UNDERSTANDING BIOLOGICAL AGING AND ITS IMPLICATIONS FOR HIV CURE

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Special Thanks Matt Mendoza UTMB and Karine Dube UCSD

March 8, 2025

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IN 2022, OVER 50% OF PLWH ARE AGED 50+ IN THE USA

People with diagnosed HIV are living longer, healthier lives because of effective HIV treatment. At the end of 2022, over half of people with diagnosed HIV were aged 50 and older.

Source: CDC. Diagnoses, deaths, and prevalence of HIV infection in the United States and 6 territories and freely associated states, 2022. *HIV Surveillance Report,* 2024;35.

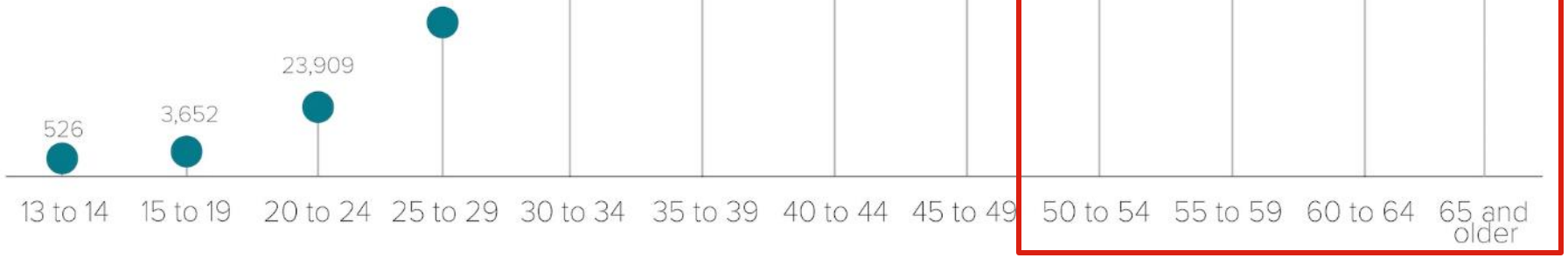
54%

of PLWH in the USA are 50+

IN 2022, OVER 50% OF PLWH ARE AGED 50+ IN THE USA

People with diagnosed HIV are living longer, healthier lives because of effective HIV treatment.
At the end of 2022, over half of people with

How does aging with HIV affect a patient's overall health and future Cure strategies?

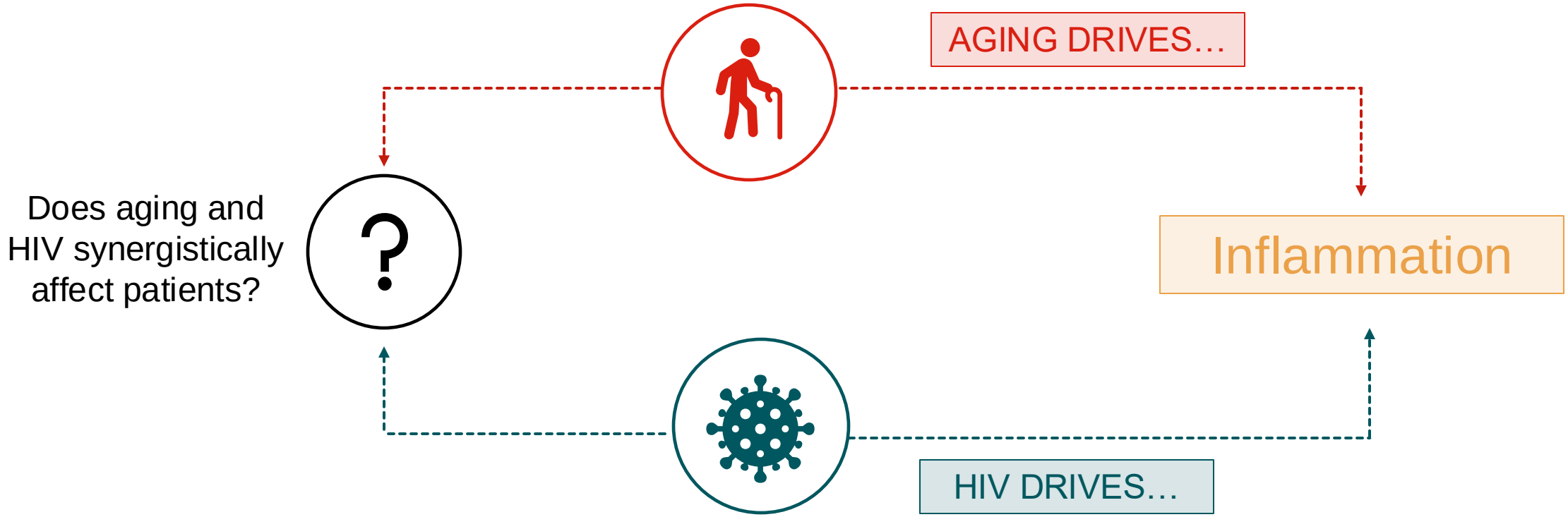


Source: CDC. Diagnoses, deaths, and prevalence of HIV infection in the United States and 6 territories and freely associated states, 2022. *HIV Surveillance Report,* 2024;35.

of PLWH in the USA are 50+

CONNECTING THE CORE THEMES OF THE PRESENTATION

What we know so far…



THE GARDEN ANALOGY: HIV, AGING, AND INFLAMMATION

HIV as Super Fertilizer

HIV acts like a super fertilizer that accelerates plant growth (aging), but not in a healthy way.

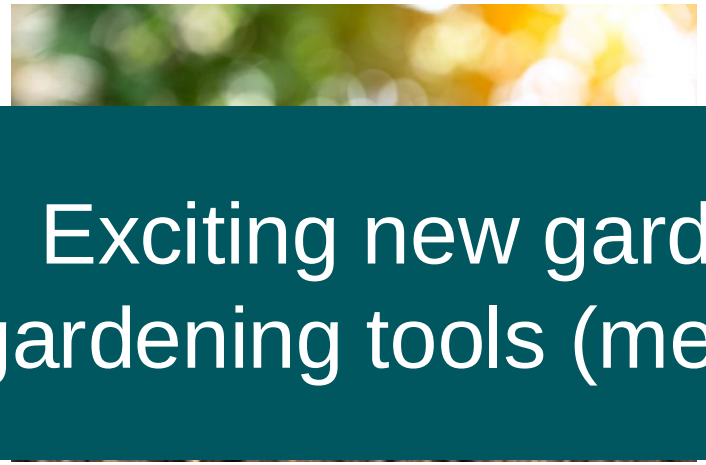
Chronic Inflammation as Weeds

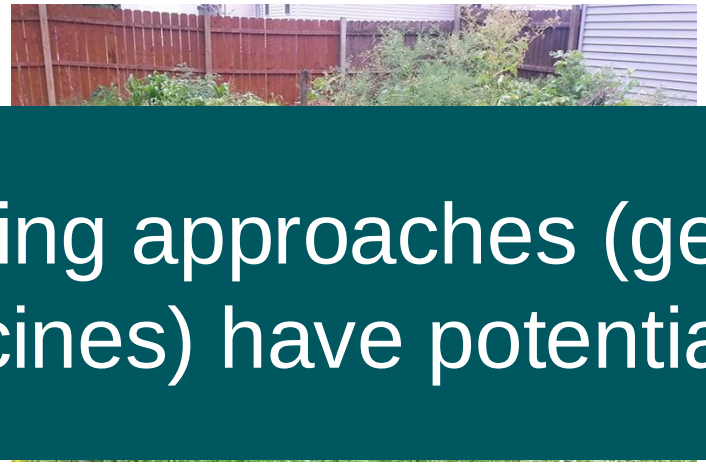
Inflammation spreads like weeds, choking out healthy growth and stressing the soil.

Patient-Centered Care as a Master Gardener

Customized care removes weeds, balances the fertilizer, and ensures the plants grow strong and resilient.

THE GARDEN ANALOGY: HIV, AGING, AND INFLAMMATION





Exciting new gardening approaches (geroscience) and new gardening tools (medicines) have potential to have a big impact

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Chronic Inflammation as Weeds

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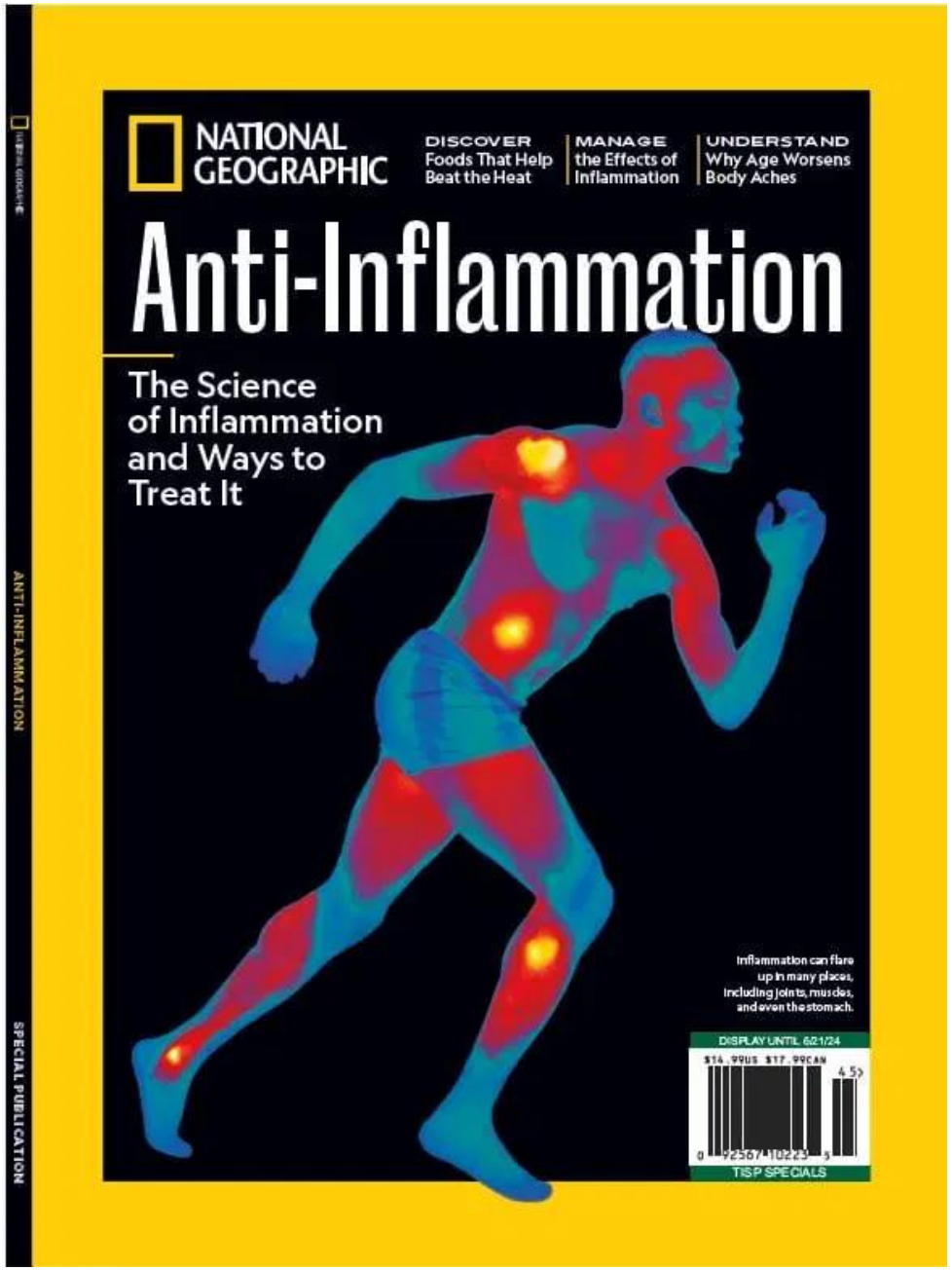
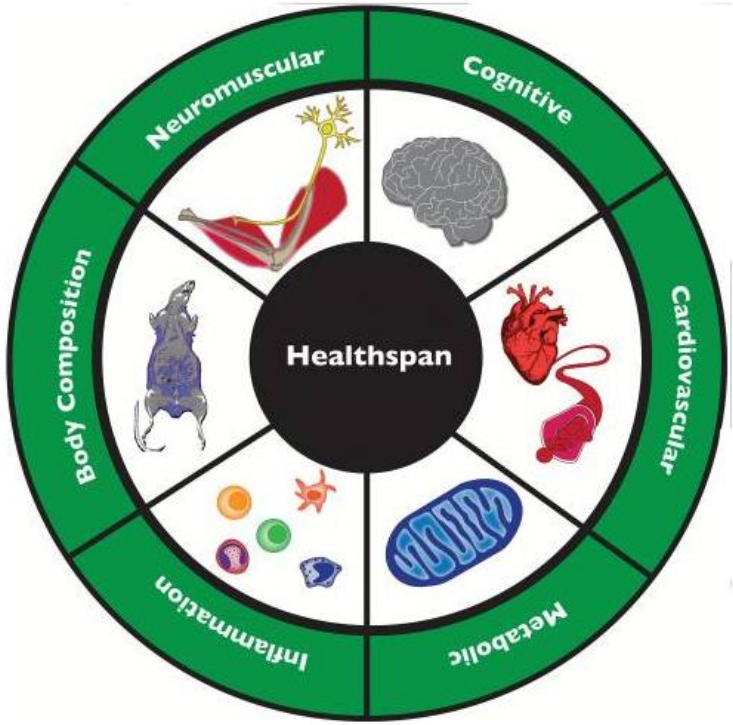
IMPORTANT DEFINITIONS TO CONSIDER

TERM	DEFINITION
Geroscience	The study of the biological processes that cause aging
Cellular Senescence	A process where cells in the body lose the ability to create new cells and do not die
Epigenetics	Environmental or behavioral factors that cause chemical modifications to DNA and change how genes are expressed
Proinflammatory	Factors that trigger or promote inflammation
Cytokine	Signaling molecules in the body that promote biological processes like inflammation


NATIONAL GEOGRAPHIC
DISCOVER Foods That Help Beat the Heat
MANAGE the Effects of Inflammation
UNDERSTAND Why Age Worsens Body Aches
Anti-Inflammation
The Science of Inflammation and Ways to Treat It
Inflammation can flare up in many places, including joints, muscles, and even the stomach.
DISPLAY UNTIL 6/21/24
ANTI-INFLAMMATION
SPECIAL PUBLICATION

IMPROVING HEALTHSPAN IS KEY TO LONG-TERM INDEPENDENCE

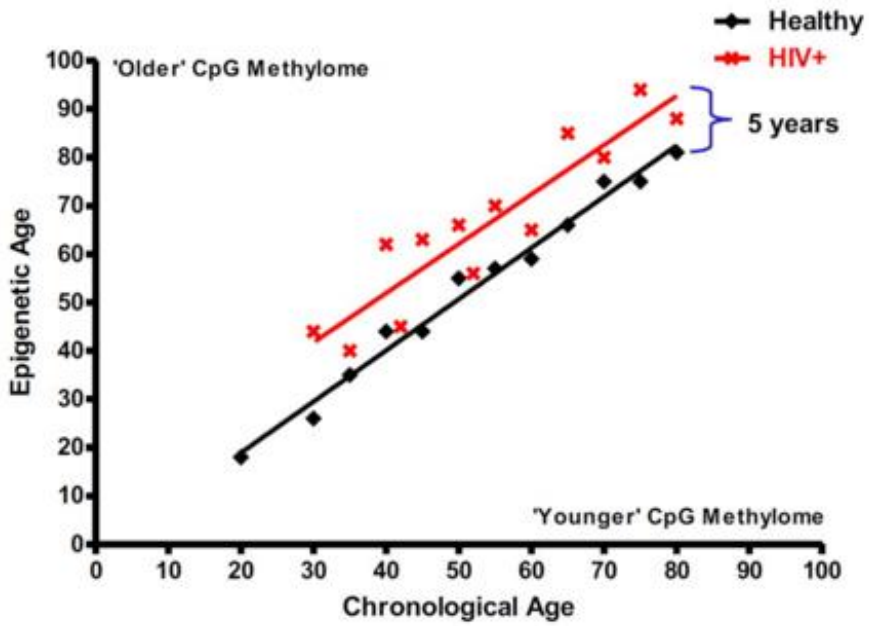
- The field of geroscience is moving from consideration of life span or longevity to consideration of healthspan
- Domains used to characterize healthspan –
  - Neuromuscular function
  - Cognitive function
  - Cardiovascular function
  - Metabolic function
  - Inflammation
  - Body Composition and Energetics
- There is a shift toward delaying and compressing the period of the lifespan when frailty and disability increase substantially, thereby extending and improving health span



EVIDENCE OF ACCELERATED AGING IN PLWH

1. Increased incidence of age-related illnesses in PLWH at relatively younger ages
2. Initial evidence of accelerated aging as been repeated by numerous research groups
3. Different biological measurements all support the notion that aging is accelerated in PLWH

Epigenetic age is accelerated in PLWH

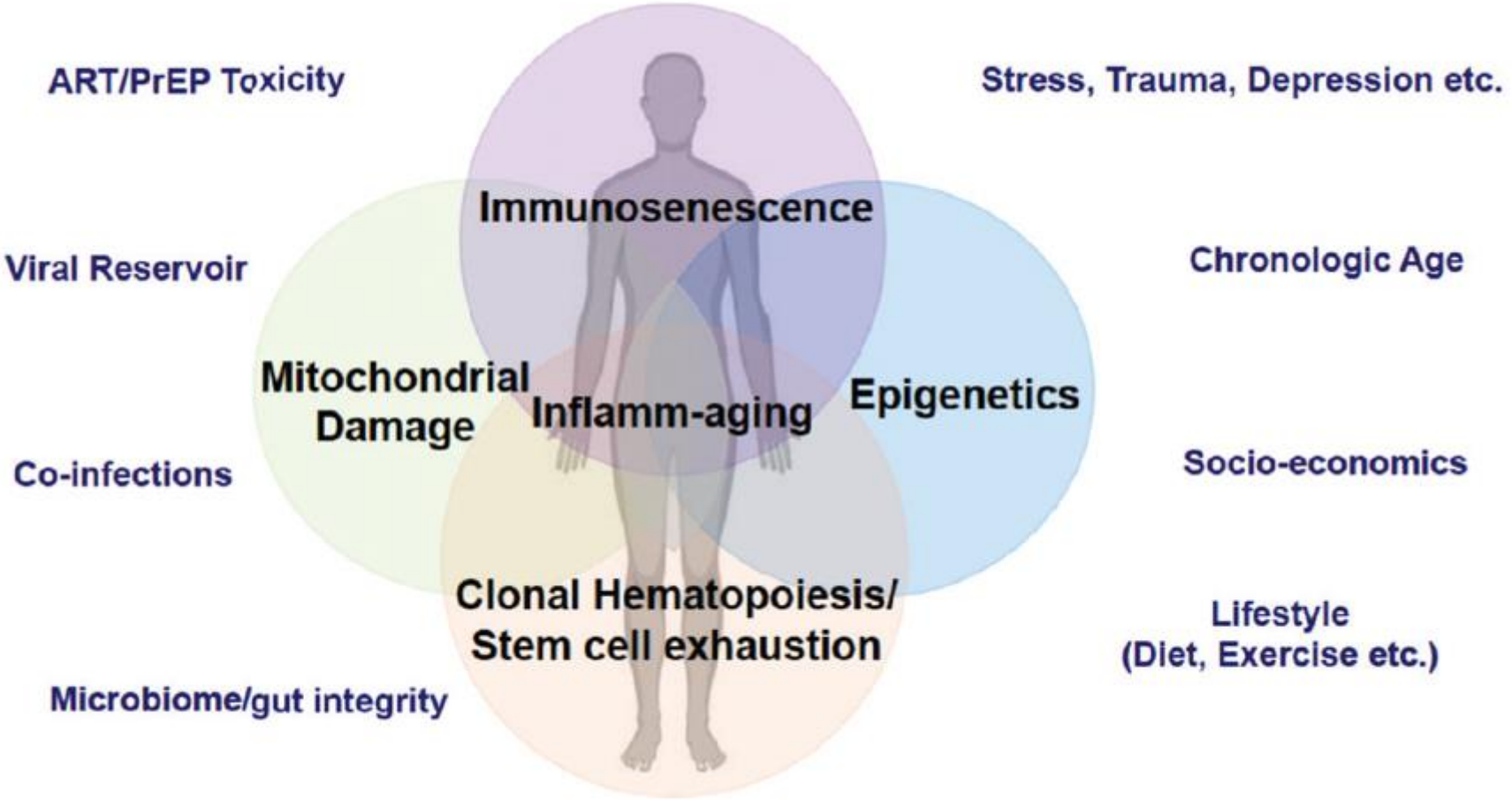


Boulias K, et al. Mol Cell 2016; Schoepf et al. JID 2022; Hunt and Payne Curr Opin HIV/AIDs 2020; Rodés et al. eBioMed 2022

AGING AND HIV:A PERSPECTIVE FOR CURE STRATEGIES

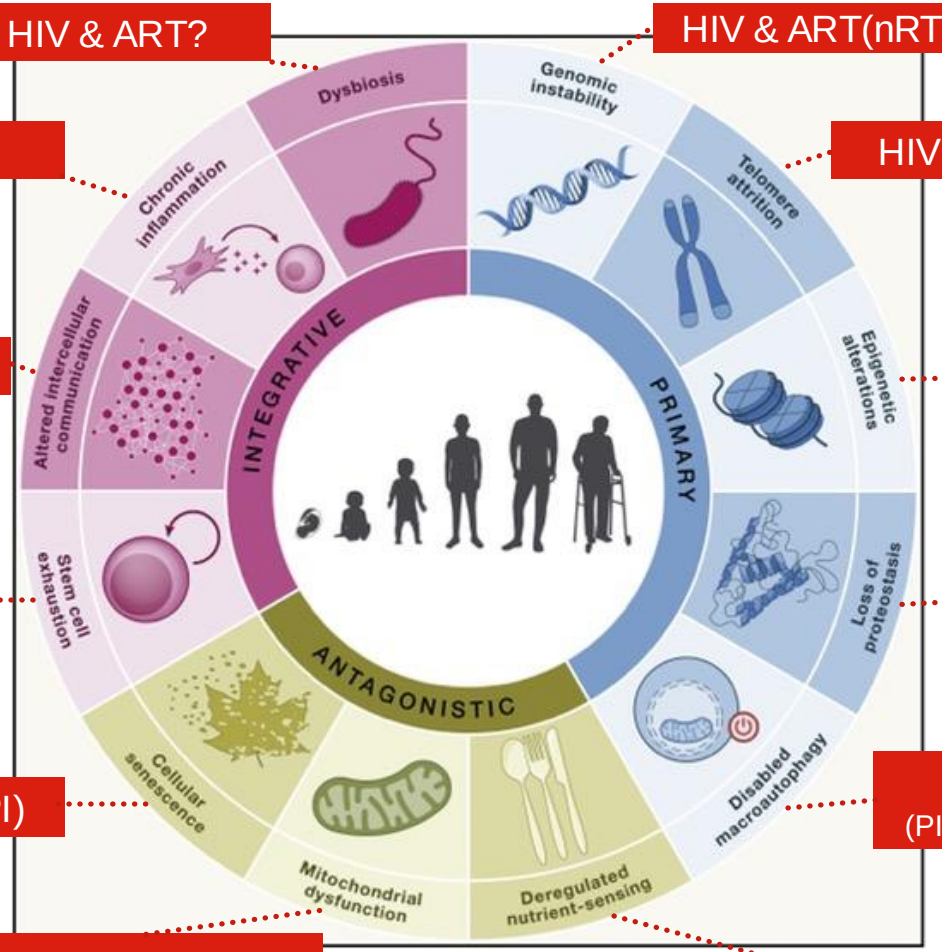
1. Are there unique features of older people living with HIV that need to be addressed with a Cure?
2. What impact does age have on the HIV reservoir?
3. What impact does inflammaging have on immune function and responses to Cure therapies?
4. What role will studies of geroscience and novel therapies have on the future of HIV Cure strategies?

DRIVERS AND MECHANISMS OF AGING WITH HIV & ART: IMPLICATION CURE STRATEGY



IMPACT ON THE HALLMARKS OF BIOLOGICAL AGING

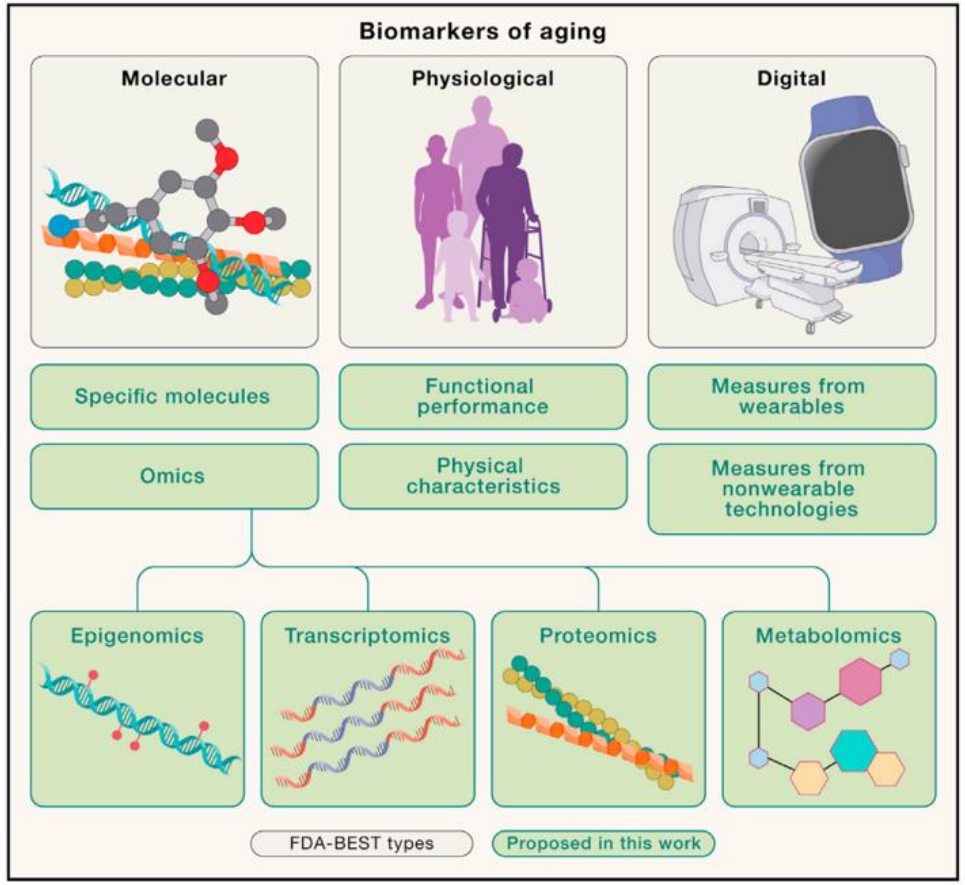
Each of these may be affected by HIV and/or ART and impact Cure



a.o. Montano M. et al Lancet Healthy Longev 2022; 3: e194–205

HOW DO WE MEASURE BIOLOGICAL AGE?

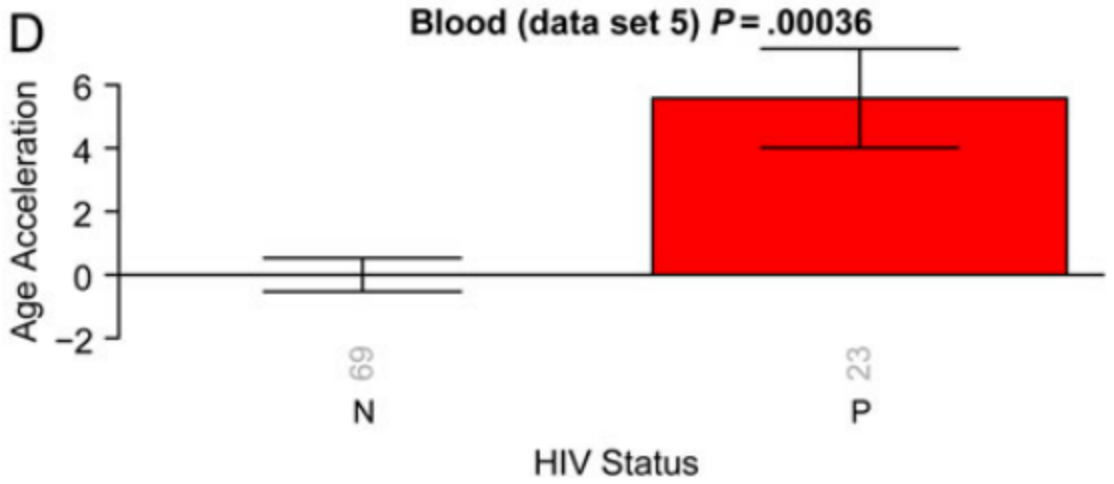
- Chronological age is the **amount of time that has passed since birth**
- Biological age is a **measure of how old a person's body is**
- Biological age is **not perfectly matched** to chronological age
- **Lifestyle, stress, and socioeconomic** factors can influence biological age
- You can measure biological age by looking at **molecules in the body or assessing physical function**

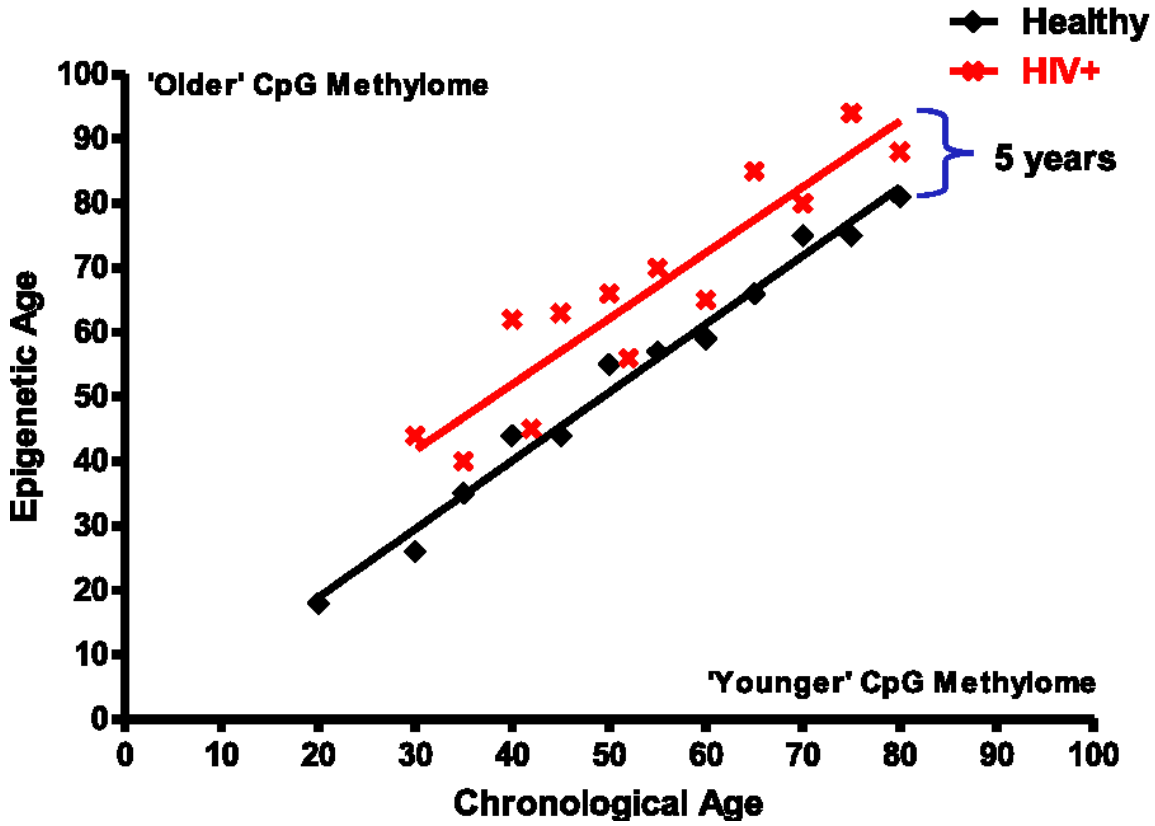


EVIDENCE OF ACCELERATED AGING IN PLWH – DNA METHYLATION

Steve Horvath[1,3] and Andrew J. Levine[2]

[1]Department of Human Genetics, [2]Department of Neurology, David Geffen School of Medicine, and [3]Department of Biostatistics, School of Public Health, University of California–Los Angeles

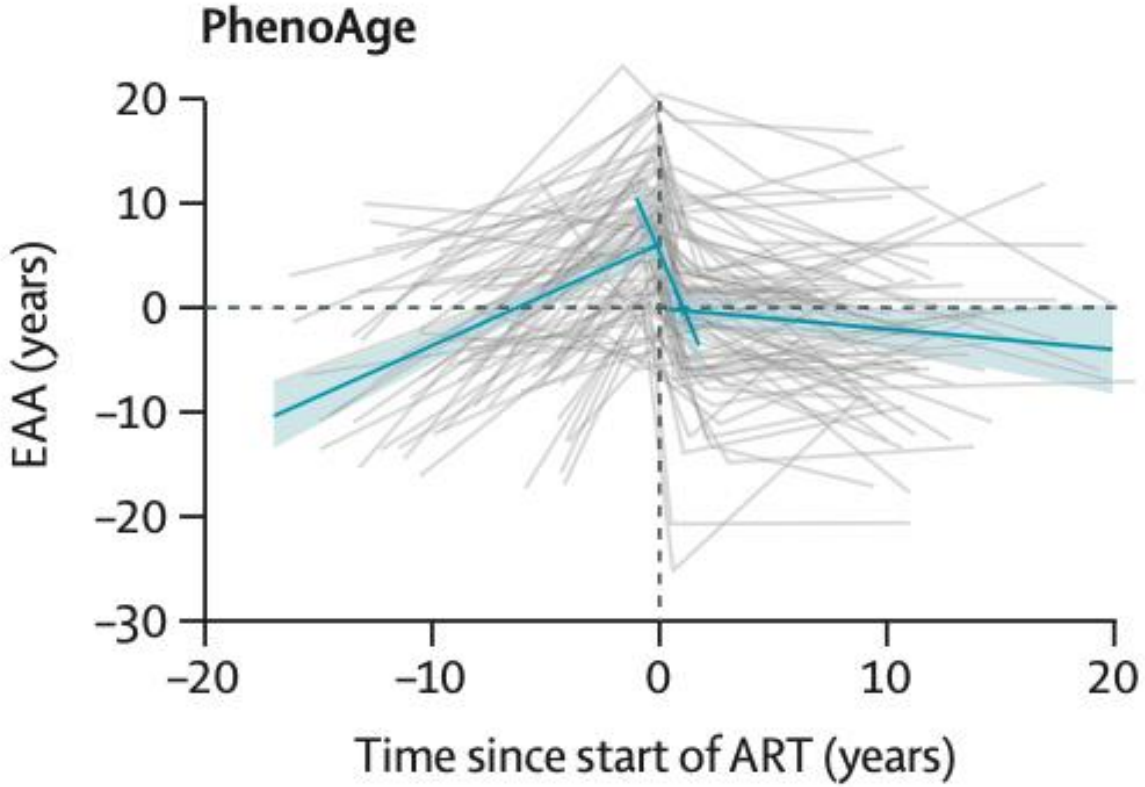




Adapted from Horath et al., 2016 and Boulias, et al., 2016.

EPIGENETIC AGING BEFORE STARTING & AFTER BEING ON ART

Epigenetic aging accelerates before antiretroviral therapy and decelerates after viral suppression in people with HIV in Switzerland: a longitudinal study over 17 years



THE LANCET
Healthy Longevity

SWISS
HIV
COHORT
STUDY

Epigenetic age acceleration over time for the «PhenoAge» epigenetic clock EAA=epigenetic age acceleration. ART=antiretroviral therapy.

EPIGENETIC AGING BEFORE STARTING & AFTER BEING ON ART - NOT THE SAME FOR EVERY INDIVIDUAL

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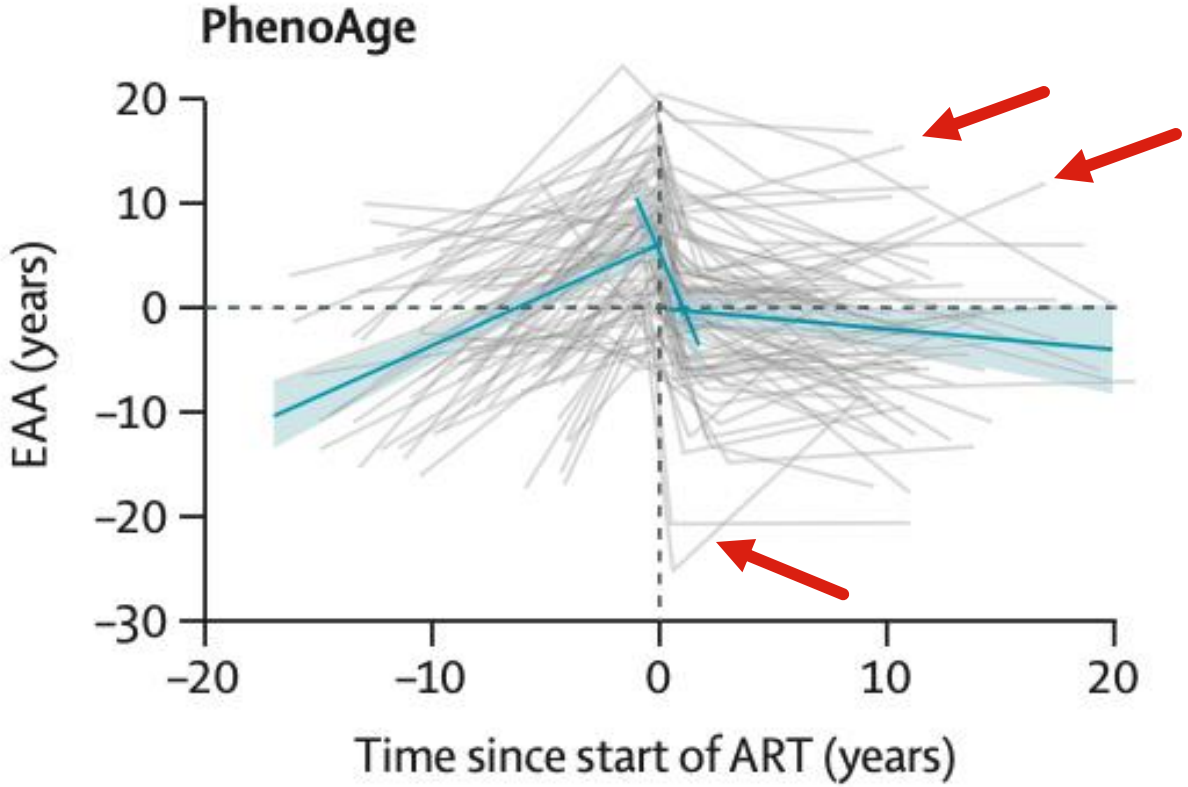

THE LANCET
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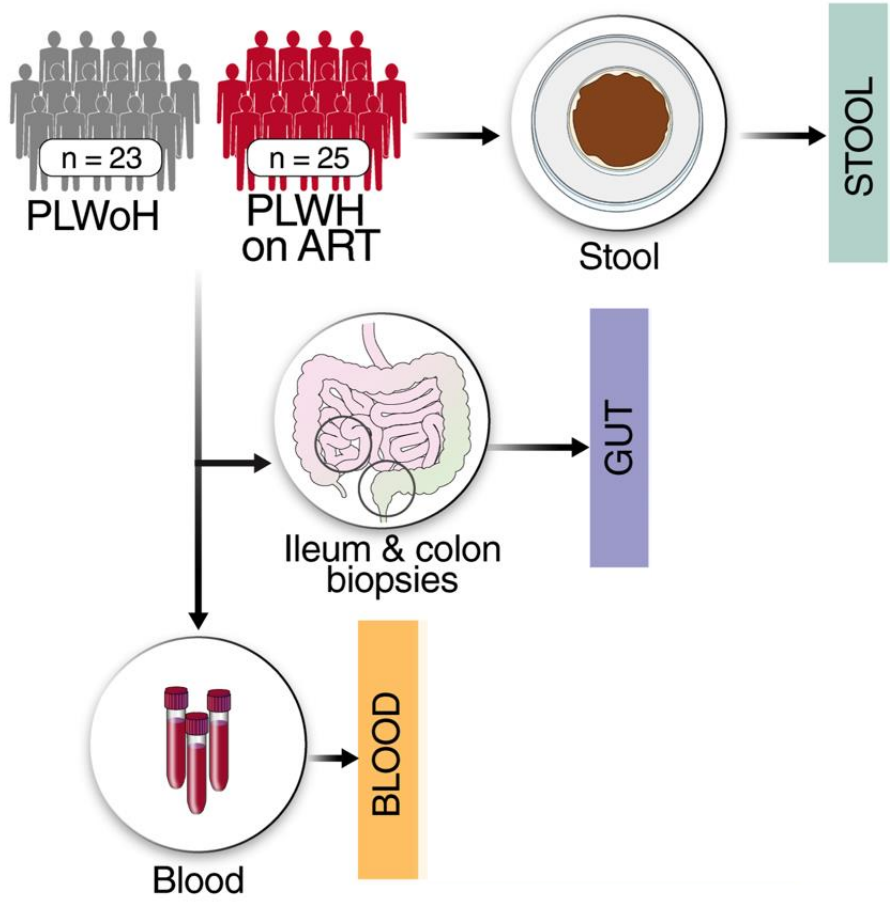
Epigenetic age acceleration over time for the «PhenoAge» epigenetic clock EAA=epigenetic age acceleration. ART=antiretroviral therapy.

RESEARCH Open Access

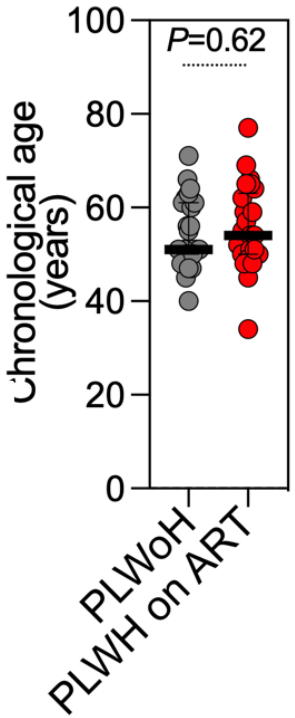
Distinct intestinal microbial signatures linked to accelerated systemic and intestinal biological aging

Shalini Singh[1], Leila B. Giron[1], Maliha W. Shaikh[2], Shivanjali Shankaran[2,3], Phillip A. Engen[2], Zlata R. Bogin[2], Simona A. Bambi[2], Aaron R. Goldman[1], Joao L. L. C. Azevedo[1], Lorena Orgaz[4], Nuria de Pedro[4], Patricia González[4], Martin Giera[5], Aswin Verhoeven[5], Elena Sánchez-López[5], Ivona Pandrea[6], Toshitha Kannan[1], Ceylan E. Tanes[7], Kyle Bittinger[7], Alan L. Landay[2,3], Michael J. Corley[8], Ali Keshavarzian[2,3†] and Mohamed Abdel-Mohsen[1*†]

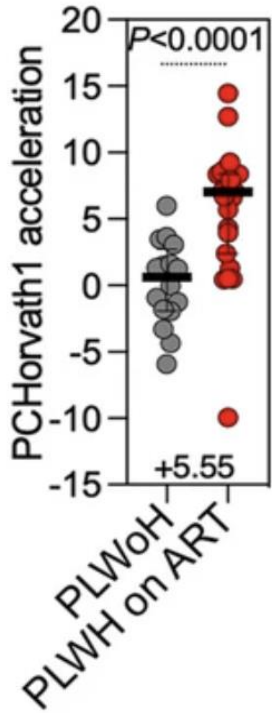
ACCELERATED INTESTINAL AND BLOOD BIOLOGICAL AGING IN PLWH ON ART



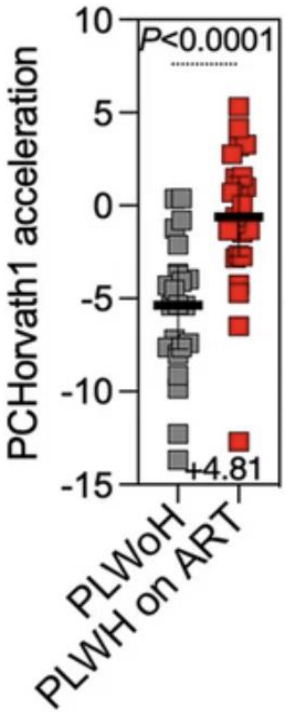
Same Chronological Age



Accelerated Blood Age



Accelerated Intestinal Age



Adapted from Singh et al., Microbiome 2024

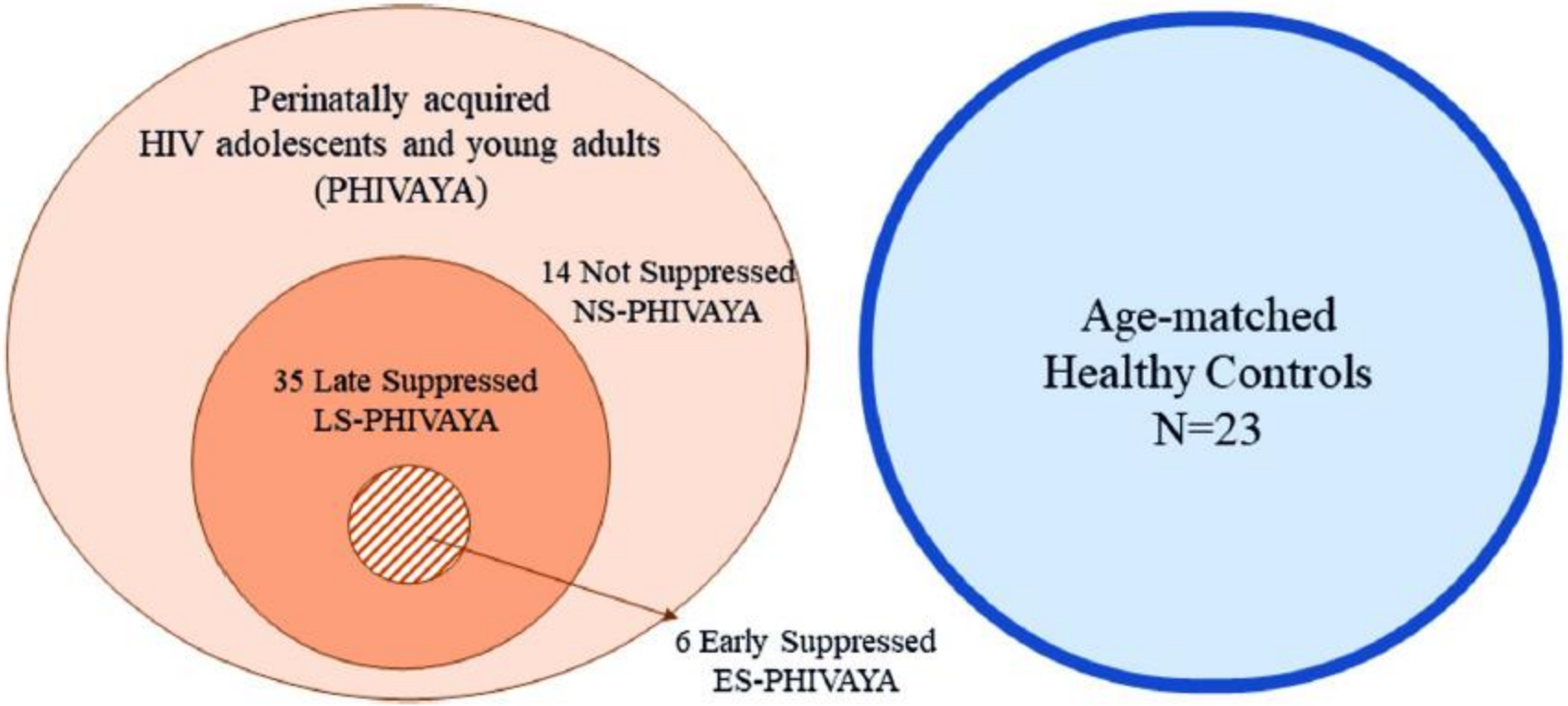
PLOS PATHOGENS

RESEARCH ARTICLE

HIV reservoir and premature aging: risk factors for aging-associated illnesses in adolescents and young adults with perinatally acquired HIV

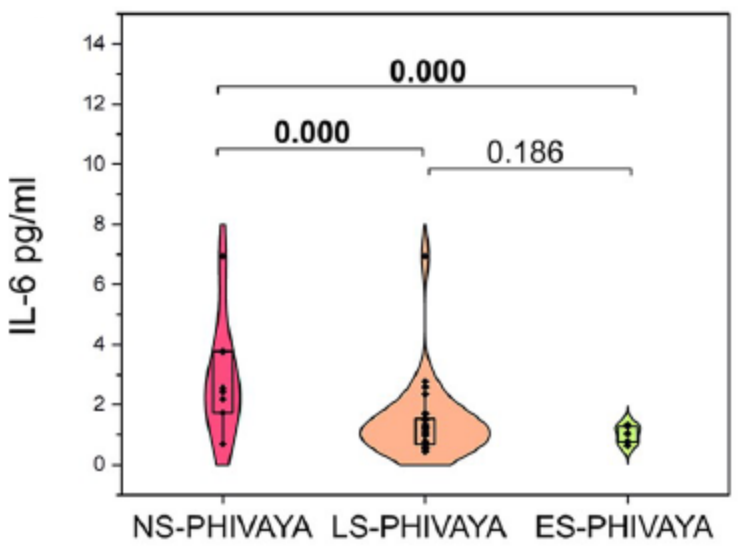
Maria Raffaella Petrara[1,2], Elena Ruffoni[1], Francesco Carmona[1], Ilaria Cavallari[1], Sandra Zampieri[3,4], Marzia Morello[1], Paola Del Bianco[5], Osvalda Rampon[6], Nicola Cotugno[7], Paolo Palma[7], Paolo Rossi[7], Carlo Giaquinto[6], Silvia Giunco[1,2], Anita De Rossi[1,2]*

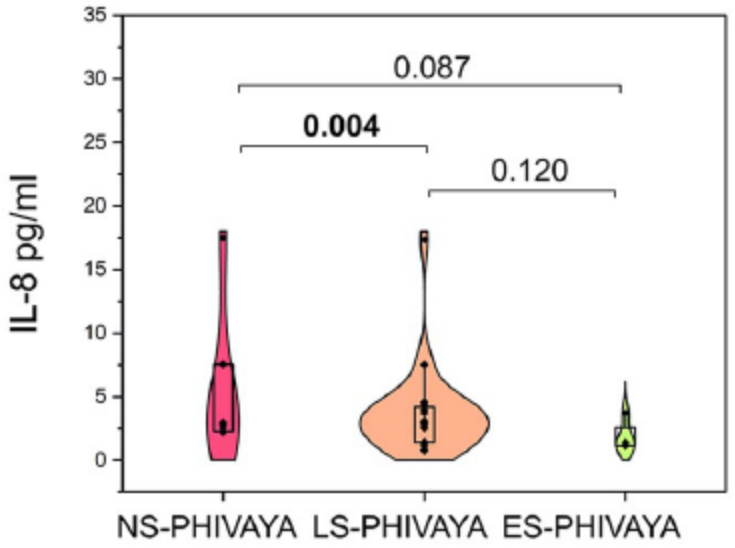
PREMATURE AGING OCCURS EVEN IN PATIENTS WHO ACQUIRED HIV PERINATALLY

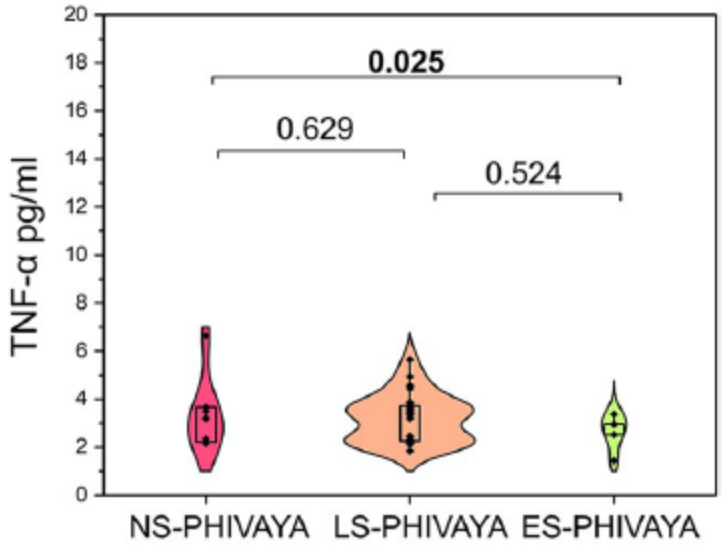


Petrara et al., PLOS Pathogen. 2024

PROINFLAMMATORY CYTOKINES ARE INCREASED IN YOUNG ADULTS WHO ACQUIRE HIV PERINATALLY

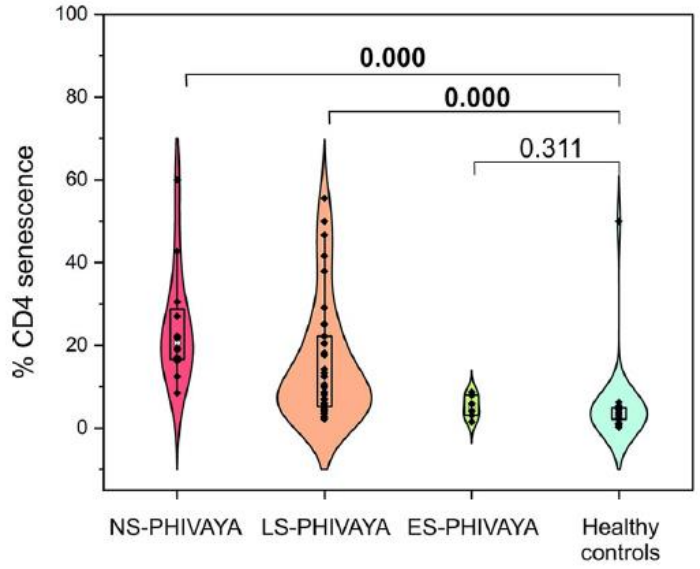


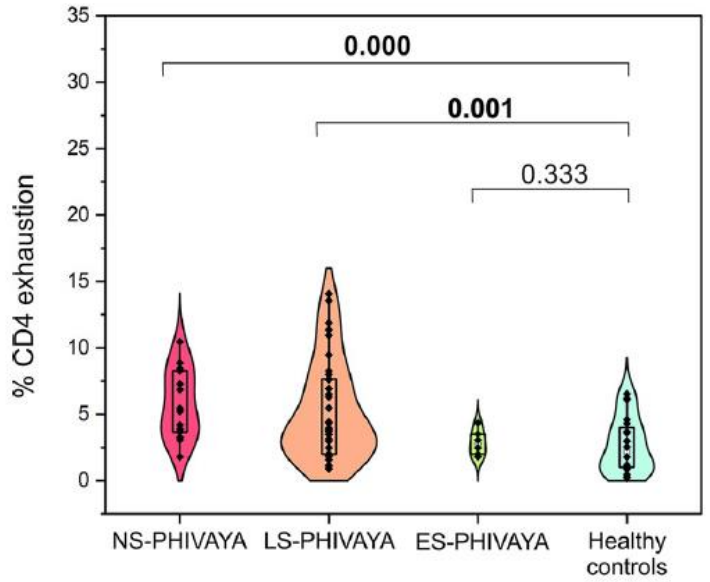


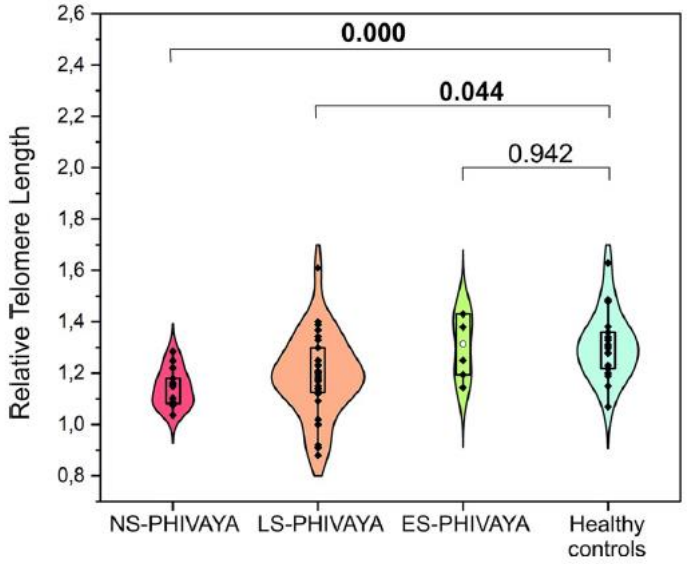


Petrara et al., PLOS Pathogen. 2024

MARKERS OF AGING ARE INCREASED IN YOUNG ADULTS WHO ACQUIRED HIV PERINATALLY







Petrara et al., PLOS Pathogen. 2024

TARGETING NEW THERAPIES IN HIV AND AGING: IMPLICATIONS FOR A CURE STRATEGY

utmb Health

CONSIDERATIONS AND CHALLENGES OF HIV CURE

Latently infected cells

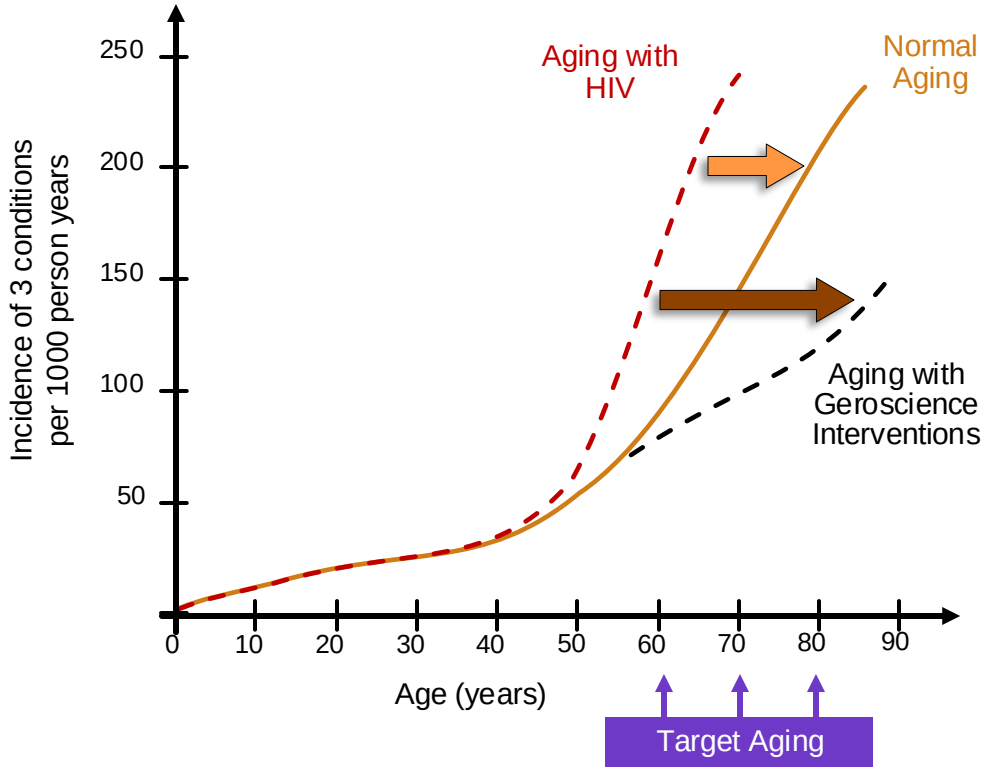
The Economist, July 17, 2011

Finding & removing HIV reservoirs

Understanding & addressing unique patient needs

CONSIDERING HIV IN GEROSCIENCE-GUIDED APPROACHES

- Geroscience is the study of **the biological processes that cause aging**
- Geroscience interventions aim to **slow down the biological aging process**
- Examples of geroscience interventions are:
  - Improved diet and caloric restriction
  - Mobility feedback devices (e.g. apple watches) and exercise
  - Novel or repurposed medications



SENOTHERAPEUTICS: NOVEL THERAPIES IN HIV AND AGING

Class	Mechanism	Example Agents
Senolytics	Selectively kill senescent cells	BCL-2/BCL-xL inhibitors (e.g. venetoclax, navitoclax) HSP-90 inhibitors Dasatinib + quercetin (D+Q) Fisetin
Senomorphics	Suppress senescence phenotypes, like SASP	JAK inhibitors (e.g., ruloxitinib, baricitinib) Rapamycin Metformin

SENOTHERAPEUTICS CAN IMPACT THE HIV RESERVOIR

Notable drugs
Panobinostat
Navitoclax
Venetoclax
Dasatinib
Ruxolitinib
Everolimus
Rapamycin
Metformin

Szaniawaski and Spivak, Current HIV/AIDS Reports, 2020.

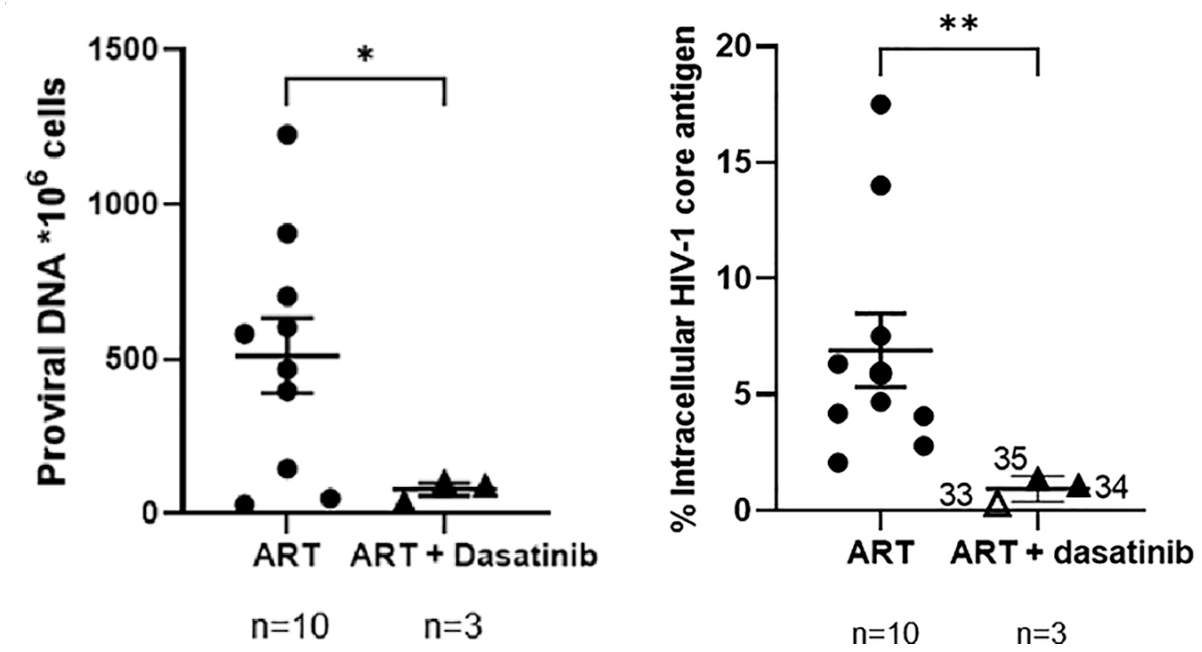
A5413: DASATINIB FOR HIV-1 RESERVOIR REDUCTION

Adam M. Spivak, M.D.

University of Utah School of Medicine

Community Representative: Lionel Hillard

INITIAL STUDIES SUGGEST THAT DASATINIB CAN REDUCE THE HIV RESERVOIR



- Initial study looked at the **HIV viral reservoir in circulating immune cells**
- ART + dasatinib **decreased the HIV viral reservoir** more than ART alone
- Importantly, dasatinib was **safe and well tolerated** by PLWH

Vigon, L et al. Biochem Pharm 2021

A5426: Improving Physical Ability and Cellular Senescence Elimination in HIV (IPACE-HIV)

Adam M. Spivak, M.D.
University of Utah School of Medicine

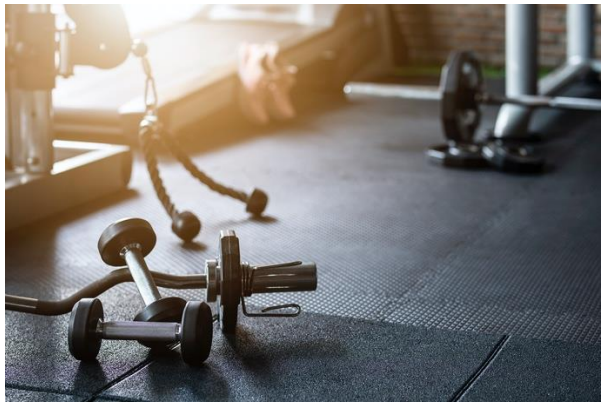
Mary Clare Masters, M.D.
Northwestern University Feinberg School of Medicine

Community Representatives: Lionel Hillard and Andy Kaytes

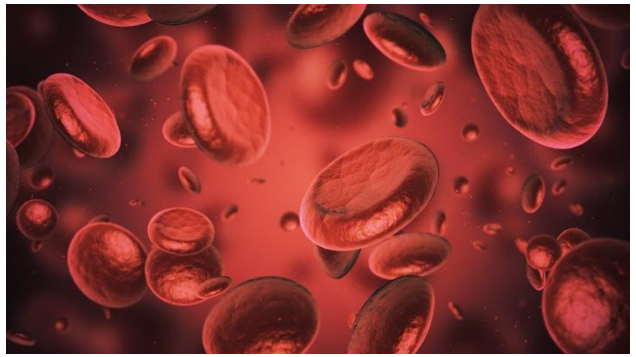
A5426: Improving Physical Ability and Cellular Senescence Elimination in HIV (IPACE-HIV)

Examples of what the study intends to measure

Impact of D+Q on chair stand pace in PWH from week 0 to 12



Impact of D+Q on exercise capacity in PWH from week 0 to 12.



Impact of D+Q in PWH on senescent cell abundance in blood.

and much more

AGING AND AN HIV CURE SUMMARY

Older adults have unique needs that might be addressed with a cure, but are less likely to tolerate and respond to many emerging therapies

Impact of age on the reservoir is unknown but likely to be important

Chronic inflammation is a well-described feature of aging and is the target of a many therapies, including some being developed in geroscience

THE GARDEN ANALOGY: HIV, AGING, AND INFLAMMATION

HIV can accelerate aging like a super fertilizer can accelerate growth of plants

Chronic inflammation from aging and HIV is like weeds which disrupts the health of the garden

A Master Gardner or doctor could use geroscience and new medicines to support healthy aging in PLWH

ACKNOWLEDGEMENTS

Epigenetic Clock Publication

Shalini Singh, PhD
Mohamed Abdel-Mohsen, PhD
And many more…

Perinatal HIV & Aging Publication

Maria Raffaella Petrara, PhD
Anita De Rossi, PhD
And many more…

Collaborators

UCSD – Michael Corely, PhD
University of Utah – Adam Spivak, MD

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ROI AG054324

UTMB Team & Colleagues

Matt Mendoza, PhD
Brice Miller, MS
Lanette Harris

Citations

1. Singh S, et al. Distinct intestinal microbial signatures linked to accelerated systemic and intestinal biological aging. Microbiome. 2024.
2. Petrara MR, et al. HIV reservoir and premature aging: risk factors for aging-associated illnesses in adolescents and young adults with perinatally acquired HIV. PLoS Pathog. 2024