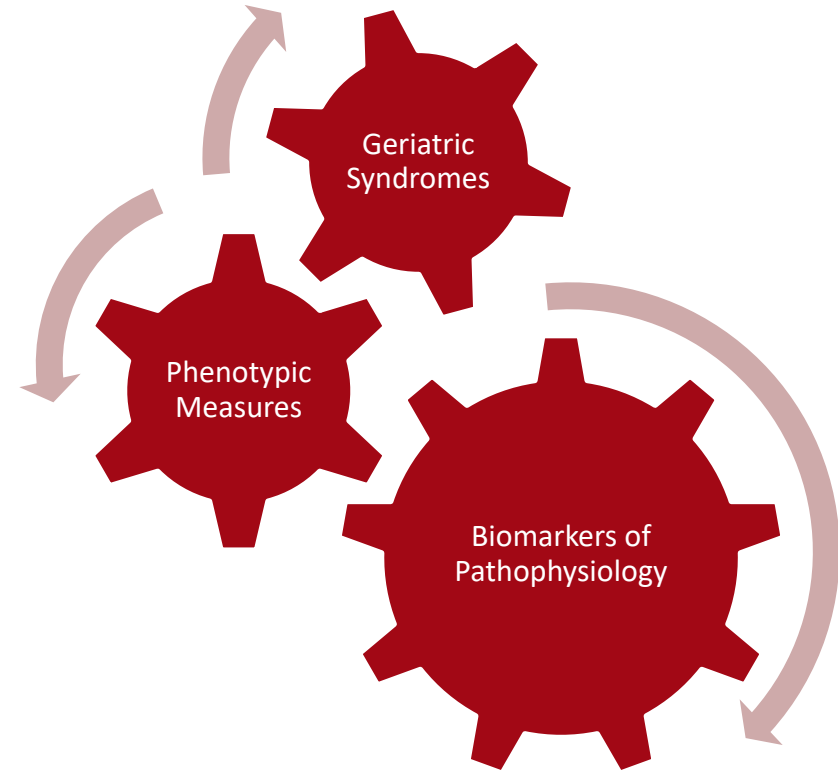
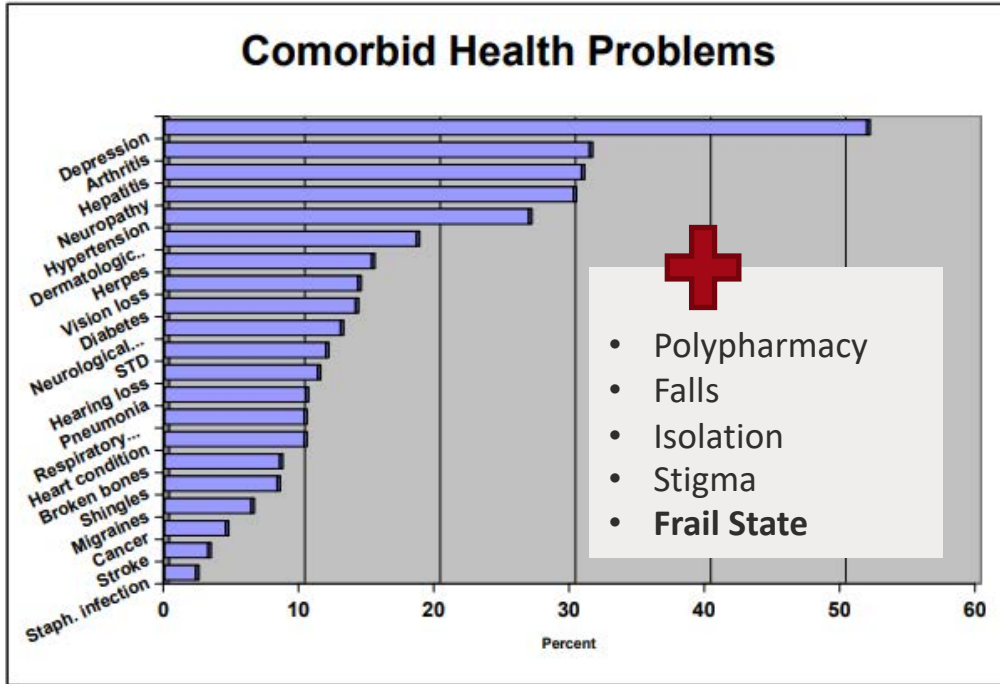
Number of new HIV infections among the uninfected population ages 15-49 expressed per 1,000 uninfected population in the year before.



Our World in Data



Increased Non-Communicable Diseases in PWH





Epidemiology



Biology of Aging



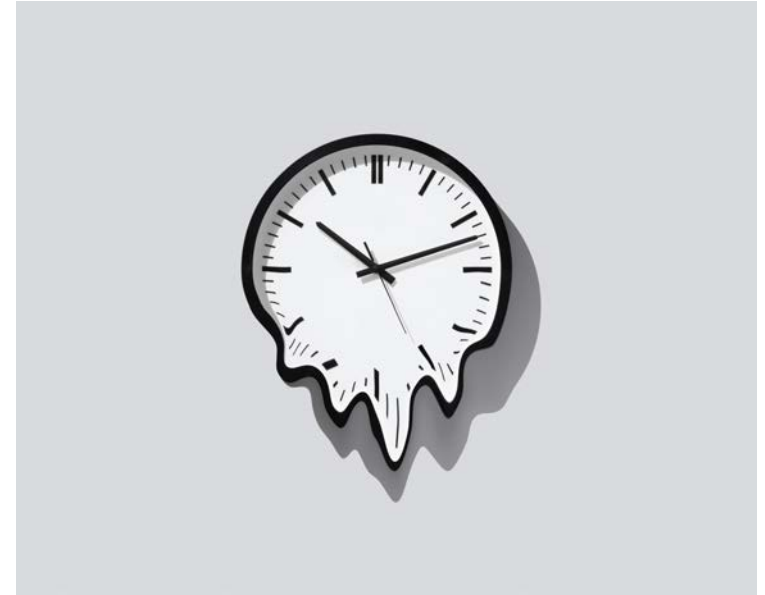
Advances in HIV
Geroscience



Care and Research for
Older Adults with HIV



Environment and genes influence how we develop and how we age



Lopez-Otin, et al. The Hallmarks of Aging. Cell, 2013 Jun; 153(6) 1194-1217

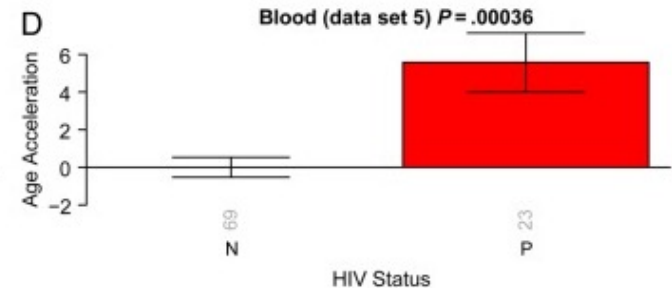
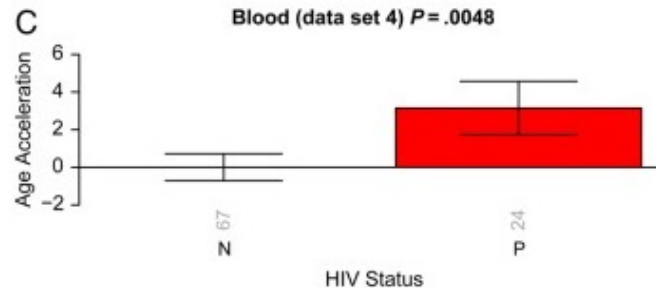
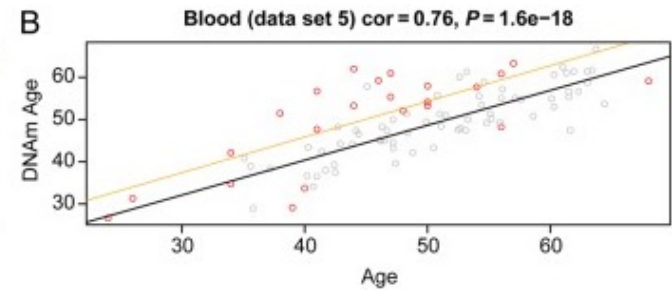
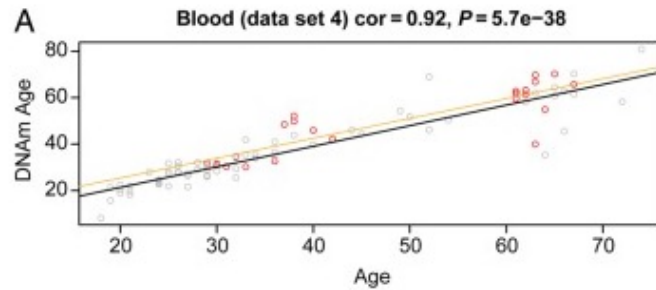
Epigenetic Aging in PWH

- People with HIV (PWH) are more likely to experience medical co-morbidities and geriatric syndromes including frailty
- **Epigenetic changes to DNA by different patterns of methylation have been associated with aging**
- **People with HIV have been demonstrated to have advancement of epigenetic-based age calculation compared to chronologic age**
- **Early and/or untreated HIV advances epigenetic age, and ART attenuates age advancement**

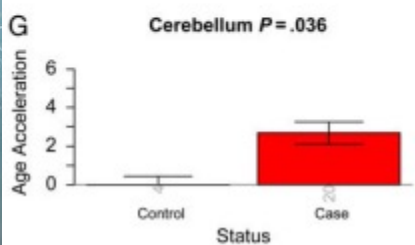
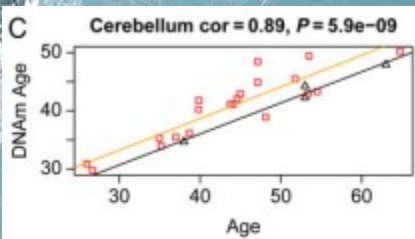
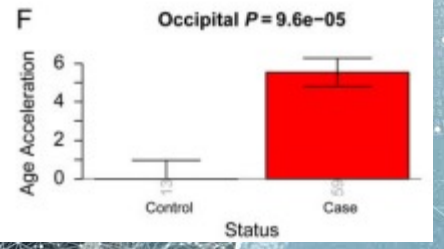
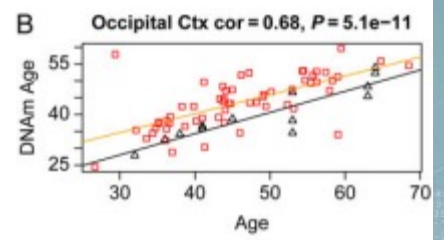
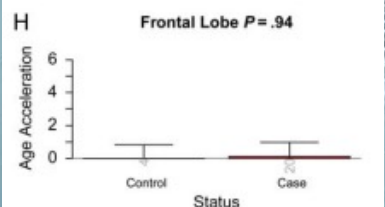
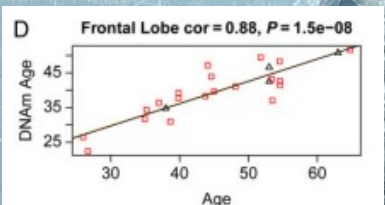
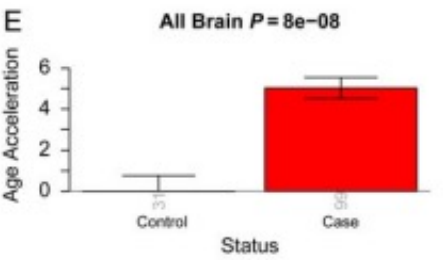
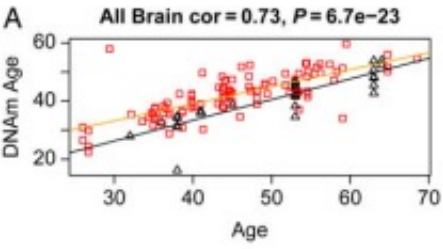
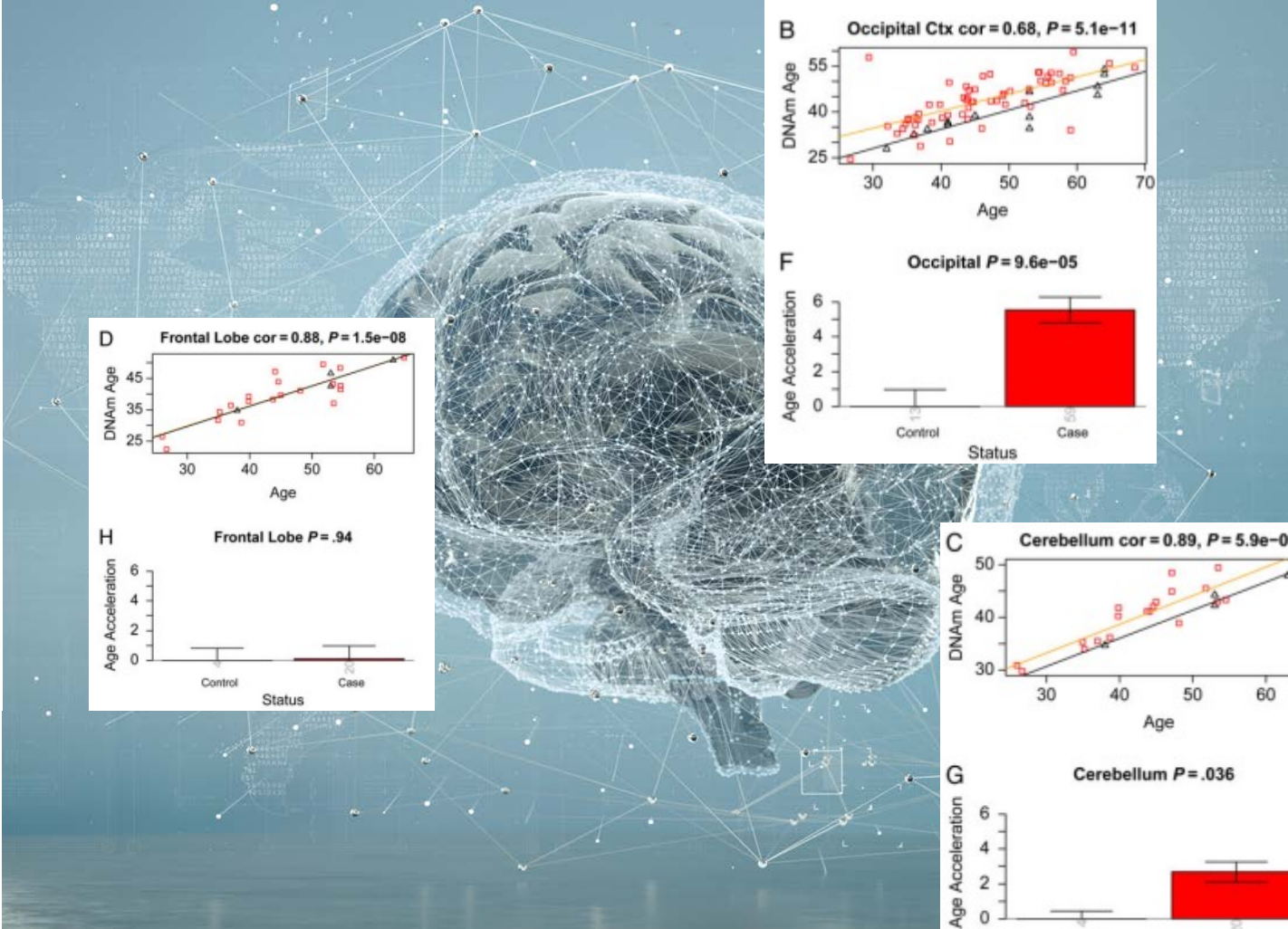
Epigenetic Clocks by Generation and Features		
Clock Generation	Clock Name	Features
1 st Generation	Hannum	Whole blood clock, gives epigenetic age
	Horvath 1 & 2	Pan-tissue clock, gives epigenetic age
2 nd Generation	PhenoAge	Phenotypic function age in relation to aging outcomes and mortality
	GrimAge	Mortality risk: increased GrimAge acceleration 2x as likely to die
3 rd Generation	Dunedin Pace of Aging	Determines accelerated or slowed aging rate. Accelerated aging has higher risk of chronic disease and death. Decelerated aging with better performance on balance, strength, and gait
	DamAge	Epigenetic measure of DNA damage, associated with adverse outcomes and mortality
	AdaptAge	Epigenetic measure of DNA adaptation, associated with beneficial adaptations
DNAm Biomarker Proxy	DNAm estimation of telomere length	Epigenetic estimation of telomere length



HIV Infection Accelerates Age According to the Epigenetic Clock



National NeuroAIDS Tissue Consortium



Sex differences in epigenetic ageing for older people living with HIV



Camie D. Johnston,^a Alina P. S. Pang,^a Eugenia L. Siegler,^b Charlene Thomas,^c Chelsie O. Burchett,^b Mia Crowley,^a Rochelle O'Brien,^a Lishomwa C. Ndhlovu,^a Marshall J. Glesby,^a and Michael J. Corley^{a,*}



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^cDepartment of Population Health Sciences, Weill Cornell Medicine, New York City, New York, USA

Summary

Background HIV-1 infection impacts biological ageing, and epigenetic clocks highlight epigenetic age acceleration in people with HIV. Despite evidence indicating sex differences in clinical, immunological, and virological measures, females have been underrepresented in most HIV epigenetic studies. Hence, we generated a more representative epigenetic dataset to examine sex differences in epigenetic ageing and relationships to clinical phenotypes and proteomics.

eBioMedicine

2025;113: 105588

Published Online xxx

<https://doi.org/10.1016/j.ebiom.2025.105588>

****CROI Poster #612
(Monday 2pm Session)**

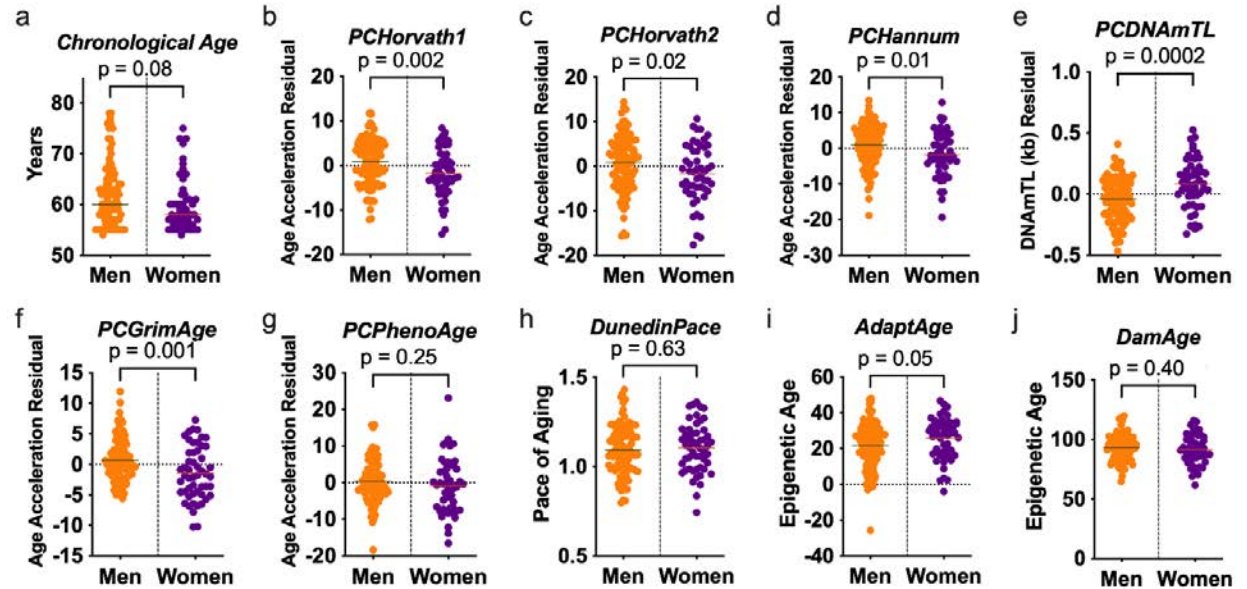


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Sex Differences in Epigenetic Aging

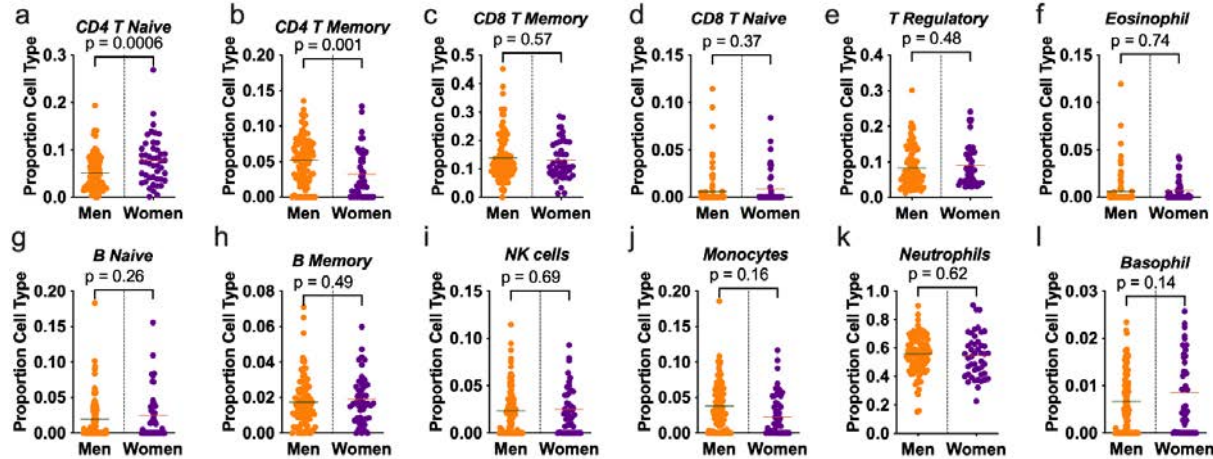
Epigenetic Age Acceleration in Males (n=103) and Females (n=46) with HIV. a-j show chronological age, epigenetic age residuals, pace of aging estimates, and causality-enriched epigenetic age of males (orange) and females (purple).

The mean epigenetic age acceleration residual for chronological epigenetic age clocks was significantly lower in females living with HIV compared to males living with HIV



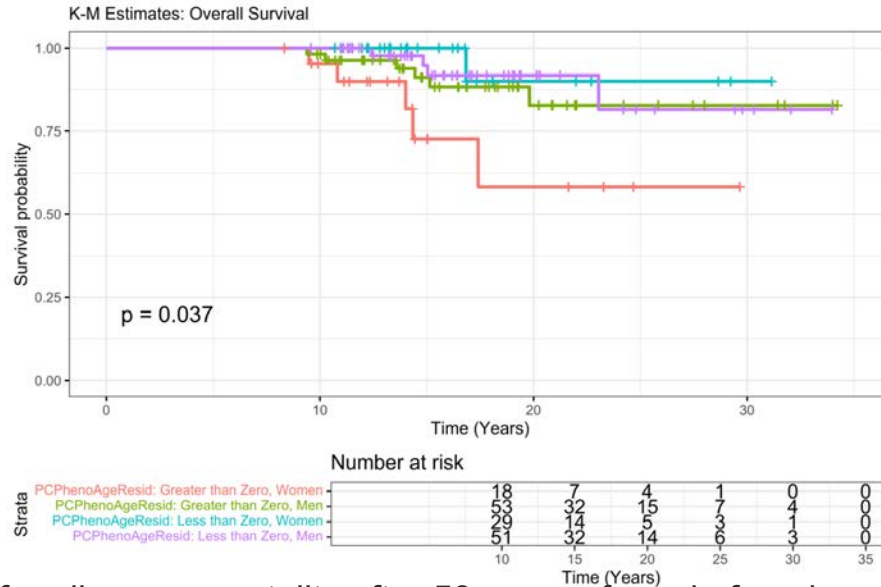
Johnston, C, Pang A, Sigler E, Thomas C, Burchett C, Crowley M, O'Brien R, Ndhlovu L, Glesby M, Corley M. Sex Differences in Epigenetic Aging for Older People Living with HIV. Feb. 2025. eBioMed. 113: 105588

Higher proportion of naïve CD4 T cells and lower memory CD4 T cells in women



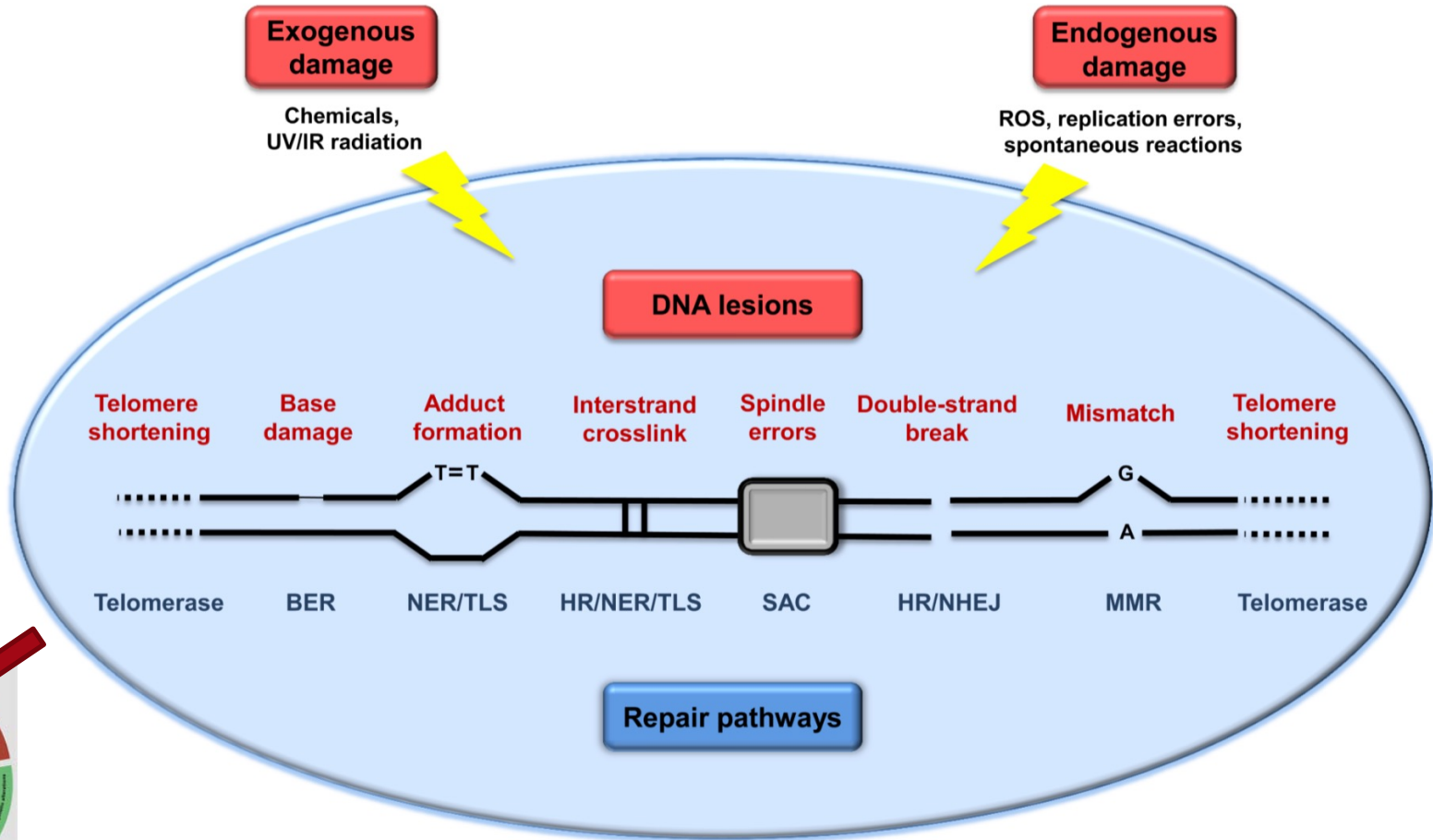
Proportional differences in CD4 T Memory and Naïve Cells in males (n=103) and females (n=46) with HIV. We found significant differences in the relative abundance of CD4 T memory and naïve cells with females having a lower abundance of CD4 T memory cells (3.2 vs. 5.2 percent of leukocytes, $p < 0.01$) and greater abundance of CD4 T naïve cells (7.7 vs. 5.1 percent of leukocytes, $p < 0.01$) as compared to males

Women with epigenetic age acceleration demonstrated the lowest 5-yr survival

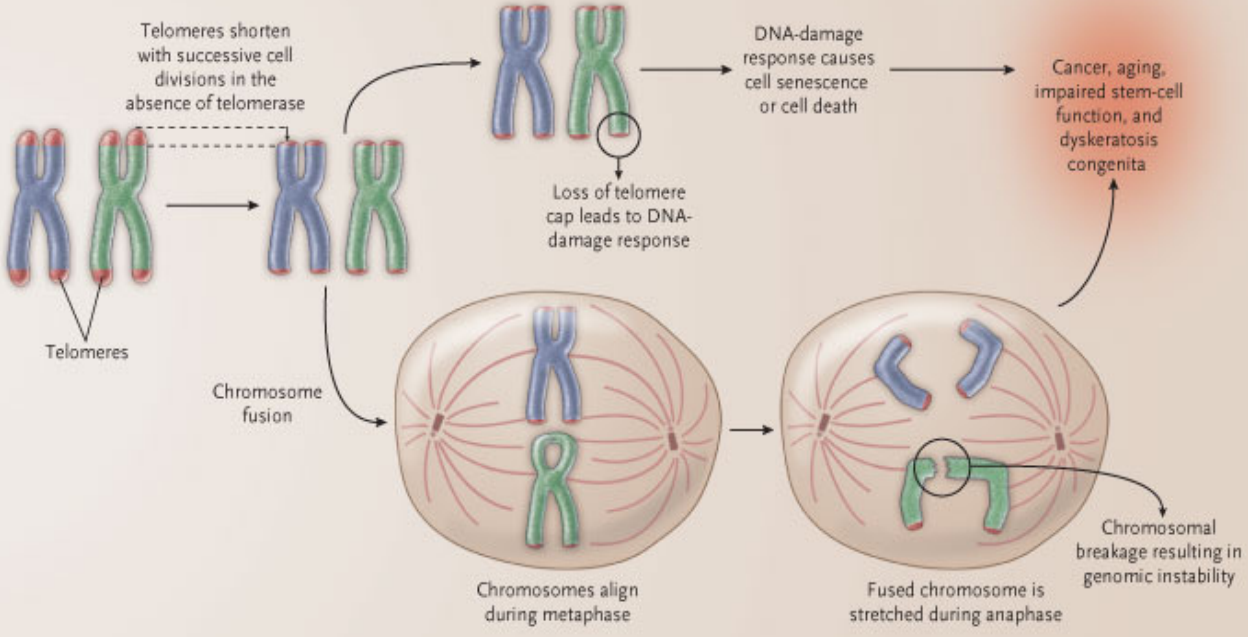


Kaplan-Meier curves for all-cause mortality after 50 years of age in females and males stratified by accelerated and decelerated epigenetic aging. p-value displayed is log-rank test

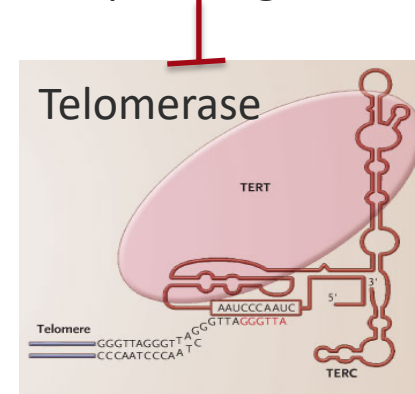
Genomic instability has endogenous and exogenous sources



Telomere attrition can lead to DNA damage



Tenofovir pro-drugs



* mean TL in people with HIV markedly shorter by 27 kbp/genome ($p < 0.001$)

* *Lower CD4 nadir, smoking, longer time with HIV associated with shorter TL*



Cellular Senescence



Ageing

Pro-Survival Signals

Pro-Apoptotic Signals

Senolytics

Compounds	Target
Dasatinib	Tyrosine Kinases
Navitoclax	BCL-2 Family
Quercetin	Tyrosine Kinases
17-DMAG	HSP90
Gal-duocarmycin	SA-β-gal



Senescent Cell Accumulation

Senomorphics

Compounds	Target
Nutlin-3a	MDM2/p53
Ruxolitinib	JAK-STAT
MI-63	MDM2/p53
Apigenin	NF-κB

SASP Factors

IL6
IP10
VCAM1
IL7
ICAM1
HGF
VEGF
MCP1

SASP

(Senescence Associated Secretory Phenotype)

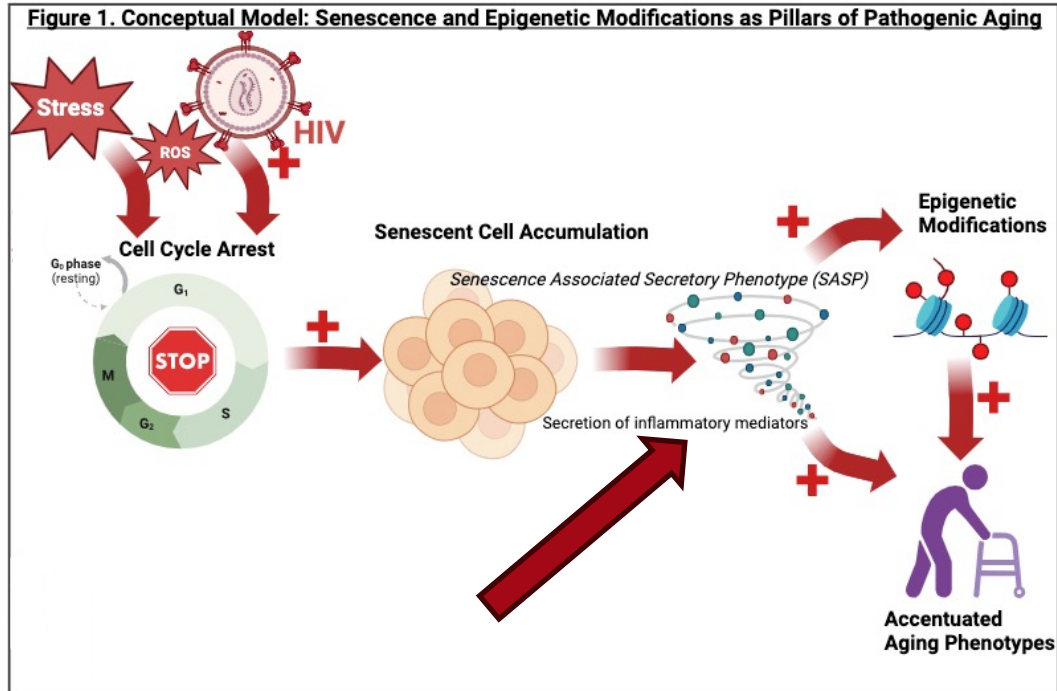
HIV promotes senescent T cell (CD28- CD45RA- CD8+) accumulation



Cellular Senescence Drives Aging

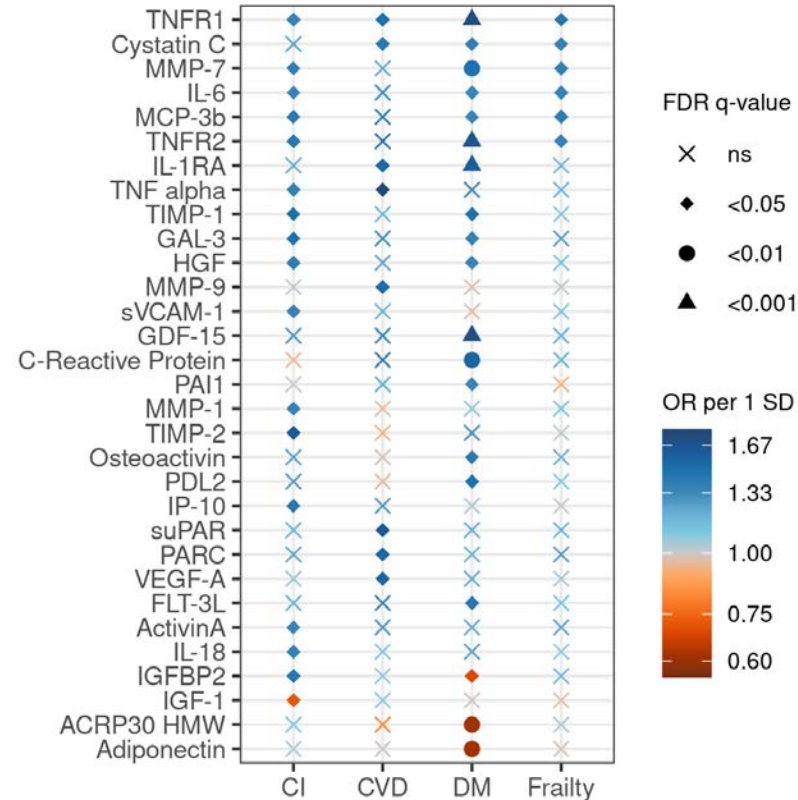
Cellular senescence is associated with age-related disease and has been a proposed mechanism in people with HIV who may experience accelerated aging.

Senescence-associated secretory phenotype:
pro-inflammatory signals secreted from senescent cells



HAILO Data: SASP associations with aging phenotypes

- N=450 participants, 59 (13%) met criteria for frailty, 104 (23%) CI, 94 (21%) DM, and 52 (12%) CVD at study entry. Participant ages: 36% were 40-49, 45% were 50-59, 19% were 60+; 78% were men
- Unique **SASP profiles exist in association with specific aging outcomes in PWH**, with some overlap between conditions.



Many Senolytic Trials Underway



Dasatinib: induces apoptosis in senescent cells by inhibiting the Src tyrosine kinase

Quercetin: inhibits the anti-apoptotic protein Bcl-xL



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Study title	Senolytic	Study design	Identifier	Status
Targeting pro-inflammatory cells in idiopathic pulmonary fibrosis: a human trial	D + Q	Phase 1, randomized, open-label	NCT02874989	Completed ⁴³
Senescence in chronic kidney disease	D + Q	Phase 2, randomized, open-label	NCT02848131	Current, preliminary report published ⁴⁴
Hematopoietic stem cell transplant survivors study (HTSS)	D + Q	Randomized, open-label	NCT02652052	Current
ALSENITE: senolytics for Alzheimer's disease	D + Q	Phase 1/2, open-label	NCT04785300	Current
Senolytic therapy to modulate the progression of Alzheimer's disease (StoMP-AD) study	D + Q	Phase 1/2, open-label, pilot study Phase 2, randomized, double-blind, placebo-controlled	NCT04063124 and NCT04685590	Current
Senolytics to improve cognition and mobility in older adults at risk of Alzheimer's disease	D + Q	Single-arm, open-label, pre-post pilot study	Pending	Pending
An open-label intervention trial to reduce senescence and improve frailty in adult survivors of childhood cancer	D + Q; F	Phase 2, randomized, open-label	NCT04733534	Current
Targeting cellular senescence with senolytics to improve skeletal health in older humans	D + Q; F	Phase 2, randomized, open-label	NCT04313634	Current
Quercetin in coronary artery by-pass surgery (Q-CABG)	Q	Phase 2, randomized double-blind, placebo-controlled	NCT04907253	Current
Use of senolytic and anti-fibrotic agents to improve the beneficial effect of bone marrow stem cells for osteoarthritis	F	Phase 1/2, randomized, double-blind, active-control	NCT04815902	Current
Senolytic drugs attenuate osteoarthritis-related articular cartilage degeneration: a clinical trial	F	Phase 1/2, randomized, double-blind, placebo-controlled	NCT04210986	Current
COVID-FISETIN: pilot in SARS-CoV-2 of fisetin to alleviate dysfunction and inflammation	F	Phase 2, randomized, double-blind, placebo-controlled	NCT04476953	Current
Alleviation by fisetin of frailty, inflammation and related measures in older women (AFFIRM)	F	Phase 2, randomized, double-blind, placebo-controlled	NCT03430037 and NCT03675724	Current
Inflammation and stem cells in diabetic and chronic kidney disease	F	Phase 2, randomized, double-blind, placebo-controlled	NCT03325322	Current
COVID-19 pilot study of fisetin to alleviate dysfunction and decrease complications (COVFIS-HOME)	F	Phase 2, randomized, double-blind, placebo-controlled	NCT04771611	Current
Pilot in COVID-19 (SARS-CoV-2) of fisetin in older adults in nursing homes (COVID-FIS)	F	Phase 2, randomized, double-blind, placebo-controlled	NCT04537299	Current
Targeting senescence to reduce osteoarthritis pain and cartilage breakdown (ROPE)	F	Phase 1/2, randomized, double-blind, placebo-controlled	NCT04770064	Current
Senolytic agent improve the benefit of platelet-rich plasma and losartan	F	Phase 1/2, randomized, double-blind, placebo-controlled	NCT05025956	Current
Safety and tolerability and long-term follow-up studies of patients with osteoarthritis of the knee treated with UBX0101 or placebo	UBX0101 (nutlin-3a or related)	Phase 2, randomized, double-blind, placebo-controlled	NCT03513016 and NCT04349956	Completed; failed to achieve primary endpoint
A study to assess the safety and efficacy of a single or repeat doses of UBX0101 in patients with osteoarthritis of the knee	UBX0101 (nutlin-3a or related)	Phase 1, randomized, double-blind, placebo-controlled Phase 2, randomized, double-blind, placebo-controlled	NCT04229225 and NCT04129944	Current
Safety and tolerability study of UBX1325 in patients with diabetic macular edema or neovascular age-related macular degeneration	UBX1325 (N or related)	Phase 1, open-label Phase 2, randomized, double-blind, sham-controlled	NCT04537884 and NCT04857996	Current

D + Q, dasatinib and quercetin; F, fisetin; N, navitoclax; Q, quercetin.

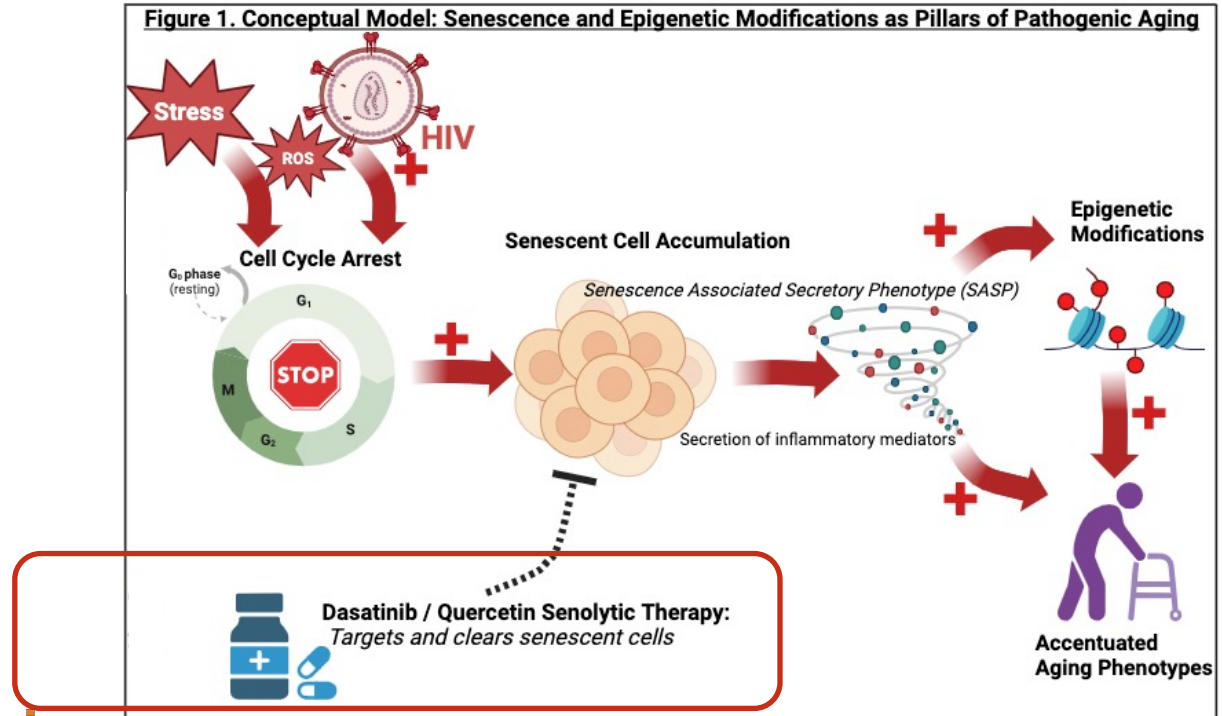
Drugs to target senescence in PWH

ACTG 5426 (iPACE)

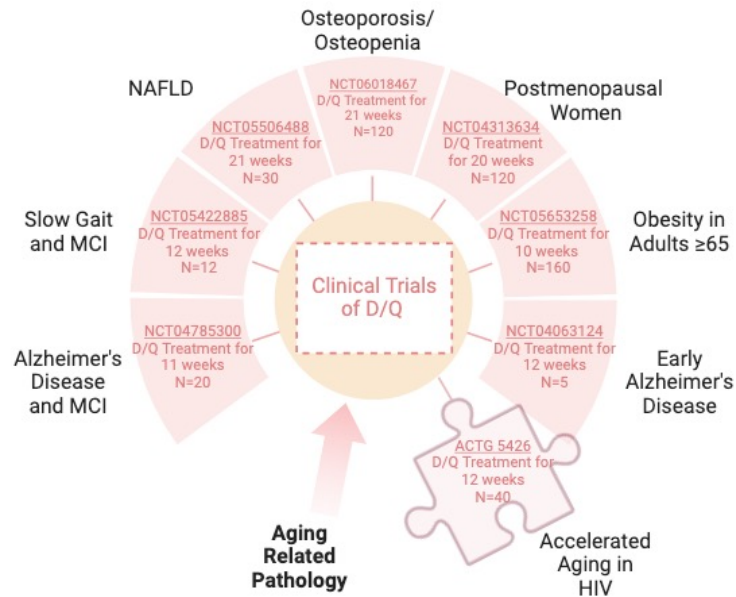
Improving Physical Ability and Cellular Senescence Elimination in HIV

Ho: In people with HIV (PWH) 50 years old or older with HIV for at least 10 years on combination antiretroviral therapy (ART), treatment with dasatinib and quercetin (D+Q) will be safe, tolerable, and improve physical function.

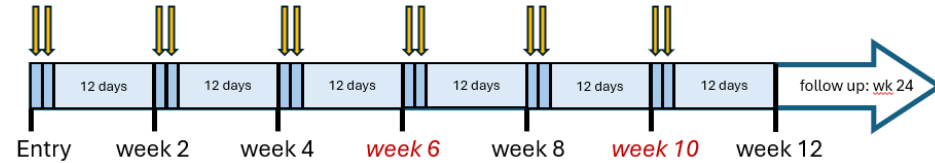
Figure 1. Conceptual Model: Senescence and Epigenetic Modifications as Pillars of Pathogenic Aging




Senescent cells can be targeted and cleared with senolytic pharmacotherapy



A5426 Dosing Schema



 = Administration of dasatinib 100mg/day plus quercetin 1250mg/day or matched placebos (1:1 randomization)
 No study visits at weeks 6 & 10

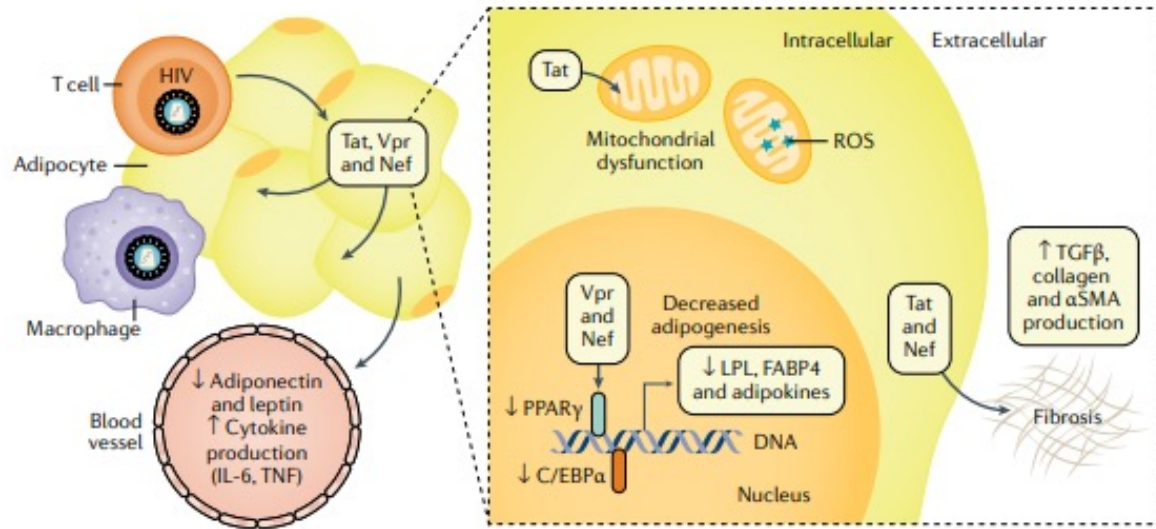
Dysregulated Nutrient Sensing & Metabolism

•The cause of age-related change in adipose tissue is complicated, ranging from external factors and internal senescence.

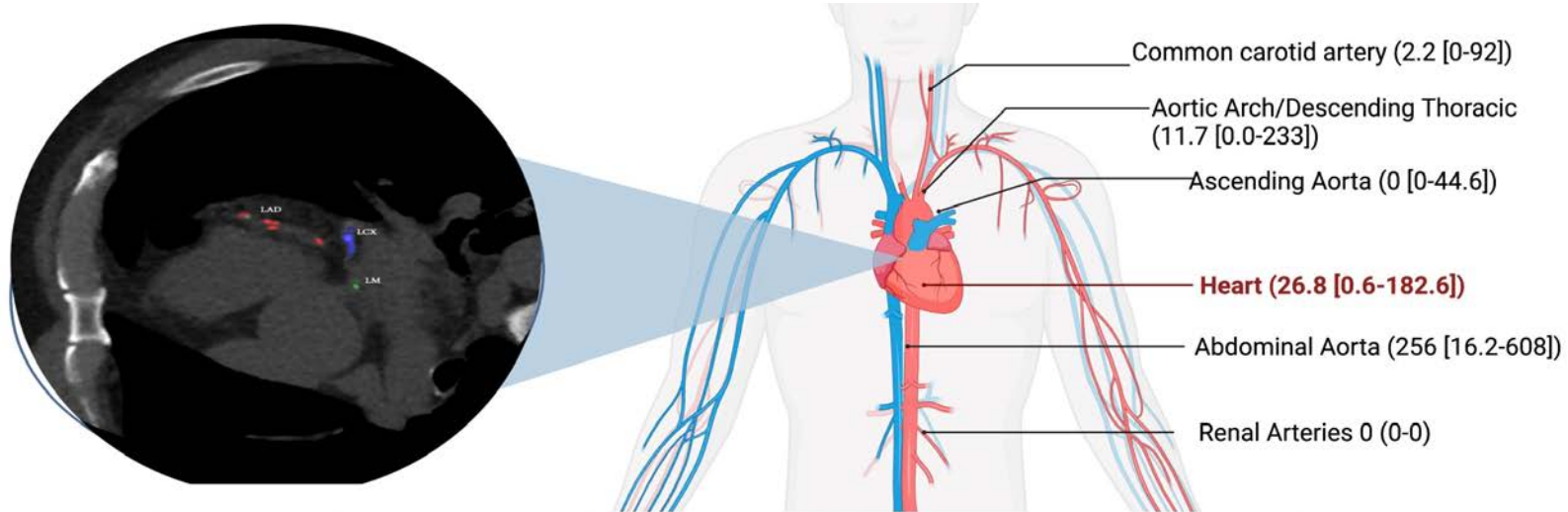
•Age-related adipose tissue alterations that accelerate the systemic aging process are promising therapeutic targets to prevent age-related disease.



The age-related redistribution of adipose tissue.



Research in Progress: Cardiometabolic study in PWH

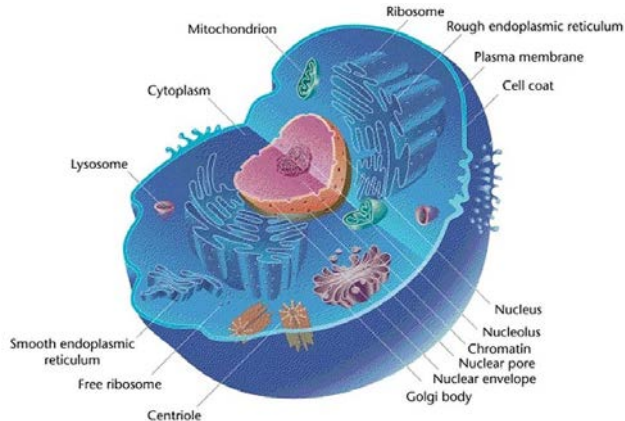


Legend: Anatomic locations of cardiac and non-cardiac vascular calcium scores from CT imaging studies displayed as median (Q1-Q3) and a representative cardiac CT image of severe burden of coronary artery calcification (Red= Left Anterior Descending, Blue= Left Circumflex, Green = Left Main coronary arteries)

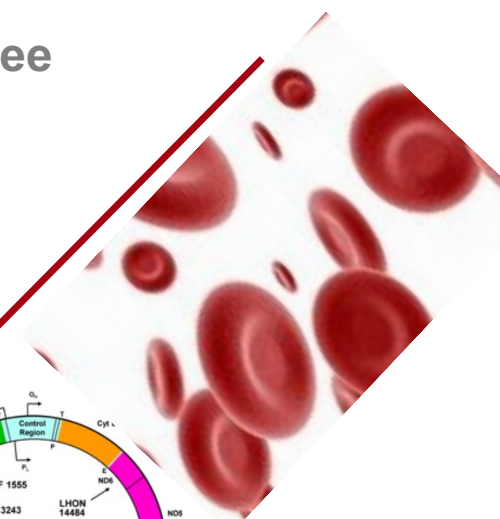
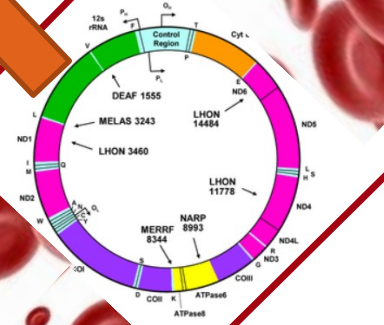
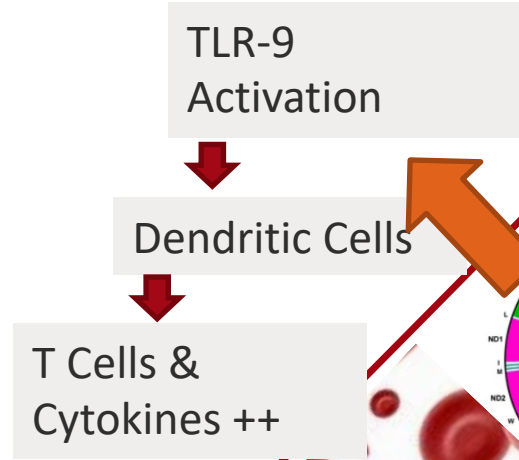


Mitochondria- Friend or Foe?

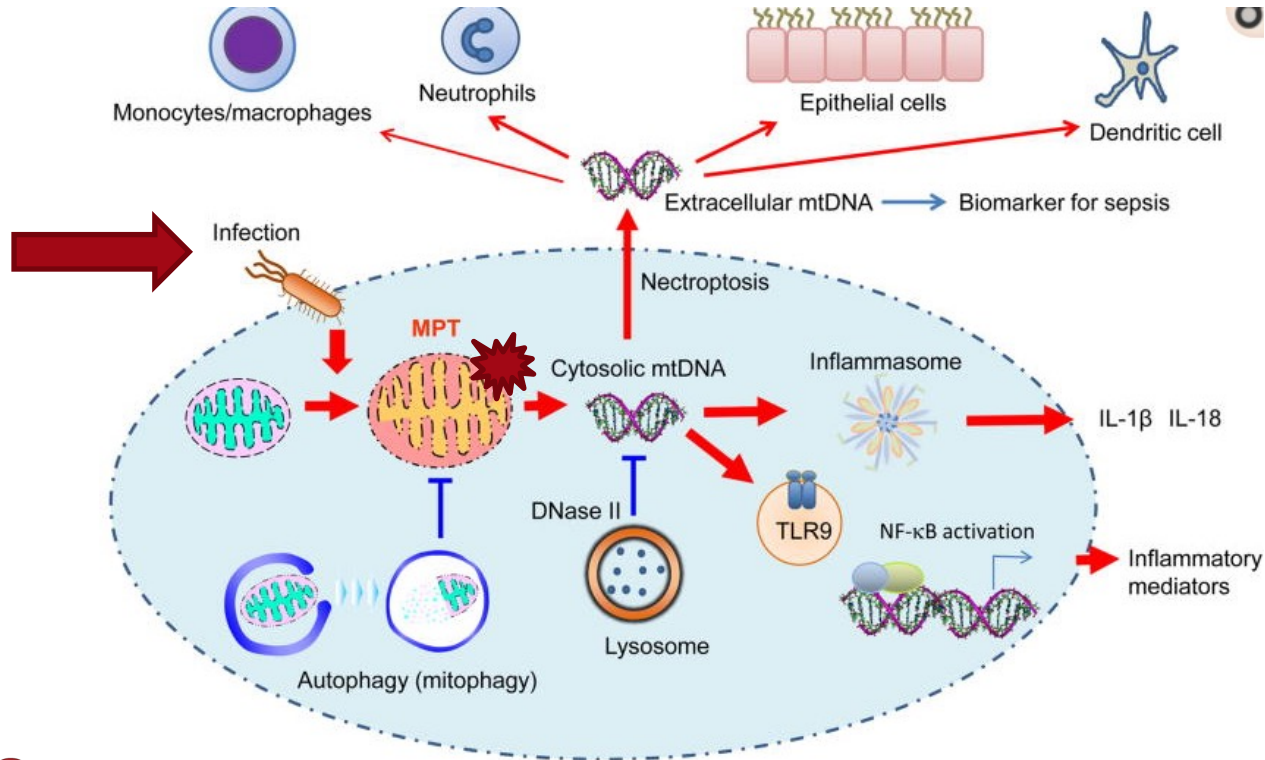
- Cell-Associated



- Cell-Free

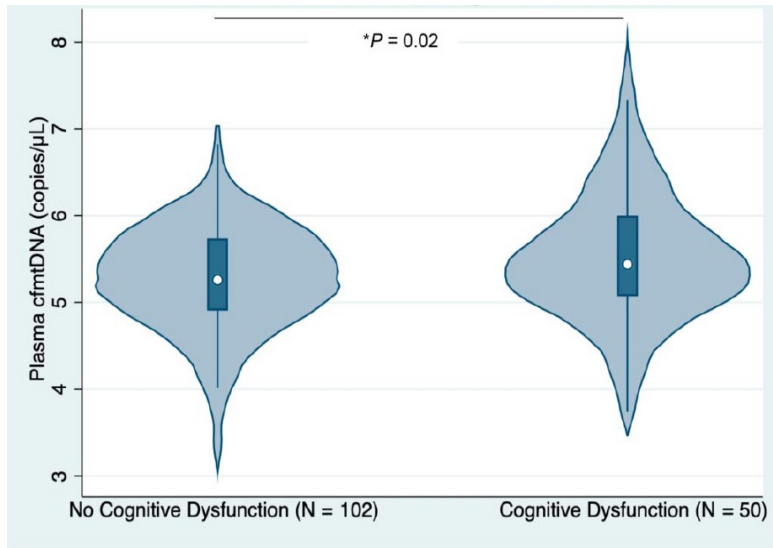


Mitochondrial DNA as a Mediator and Marker Inflammation

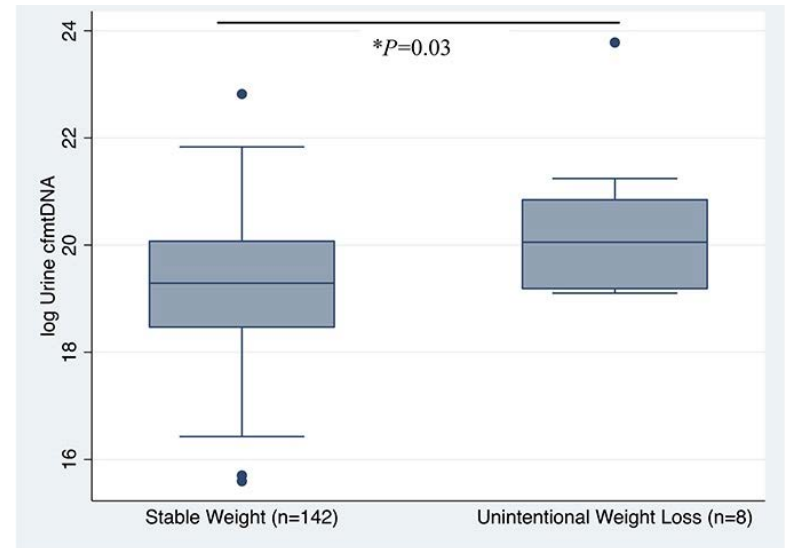


Cell-Free Mitochondrial DNA Measurement in Older Adults with HIV

Plasma cfmtDNA levels by cognitive dysfunction



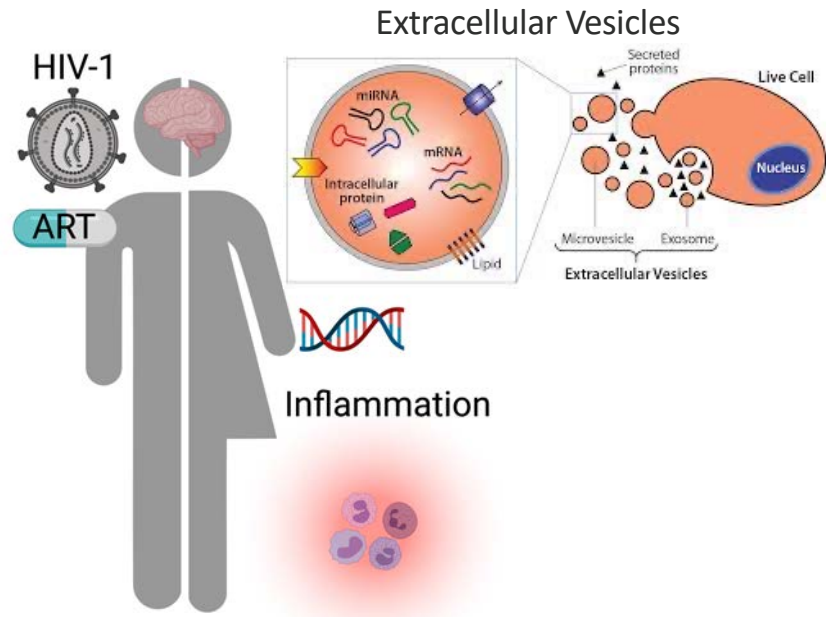
Urine cfmtDNA levels by unintentional weight loss



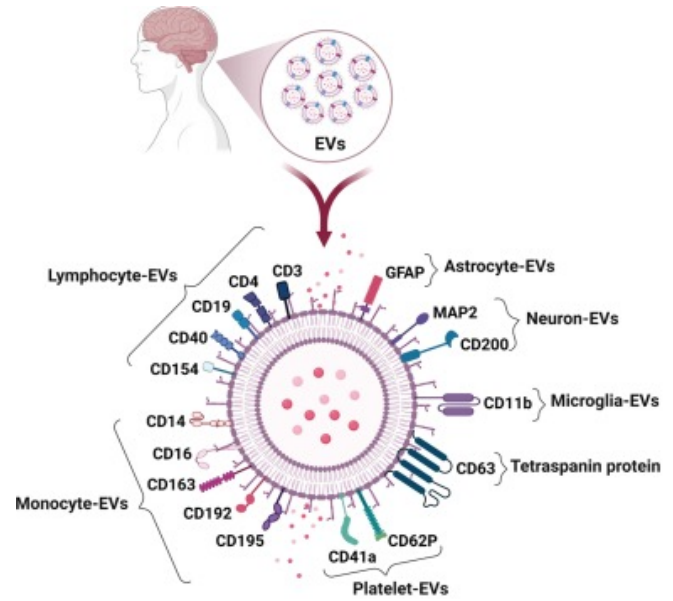
Johnston CD, Siegler EL, Rice MC, Derry-Vick HM, Hootman KC, Zhu YS, Burchett CO, Choi ME, Glesby MJ. Plasma Cell-Free Mitochondrial DNA as a Marker of Geriatric Syndromes in Older Adults with HIV. *JAIDS*. 2022 Apr 26

Johnston CD, Siegler EL, Rice MC, Derry-Vick HM, Hootman KC, Zhu YS, Burchett CO, Gupta SK, Choi ME, Glesby MJ. Urine Cell-Free Mitochondrial DNA as a Marker of Weight Loss and Body Composition in Older Adults with HIV. *JAIDS* 88(3) 2021

Extracellular vesicles play a key role in cell-to-cell communication



EVs expressing monocyte activation and neuronal markers associated with HIV-related cognitive impairment





Epidemiology



Biology of Aging



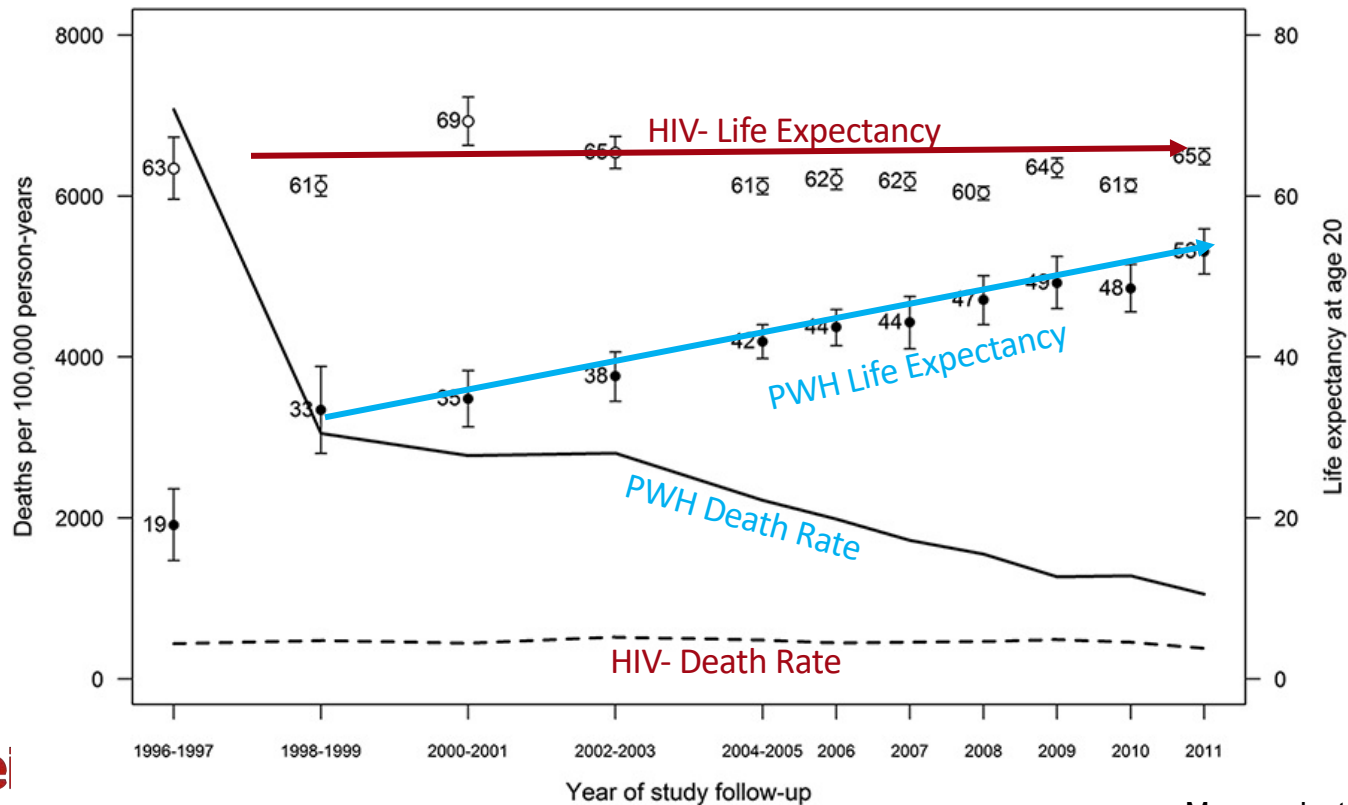
Advances in HIV
Geroscience



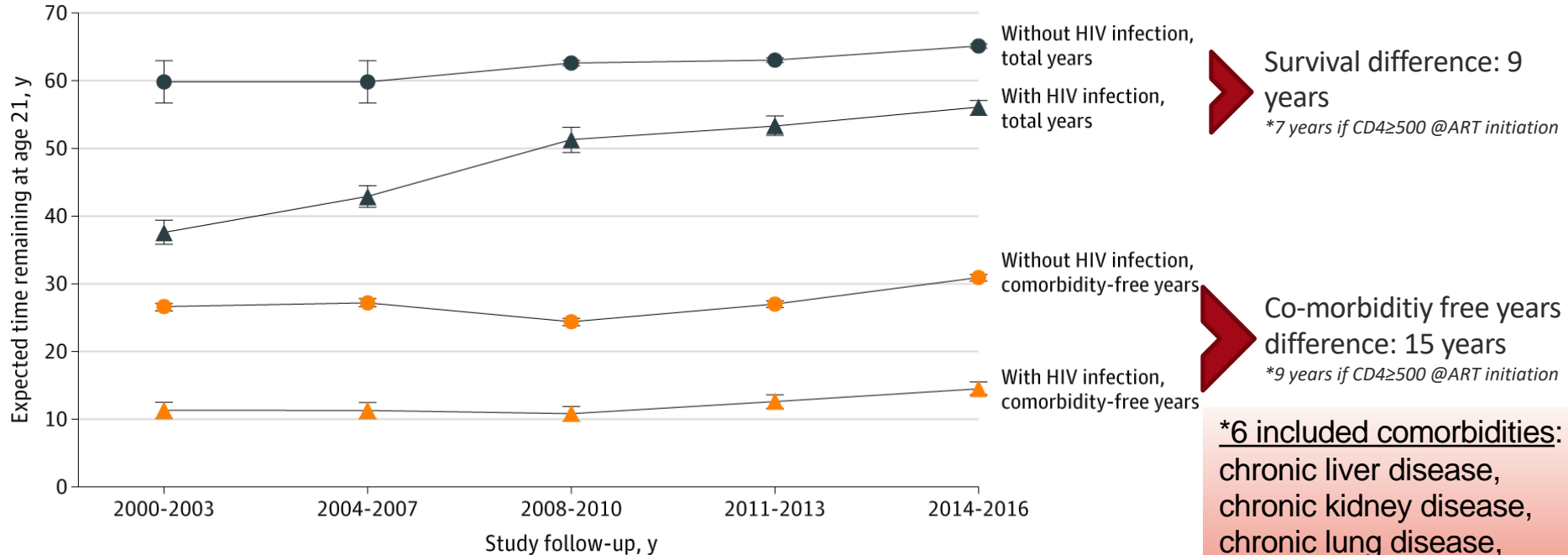
Care and Research for
Older Adults with HIV



Life Expectancy Differs for Adults with HIV



Overall, Mortality Gap Persists in Modern Era

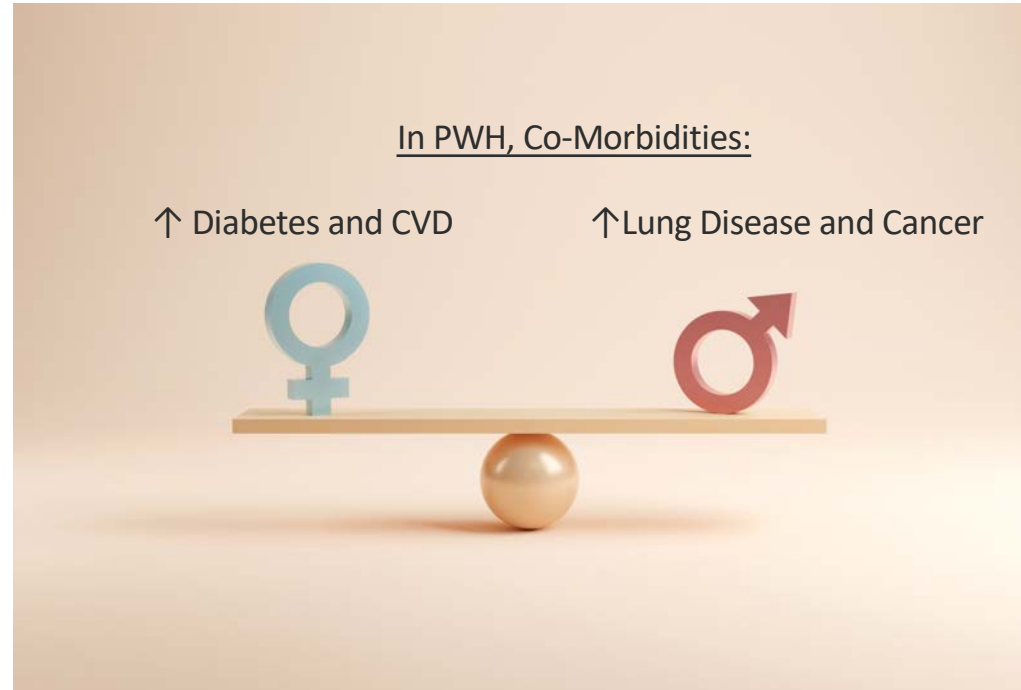


*6 included comorbidities:
chronic liver disease,
chronic kidney disease,
chronic lung disease,
diabetes, cancer, or
cardiovascular disease.



*Women may age differently

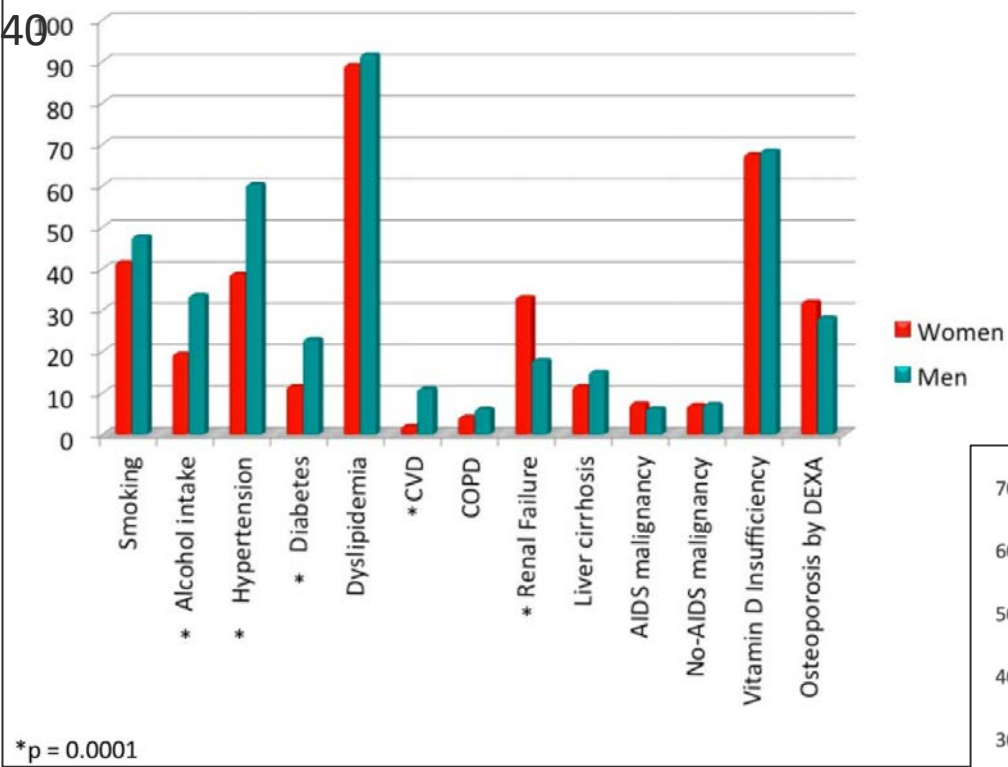
- Overall mortality difference for women is higher (12 years) compared to men (9 years)
- However, less dramatic difference in co-morbidity free years (13 years vs 16 years)



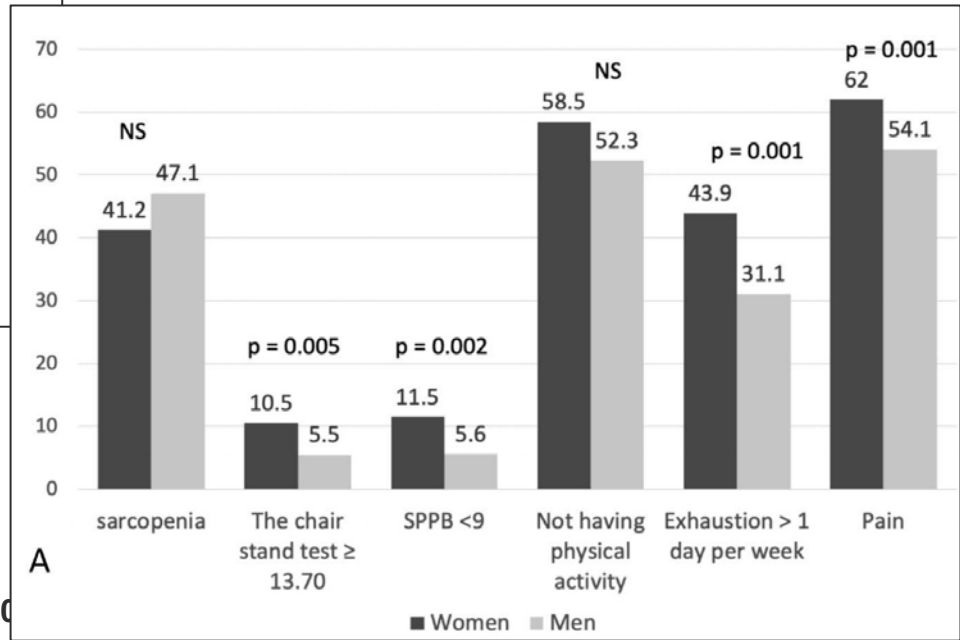
? Metabolic Differences – Effect of Menopause, Weight Gain

? Gender Non-Binary Individuals





Women with HIV may age differently from men with HIV



Brañas F, Sánchez-Conde M, Carli F, et al. Sex Differences in People Aging With HIV. *J Acquir Immune Defic Syndr.* 2020;83(3):284-291. doi:10.1097/QAI.0000000000002259

Aging increases the risk of geriatric (aging-related) syndromes like frailty



Frailty is not disability



Frailty is a state of vulnerability



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HIV increases the risk of frailty progression

RF	OR Non-frail to frail (95% CI)
Lower age (5 yr decrease)	0.93 (0.87, 0.98)
HIV positive	1.23 (1.03, 1.47)
No hazardous ETOH	0.82 (0.68, 0.99)
No depression	0.61 (0.51, 0.73)
Recent IDU	0.83 (0.69, 0.99)

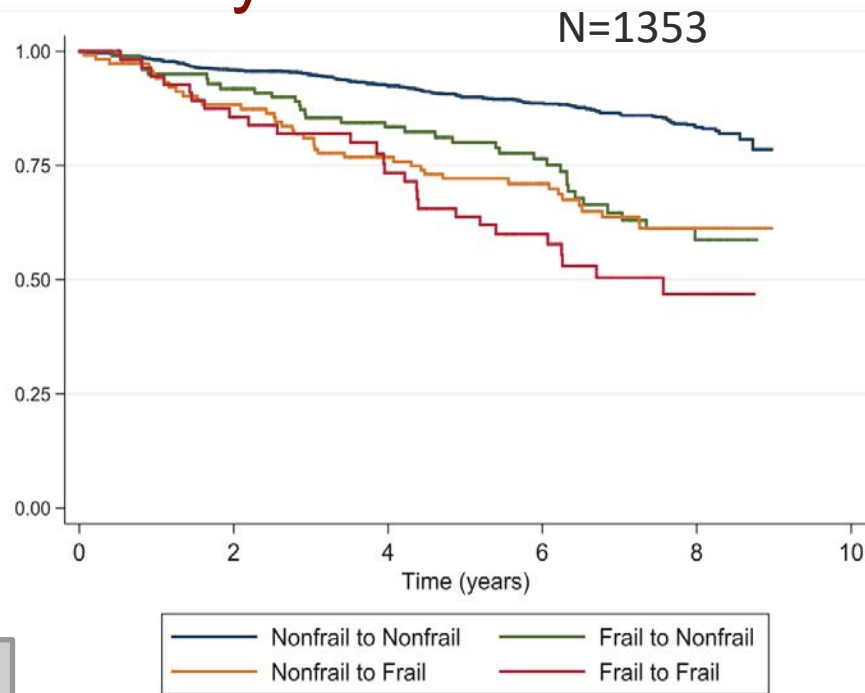
Also increasing risk: unemployment, < high school education, 3+ comorbidities

Also reducing risk: VL UD, nadir >500, no AIDS



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Being persistently frail confers the highest mortality rate





Epidemiology



Biology of Aging



Advances in HIV
Geroscience



Care and Research for
Older Adults with HIV



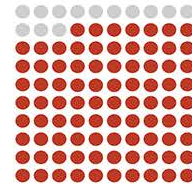
Weill Cornell Medicine

HIV in the US by Age, 2019*



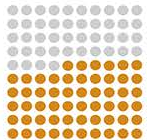
In 2019, an estimated **1,189,700 PEOPLE** had HIV.

For every 100 people with HIV



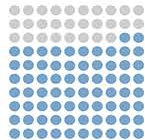
87
knew their
HIV status.

For every 100 people
with HIV aged 13 to 24



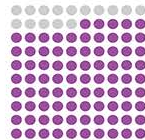
56
knew their
HIV status.

For every 100 people
with HIV aged 25 to 34



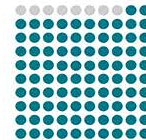
72
knew their
HIV status.

For every 100 people
with HIV aged 35 to 44



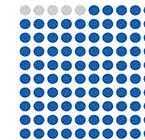
85
knew their
HIV status.

For every 100 people
with HIV aged 45 to 54



92
knew their
HIV status.

For every 100 people
with HIV aged 55 and older



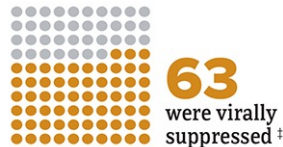
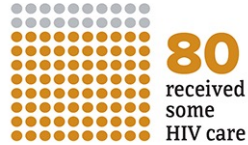
95
knew their
HIV status.

* Data not available for children aged 12 and under.

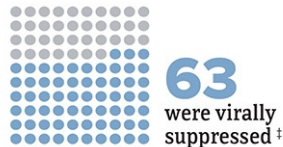
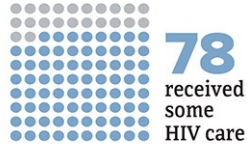
Source: CDC Estimated HIV incidence and prevalence in the United States, 2015–2019. *HIV Surveillance Supplemental Report* 2021;26(1).

People with Diagnosed HIV in 44 States and the District of Columbia by Age, 2019*

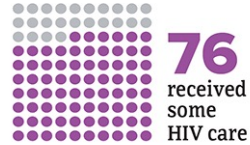
For every 100 people with diagnosed HIV aged 13 to 24:



For every 100 people with diagnosed HIV aged 25 to 34:



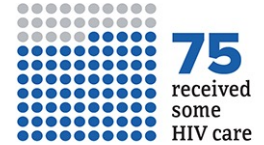
For every 100 people with diagnosed HIV aged 35 to 44:



For every 100 people with diagnosed HIV aged 45 to 54:



For every 100 people with diagnosed HIV aged 55 and older:



For comparison, for every **100 people overall** with diagnosed HIV, **76 received some care**, **58 were retained in care**, and **66 were virally suppressed**.

* Data not available for children aged 12 and under.

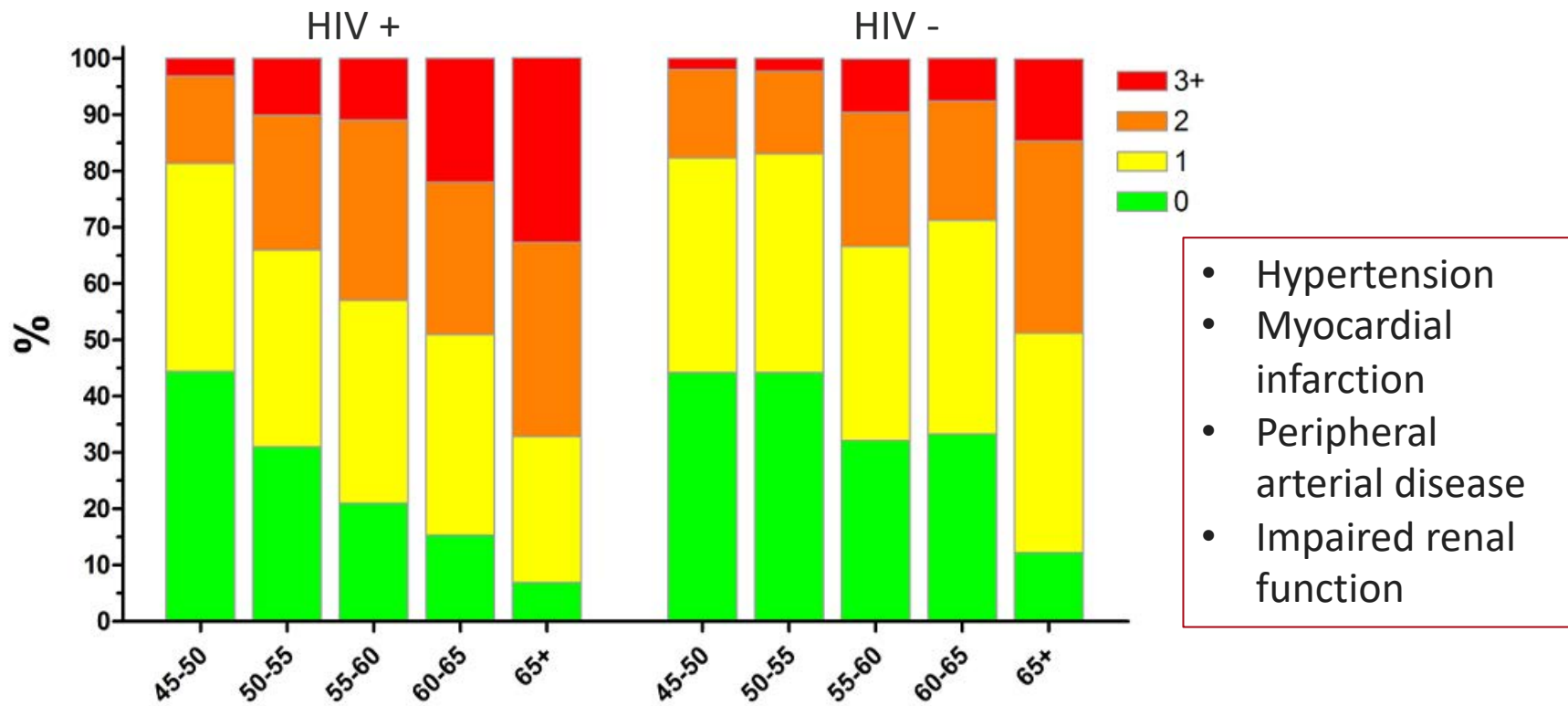
† Had 2 viral load or CD4 tests at least 3 months apart in a year.

‡ Based on most recent viral load test.

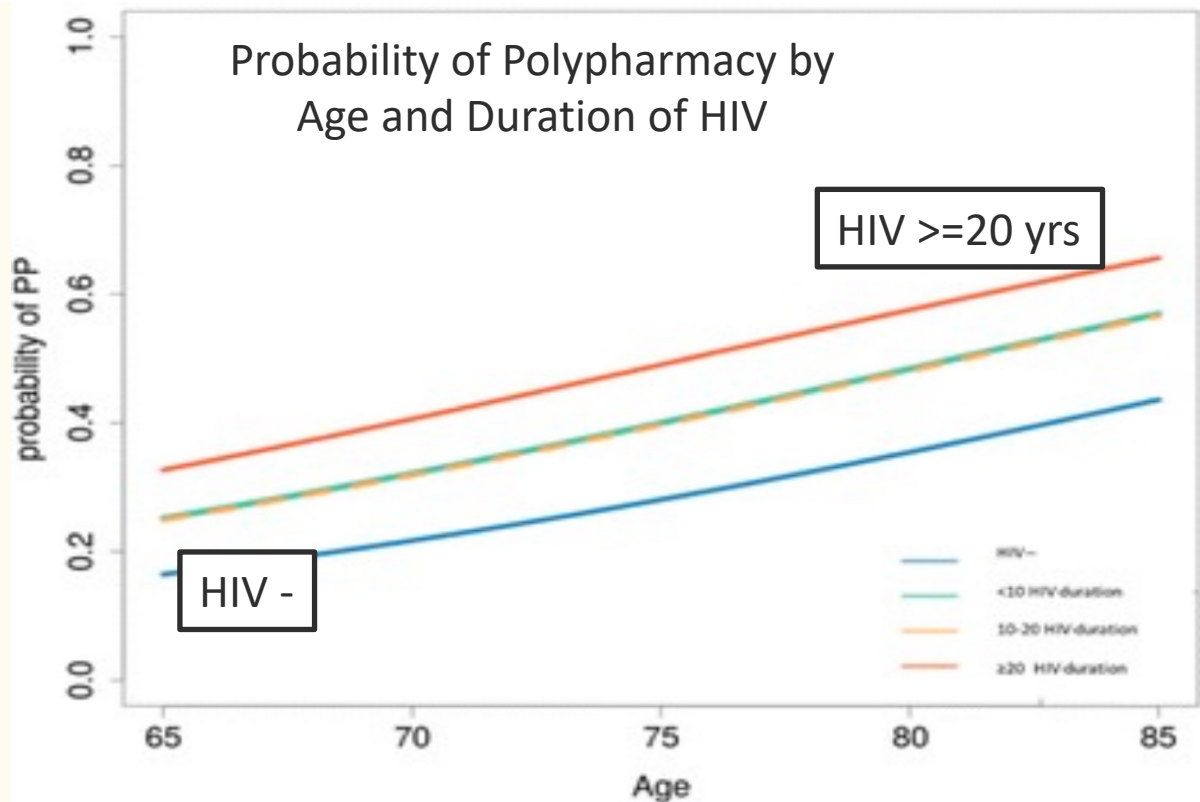
Goal: 90-90-90



Multimorbidity in Older Adults with HIV



Multimorbidity \leftrightarrow Polypharmacy



*The use of multiple medications does not necessarily indicate poor prescribing but rather may merely be an indicator of multimorbidity

Are Older Adults included in HIV Rx Trials?



“Major reasons for the underrepresentation of elderly patients in drug trials are **the use of arbitrary age limits and exclusion criteria for conditions highly prevalent in the elderly.**”

Approved ART: 2025

nucleoside/tide RTIs (NRTIs)

- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs

- nevirapine (NVP)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)
- doravirine (DOR)

protease inhibitors (PIs)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

Capsid Inhibitor (CI)

- lenacapavir



entry inhibitors (EIs)

- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhibitor)
- fostemsavir (FTR, CD4 attachment inhibitor)

integrase inhibitors (IIs)

- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)



Inclusion of Older Adults Increases External Validity

Lenacapavir

- **CAPELLA Trial**
- Median age 52 (range 23-78)
- Exclusion criteria: OI, TB, HBV, HCV, chemotherapy, malignancy, abnormal EKG, substance use, CrCl <60, certain statins

Cabotegravir-Rilpivirine

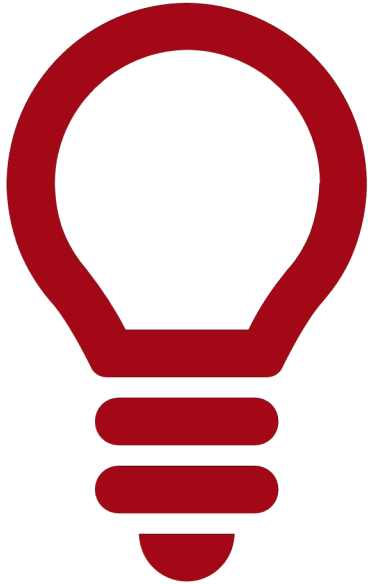
- **FLAIR Trial**
- Median age 34 (range 18-68)
- Exclusion criteria: CVD, HBV, +RPR, malignancy, NNRTI resistance (K103N allowed), II resistance, CrCl <50

Segal-Maurer NEJM 2022;386:1793

Orkin NEJM 2020;382:1124, Swindells NEJM 2020;382:1112

Research Future Directions

To Improve the Health of Older Adults with HIV



Weill Cornell research projects examine HIV and Aging at many levels



Completed	In progress
<ul style="list-style-type: none"> • Characteristics of adult HIV+ patients undergoing geriatric evaluation; evaluation of impact of consultation • Focus group on stigma intersectionality 	<ul style="list-style-type: none"> • Using telehealth to address loneliness • NYS QIPS project to improve screening of LTS for functional needs • Impact of Social Determinants of Health on Aging with HIV
<ul style="list-style-type: none"> • Role of depression on stress biomarkers in older HIV+ • Impact of childhood sexual abuse on comorbidities and inflammation • Association of food insecurity with functional limitations 	<ul style="list-style-type: none"> • Association of social determinants of health on social engagement and generativity
<ul style="list-style-type: none"> • Plasma mitochondrial DNA is associated with cognitive dysfunction and key components of frailty • Association of urine mitochondrial DNA with weight loss and body composition • Association of microalbuminuria with prognostic indicators 	<ul style="list-style-type: none"> • Mitochondrial DNA and other biomarkers of aging, frailty and arterial disease • Relationship between CH and inflammaging, cognitive impairment and frailty in older HIV+ • Epigenetic Age Advancement

- Investigators**
- Marshall Glesby
 - Genie Siegler
 - Carrie Johnston
 - Michael Corley
 - Atami DeMain

 - Mark Brennan-Ing
 - Mary Choi
 - Sara Czaja
 - Brad Jones
 - Jerad Moxley
 - Lishomwa Ndhlovu

Acknowledgements



**Weill Cornell
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*Thank You to the
Study Participants*

ID Division:

- Dr. Marshall Glesby
- Dr. Lishomwa Ndhlovu
- Dr. Michael Corley
- Dr. Douglas Nixon
- Dr. Trip Gulick

Geriatrics Division:

- Dr. Eugenia Siegler
- Dr. Heather Derry
- Dr. Cary Reid
- Dr. Atami DeMain

Choi Laboratory:

- Dr. Mary Choi
- Dr. Luis Gomez-Escobar
- Dr. Edwin Patino
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CTSC:

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