LOS ANGELES COUNTY
COMMISSION ON HIV

AGING CAUCUS

VIRTUAL MEETING AGENDA

TUESDAY, September 6, 2022

1:00 PM – 3:00 PM

TO JOIN BY WEBEX, CLICK:

https://lacountyboardofsupervisors.webex.com/lacountyboardofsupervisors/j.php?MTID=m20513a327b13dbea02e851e618070e63

PASSWORD: AGING

TO JOIN BY PHONE: +213-306-3065 **MEETING #/ACCESS CODE:** 2590 318 9149

1. Welcome & Introductions 1:00pm-1:10pm

2. Co-Chairs' Report 1:10pm-1:25pm
   a. Ryan White National Conference

3. Division of HIV and STD Programs (DHSP) Report 1:25pm-1:40pm
   DISCUSSION: Feedback on "Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging" Document

4. DISCUSSION: Develop an addendum to recommendations to include activities and strategies to address the needs of long-term survivors and individuals who acquired HIV perinatally 1:40pm-2:25pm

5. Executive Director/Staff Report 2:25pm-2:35pm
   a. Comprehensive HIV Plan 2022-2026
   b. Training and Membership Recruitment

6. Next Steps and Agenda Development for Next Meeting 2:35pm-2:45pm

7. Public Comments & Announcements 2:45pm-3:00pm

8. Adjournment 3:00pm

LOS ANGELES COUNTY
COMMISSION ON HIV

AGING CAUCUS
August 2, 2022
Virtual Meeting Summary

In attendance:

Joe Green (Co-Chair)	Alasdair Burton	Genevieve Clavreul
Viviana Criado	Kevin Donnelly	Lee Kochems
Sandrine Lewis	Paul Nash	Maria Scott
Cheryl Barrit (COH Staff)	Catherine Lapointe (COH Staff)	Jose Rangel-Garibay (COH Staff)
Sonja Wright (COH Staff)		

CHP: Comprehensive HIV Plan
COH: Commission on HIV
DHSP: Division of HIV and STD Programs
DPH: Department *of Public Health*

Meeting packet is available at https://assets-us-01.kc-usercontent.com/0234f496-d2b7-00b6-17a4-b43e949b70a2/2ec6eae3-238a-43b8-9287-27eb6935b77b/Pkt-AgngCauc_080222-Revised.pdf

1. **Welcome & Introductions**
   Cheryl Barrit, Executive Director, welcomed attendees and led introductions.

2. **Co-Chairs' Report**
   a. **International AIDS Society Conference**
      - Al Ballesteros, Co-Chair, and several commissioners are attending the International AIDS Conference. C. Barrit suggested dedicating time at the next Commission on HIV (COH) meeting to hear from attendees on what they learned at the conference.
      - Joe Green, Co-Chair, reported that he has been attending virtual sessions from the International AIDS Society Conference. He learned more about how COVID-19 has affected the HIV epidemic in developing countries.

3. **Division of HIV and STD Programs (DHSP) Report**
   - DHSP staff was not able to attend the meeting and no report was provided; however, Dr. Michael Green requested that the Aging Caucus review the Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging and provide feedback. C. Barrit provided an overview of the document, which can be found in the meeting packet. The document is categorized by five goals: 1) Housing for All Stages and Ages, 2) Health Reimagined, 3) Inclusion and Equity, Not Isolation, 4) Caregiving That Works, and 5) Affording Aging.

- Viviana Criado recommended including resources for funding opportunities.
- Maria Scott recommended including people who acquired HIV perinatally, as they are affected by accelerated aging.

4. **DISCUSSION: Revisit recommendations to include activities and strategies to address the needs of long-term survivors and individuals who acquired HIV perinatally**
   - At the July Aging Caucus meeting, Dr. Allison Agwu gave a presentation titled, "Understanding Aging Among Individuals who Acquired HIV Perinatally and Long-term Survivors under 50." The presentation slides can be found in the meeting packet.
   - C. Barrit discussed revising the previous set of recommendations made by the Aging Caucus to include those who acquired HIV perinatally and long-term survivors under 50. Kevin Donnelly suggested adding an addendum to the set of recommendations to include this population. Paul Nash concurred.

5. **Executive Director/Staff Report**
   a. **Social Media Update**
      - Catherine Lapointe provided an update on the COH's social media engagement efforts. The update can be found in the meeting packet. She invited commissioners to participate in the Commissioner Testimonial project, which highlights commissioners and their contributions to the COH.
   b. **Comprehensive HIV Plan 2022-2026**
      - C. Barrit informed the Aging Caucus that AJ King, Comprehensive HIV Plan (CHP), Consultant has sent out two surveys to help inform the CHP. One is for the HIV workforce, and one is for HIV service consumers. The surveys are available in English and Spanish.
      - A. King has been conducting community listening sessions to hear from the seven priority populations, including Latinx men who have sex with men (MSM) Black/African American MSM, women of color, transgender persons, people who inject drugs, people aged 30 and under, and people aged 50 and over.
      - A. King will have a first draft of the CHP available for review in early September.

6. **Next Steps and Agenda Development for Next Meeting**
   - Aging Caucus co-chairs and COH staff will work on a draft addendum to include people who acquired HIV perinatally and long-term survivors under 50 in the Aging Caucus recommendations.
   - C. Barrit will send the Alignment of Los Angeles County's Ryan White Program with the California Master Plan document to the Aging Caucus for feedback.

7. **Public Comments & Announcements**

- J. Green announced that the FDA is conducting a study to determine eligibility for blood donations from MSM. The study is recruiting participants who are HIV-negative MSM between the ages 18 and 39. More information can be found at www.advancestudy.org.

8. Adjournment

The meeting was adjourned by J. Green.

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging
Notes Contain Ranking Received from Aging Caucus

BACKGROUND: Currently more than 52% of people living with diagnosed HIV (PLWDH) in Los Angeles County are 50 years of age or older, and by 2030 more than 70% of PLWDH will be over the age of 49. As people age, they typically have more co-morbidities, take more medications, and are more vulnerable to side effects complicating the management of their HIV disease. PLWDH who are 50 years or older (50+) experience accelerated CD4 loss, decreased immune recovery, and are at an increased risk of acquiring serious non-AIDS illnesses. Long term health complications from HIV include poor mental health and bone, kidney, cardiovascular, and liver diseases.

This workplan aims to anticipate and address the physical, mental, social, and economic needs of PLWDH 50+ for good quality of life.

KEY SOURCE DOCUMENTS:
CA Master Plan on Aging document https://mpa.aging.ca.gov/

Goal One: Housing for All Stages and Ages

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes (Numbers denote ranking suggestions from Aging Caucus)
Increase coordination among housing agencies to include intergenerational housing options	Identify if/how housing for HIV positive seniors is prioritized	RWP housing providers, HOPWA, CoC			**3**
Examine housing inventory to ensure that it provides safe and welcoming environments for seniors	Investigate if there is a list of housing regulations specifically for seniors				**1, 1**
Blend funding to support housing and rental assistance for seniors living with HIV	Identify all available housing assistance for seniors in LAC, note				**5**

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes (Numbers denote ranking suggestions from Aging Caucus)
	eligibility criteria, and assistance amount $				
Identify services that can assist seniors in transitioning from different levels of residential support (i.e. independent living to assisted living) based on physical and cognitive needs	Research services provided by other LAC programs and cities				**2**
Support training for housing service providers on needs of PLWH and LGBTQI persons to improve cultural competencies among staff	Research what training PAETC and other TA providers offer				**4**
Foster mentorships between seniors and youth to improve understanding across generations of the HIV pandemic, its effects, and how seniors can be supported and honored within the community					**6**

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Goal Two: Health Reimagined

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Add gerontology training to Ambulatory Outpatient Medical, Oral Health, Medical Care Coordination and Mental Health services providers to improve awareness and understanding of age-related inequities in care and treatment	Research what training PAETC and other TA providers offer.				**1**
Add Quality of Life (QOL) metrics to data collection variables to identify areas where changes in services and service access can lead to improved QOL	Identify validated QOL measures and discuss with Standards and Best Practices Committee				**3**

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
among all people living with HIV					
Standardize age categories to identify priority populations for specialized services	Research age categories used in gerontology studies				**8**
Review/update diagnostic screenings to include age-related conditions (i.e. screen for loneliness, ACEs, depression, anxiety, experiences of discrimination)	Compile list of diagnostic screenings and associated costs. Determine frequency of screenings and referral plan.				**2, 2**
Revise HIV Home Health and Support services to blend with existing services for PLWH over age X	1. Identify existing services (State OA, Cal-AIM expansion) 2. Convene internal DHSP HBCM workgroup				**4**
Expand access to services that can prevent or slow age-related physical and mental declines					**6**
Develop and maintain robust resource directories and train PLWH to access and use them	Identify existing resource directories				**7**

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Develop case management services that can monitor if care and support services are meeting the needs of seniors post-transition to Medi-Cal/Medicare	Standards and Best Practices will develop draft of service standards				**5**

Goal Three: Inclusion and Equity, Not Isolation

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Develop strong linkages to community social support programs for all PLWH, especially youth and seniors					**This is essentially the same at point 6**
Acknowledge and support nontraditional family relationships that nurture well-being and social connection					3, 1 COH recommends the Village model The Village Movement | Grantmakers in Aging (giaging.org). One of the core

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
					components of this model are volunteers. Volunteerism has declined over the past decade, especially in Los Angeles
Connect to ongoing education and learning programs to foster community engagement and physical activities that promote healthy living					**2**
Improve all access, including digital access and understanding of digital programs	Research what training other LAC programs, PAETC, and other TA providers offer				**5**
Develop linkages to community employment and volunteer training and opportunities	Collaborate with Job Corps and other agencies				**4**
Foster mentorships between seniors and youth to improve understanding across generations of the HIV pandemic, its effects, and how seniors can be supported and honored within the community					COH recommends that we remove HIV to address all life experiences
Add provider training that requires history of HIV, HIV politics and advocacy (this should be a mandatory Commission training as well)					**5**

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Develop transitional case management programs that help PLWH transition from RWP into Medicare, CalAIM, etc.	Standards and Best Practices will develop draft of service standards				This service should provide a single point of contact that seniors can reach out to for assistance
Foster strong community engagement and community planning that honor lived experiences of PLWH					**Included with other training**

Goal Four: Caregiving That Works

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Develop/support educational programs for service providers on sexual health for PLWH aged 50+ or (age X)	Research what training PAETC and other TA providers offer				4, 2 These services should be provided online as well as in person. In person appointments may be the only social contact some seniors may have
Support educational and vocational training programs that blend HIV medicine and social services with the broader needs of youth and an aging population of PLWH					**3**

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Seek out mental health specialists who can treat both HIV and age-related conditions					**1**
Develop training programs for nontraditional families to support each other as they age with HIV					**4**
Reduce the digital divide by promoting access to and understanding of digital and online services	Research what training other LAC programs, PAETC, and other TA providers offer				**5, 5**

Goal Five: Affording Aging

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
Support robust benefits enrollment, financial and retirement planning for PLWH					**6, 1**
Expand access to emergency financial assistance and financial	Obtain and review data on what % of EFA clients are 50+				**7, 3**

Commented [PO1]: COH recommends a peer support model with a single point of contact

Alignment of Los Angeles County's Ryan White Program with the California Master Plan on Aging

Notes Contain Ranking Received from Aging Caucus

Objective	Activity	Partners	Timeline	Performance Measure (Baseline/Target)	Notes
planning services to senior PLWH					
Develop and maintain strong linkages with nutrition and housing programs to eliminate barriers to access, safe, and affordable housing and nutrition services					**2**

LOS ANGELES COUNTY
COMMISSION ON HIV

ADDENDUM TO AGING CAUCUS RECOMMENDATIONS
Addressing the Needs Individuals who Acquired HIV Perinatally and Long-term Survivors under 50

List of Ideas

Source: Dr. Agwu's Presentation

Treatment for youth:

- Multimodal, combination strategies & approaches
- ART modified (stronger, longer, safer, simpler)
- ART Resistance
- Different delivery modes & strategies
- Monoclonal ab
- Vaccines
- Latency reversing agents
- Activated T cells
- Improved engagement strategies
- Behavioral and community interventions
- Optimizing care models
- Alternative "venues" for care delivery
- Increased use of technology ➢Personalized medicine?

Screening:

- Take a good history
- Assess risk factors
    - HTN, CVD
    - Diabetes
    - Mental health
    - STIs
    - Physical activity
    - Obesity
    - Tobacco
    - Substances
    - Sex
    - Activities
    - Diet
    - Helmets
    - Firearms
- Detailed family history
- Physical examination

- Education (patient and staff)
- Counseling
    - Nutrition
    - Exercise
    - Smoking (cigarettes, vaping, cigarillos, e-cigarettes)
    - Substance, alcohol use
    - Sex
    - Etc
- Screening: BP, lipids (fasting/non-fasting), glucose, weight

Actions:

- Smoking cessation
- Lifestyle modification
- Treatment
    - HTN
    - Hyperlipidemia
- Weight loss
- Substance use treatment
- STI counseling, screening, and treatment; family planning
- Immunizations

General Recommendations:

- Providers must be aware of their unique milieu and potential comorbidities to optimize care and outcomes
- Important to screen for and address comorbidities with prevention and early treatment

From: Shiau S., et al

- Future work should examine the dynamic nature of epigenetic age, through examinations of differences in viral load over time, or how interventions leading to improved adherence impact epigenetic age.

Other ideas:

- Conduct targeted studies and data collection on how accelerated aging affects long-term survivors under 50 years of age
- Expand benefits counseling (from all program types, not just Ryan White funded) to include long-term planning and how to transition into Medicare
- Expand counseling services to include self-advocacy for care and treatment options
- Assessments for older PLWH may need to be discussed with medical provider earlier in age/lifespan
- Consider using biomarker testing for long-term survivors under 50 to determine the rate and impact of accelerated aging.
- Work with providers to look for opportunities to address health inequities early in the lifespan.

Understanding Aging Among Individuals who Acquired HIV Perinatally and Long-term Survivors under 50

Allison Agwu, MD ScM, FAAP FIDSA
Professor, Pediatric and Adult Infectious Diseases
Director, Pediatric Adolescent HIV/AIDS Program and Accessing Care Early Clinic
Johns Hopkins School of Medicine, Baltimore, Maryland, USA
July 5, 2022

Disclosures

- Gilead scientific advisory board, site investigator under clinical research contract managed through JHU
- Merck scientific advisory board, consultant, site investigator under clinical research contract managed through JHU

Objectives

- Review the epidemiology of individuals with early-acquired HIV
- Describe risk factors for developing comorbidities over the life course
- Discuss opportunities to prevent comorbidities and optimize outcomes

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Acquired Immunodeficiency Syndrome in Children: Report of the Centers Control National Surveillance, 1982 to 1985
Martha F. Rogers, Pauline A. Thomas, E. Thomas Starcher, Mary C. Noa, Timothy J. Bush and Harold W. Jaffe

"although they make up only 1% of AIDS patients, they have unique clinical, social, and public health problems that require special attention." Rogers

First known infant to be born with HIV

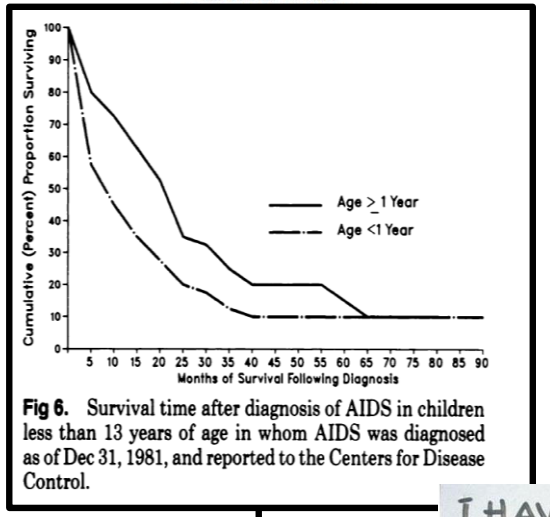
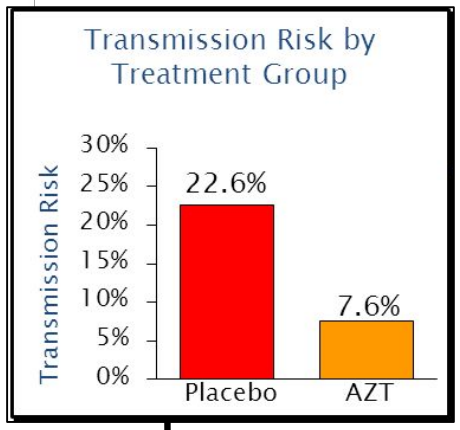
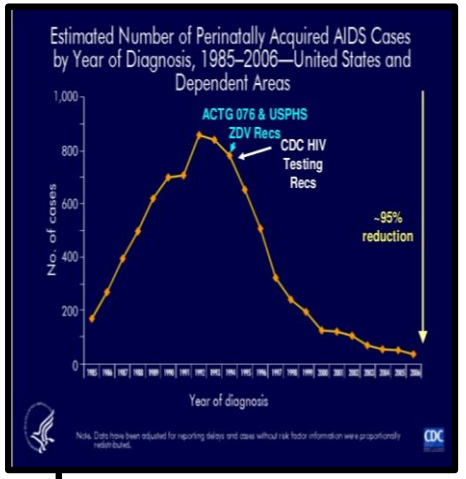
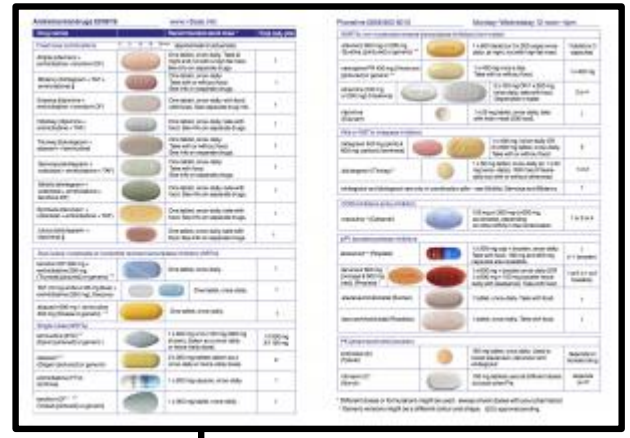
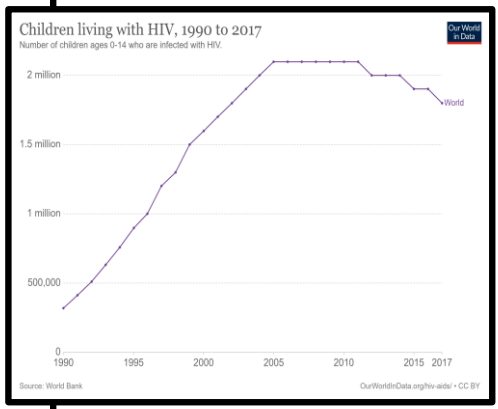


Fig 6. Survival time after diagnosis of AIDS in children less than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1981, and reported to the Centers for Disease Control.









RARE CANCER SEEN IN 41 HOMOSEXUALS

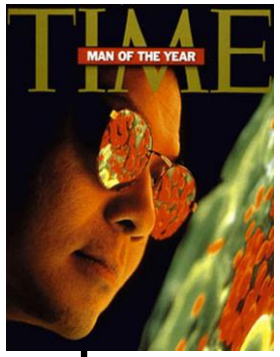
Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the

FDA approves 1st HIV ab test



FDA approves Nelfinavir for kids

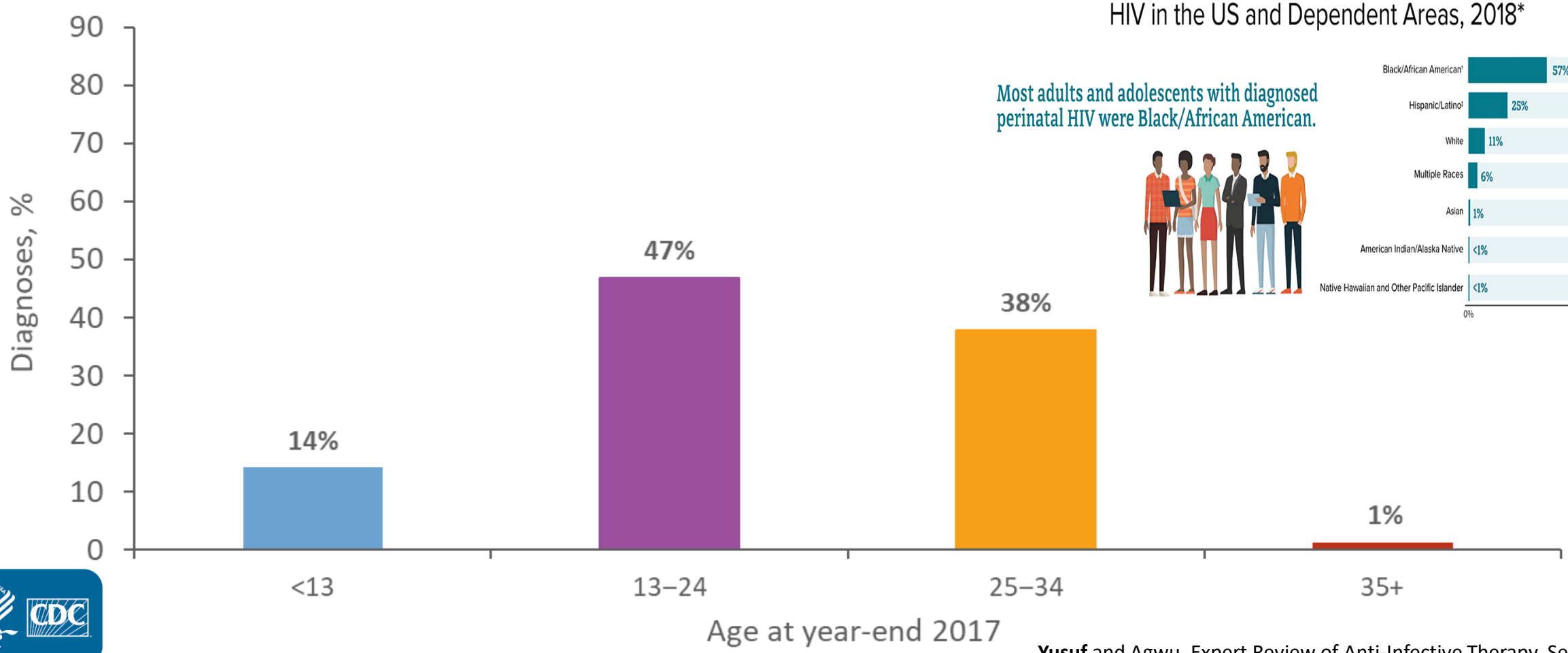
'Cured' HIV Baby is Infected, Doctors Find

South African child in HIV remission without drugs

1977 1980 1982 1985 1987 1988 1990 1994 1996 2003 2006 2013 2014 2015 2017 2020 2021

https://www.hiv.gov/sites/default/files/aidsgov-timeline.pdf; Rogers et al. 1987 (79): 1008-1014

Age Distribution of Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2017—United States and 6 Dependent Areas (N = 11,924)



Yusuf and Agwu. Expert Review of Anti-Infective Therapy. Sep 2020

Many AYA born with HIV are thriving……

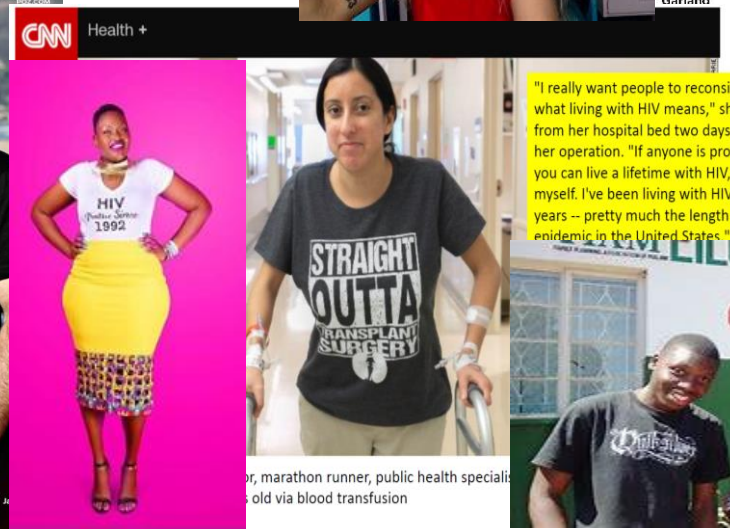
Health | Nation & World

First wave of babies born with HIV nearing 30

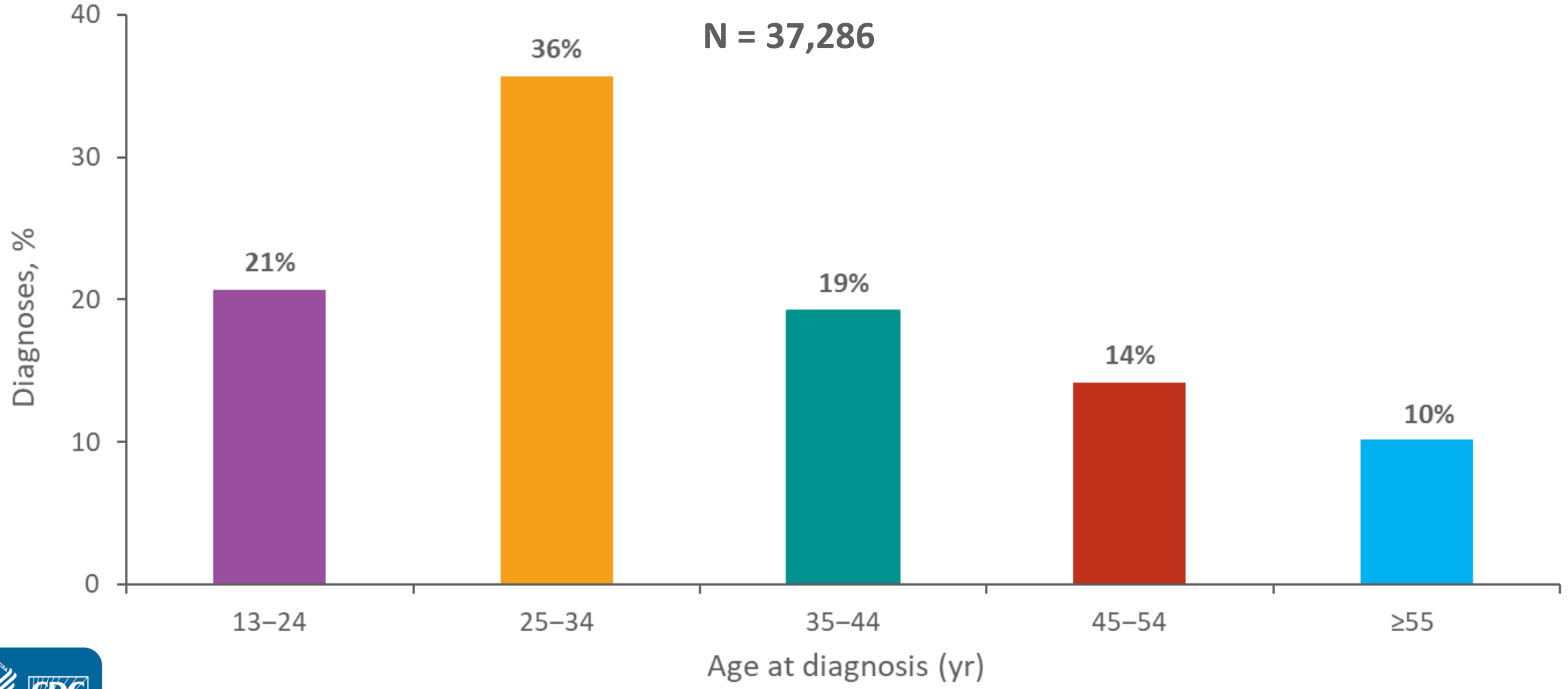
Originally published October 9, 2010 at 6:15 am | *Updated October 9, 2010 at 8:16 am*

Chaneil Scott, left, and Lafayette Sanders, of Philadelphia, were both infected with HIV at birth. Both of the… have died, too. Scott is a college sophomore; Sanders is a brand rep for a… More

…as said

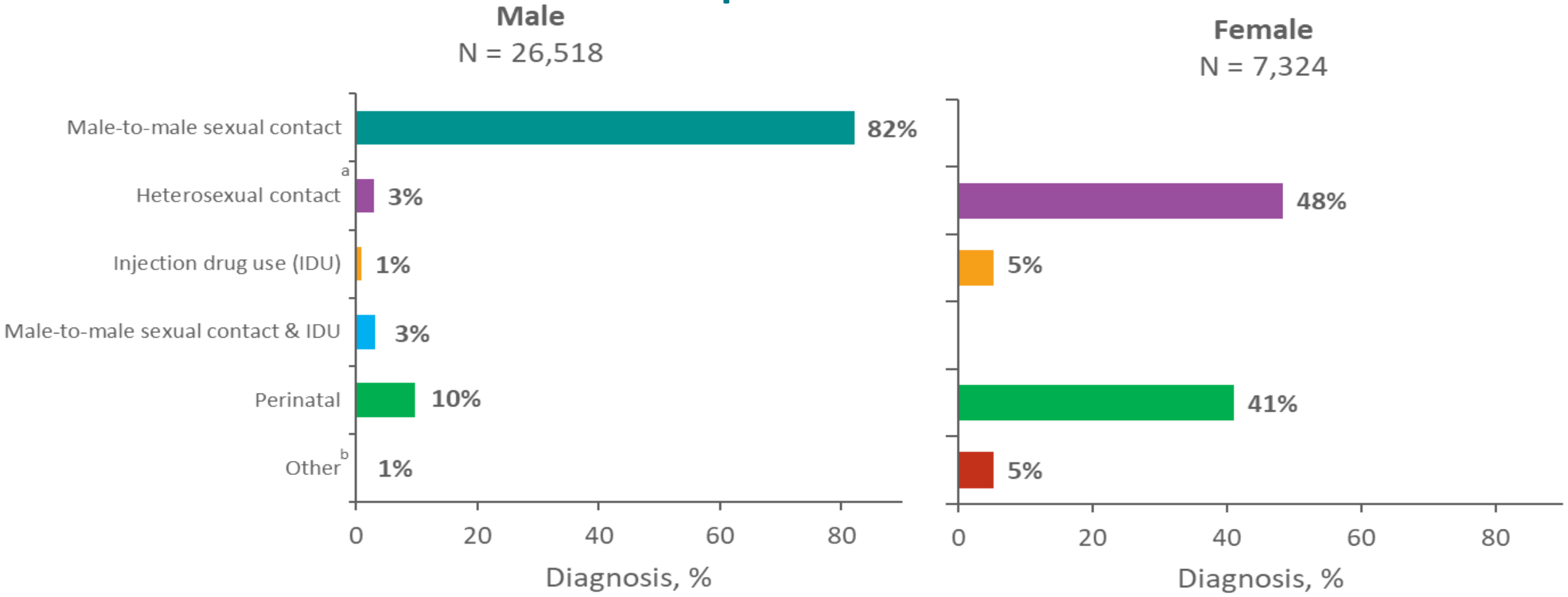


Diagnoses of HIV Infection among Adults and Adolescents by Age at Diagnosis, 2018—United States



Note. Data for the year 2018 are considered preliminary and based on 6 months reporting delay.

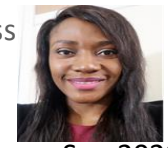
Adolescents and Young Adults Aged 13–24 Years Living with Diagnosed HIV Infection by Sex and Transmission Category, Year-end 2017—United States and 6 Dependent Areas



Note. Data have been statistically adjusted to account for missing transmission category. "Other" transmission category not displayed as it comprises 1% or less cases.

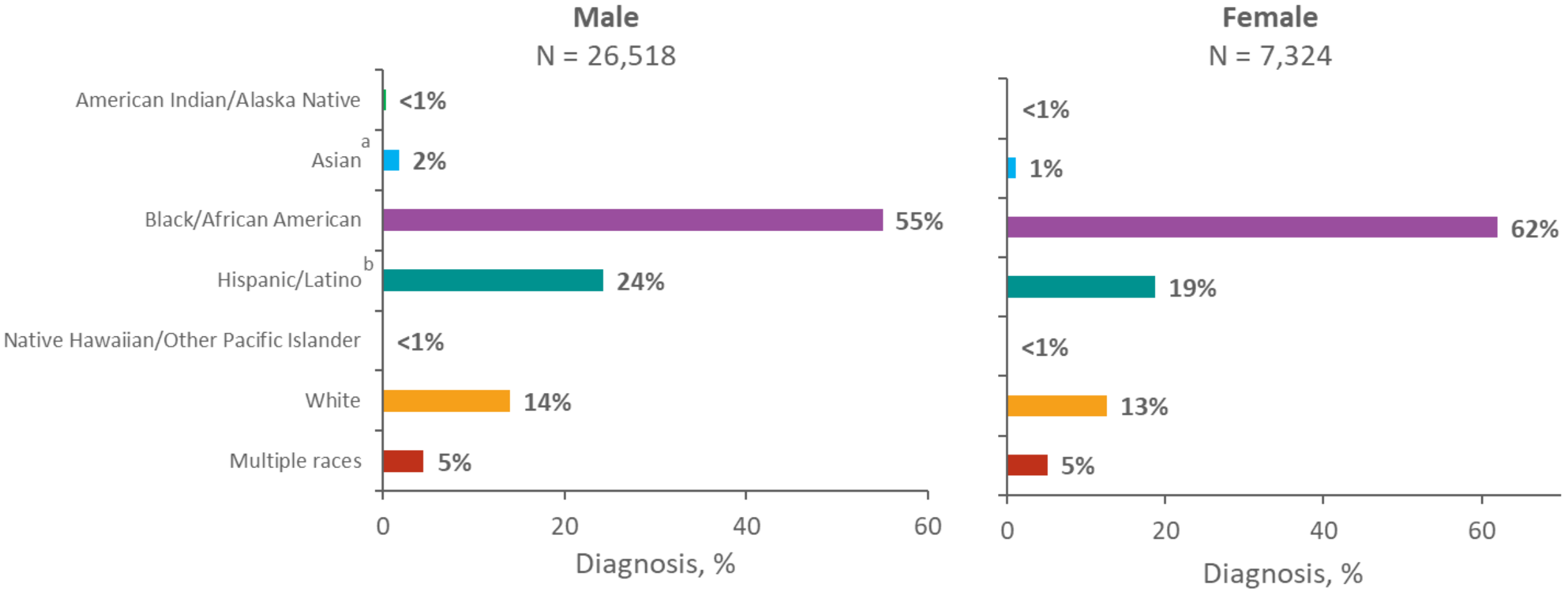
[a] Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

[b] Includes hemophilia, blood transfusion, and risk factor not reported or not identified.



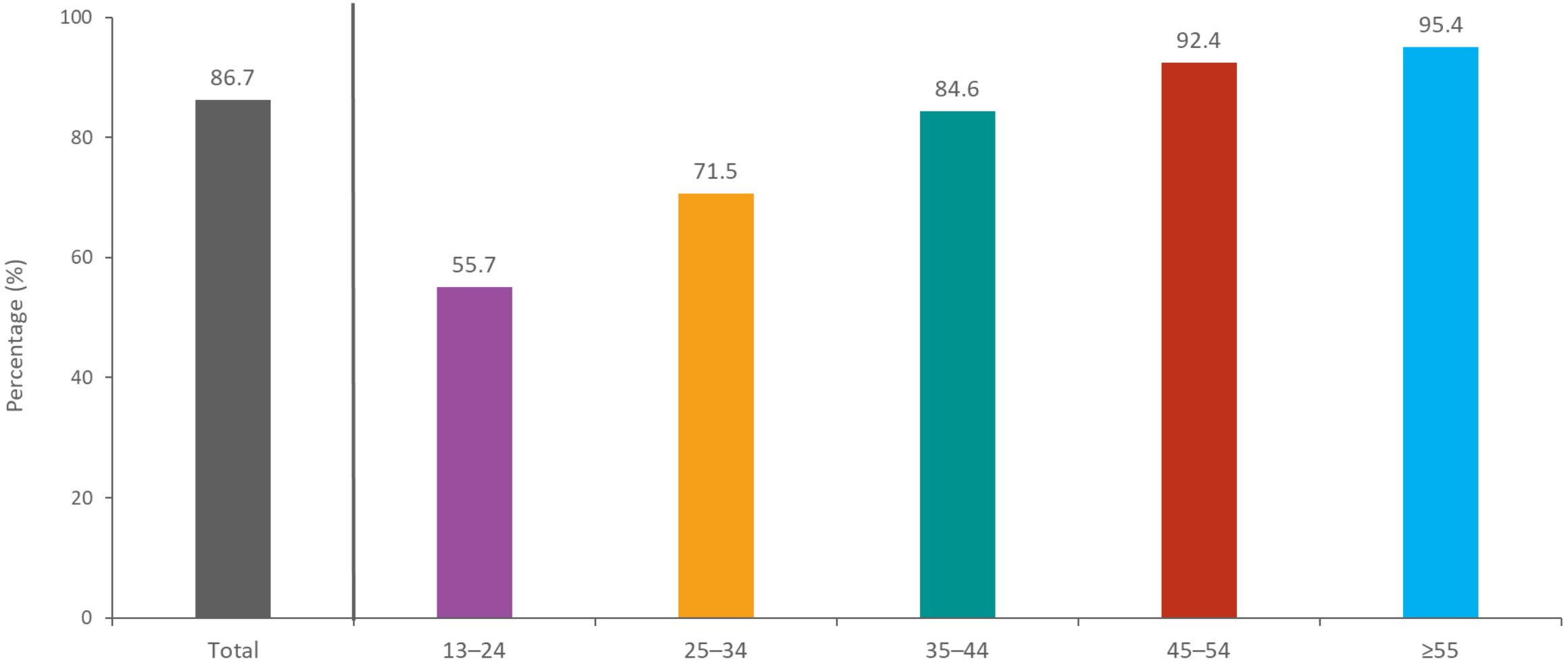
Yusuf & Agwu. Expert Review of Anti-Infective Therapy. Sep 2020

Adolescents and Young Adults Aged 13–24 Years Living with Diagnosed HIV Infection, by Sex and Race/Ethnicity, Year-end 2017—United States and 6 Dependent Areas



[a] Includes Asian/Pacific Islander legacy cases.
[b] Hispanics/Latinos can be of any race.

Diagnosed Infection among Persons Aged ≥13 Years Living with Diagnosed or Undiagnosed HIV Infection, by Age, 2019—United States



Note. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates for the year 2019 are preliminary and based on deaths reported to CDC through December 2020.

Persons Living with Diagnosed or Undiagnosed HIV Infection
HIV Care Continuum Outcomes, by Age, 2018—United States

OPPORTUNITIES

Note. Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2018. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2018. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2018.

Next for treatment for youth

- Multimodal, combination strategies & approaches
  - ART modified (stronger, longer, safer, simpler)
    - ART Resistance
  - Different delivery modes & strategies
  - Monoclonal ab
  - Vaccines
  - Latency reversing agents
  - Activated T cells
- Improved engagement strategies
- Behavioral and community interventions
- Optimizing care models
  - Alternative “venues” for care delivery
  - Increased use of technology
- Personalized medicine?

JOHNS HOPKINS MEDICINE

I>AV

I>AV

I am greater than my highs and lows.

T1D INTERNATIONAL

I>AV

Life course perspective for adolescents with HIV

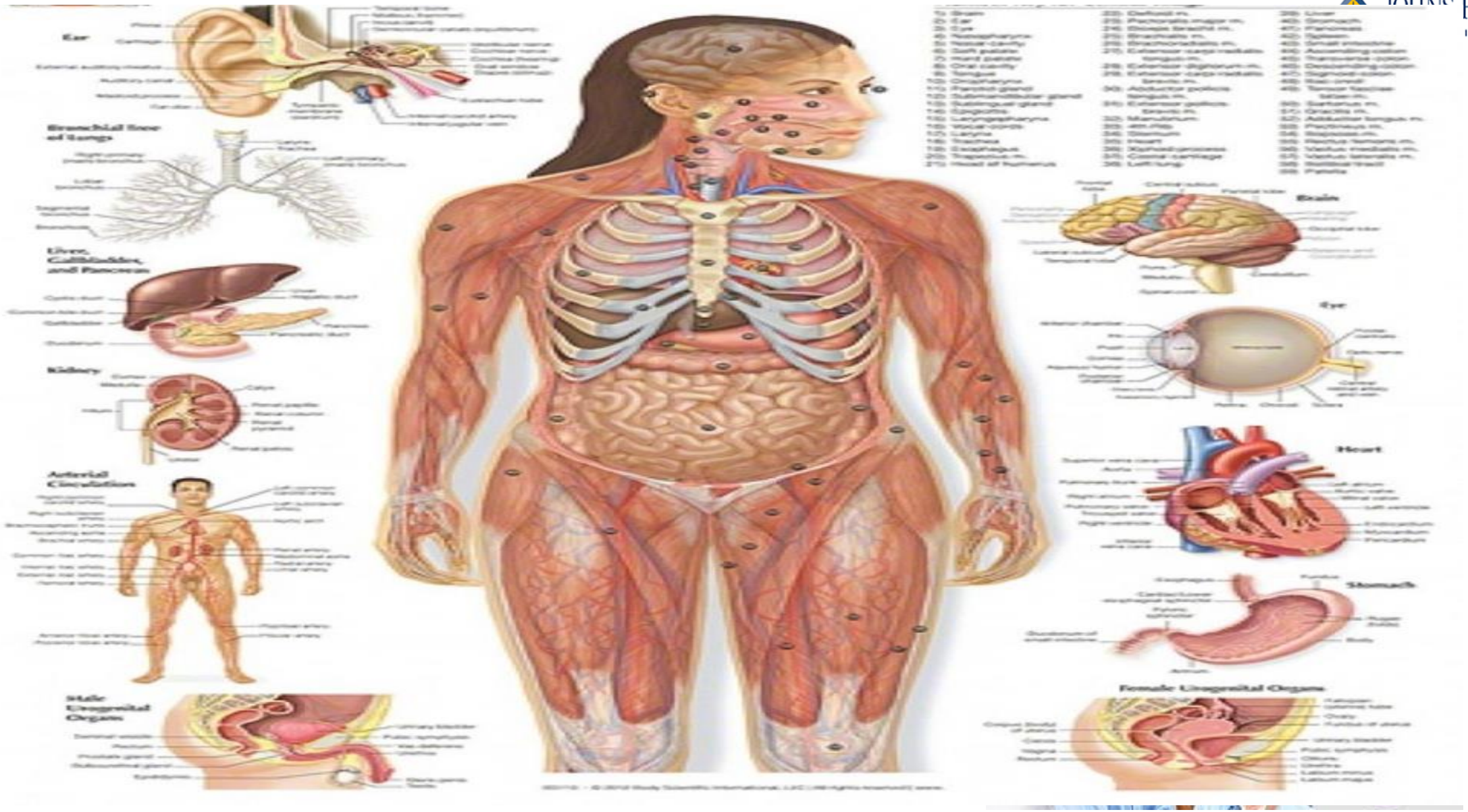
	2nd Decade 10-19 years	3rd Decade 20-29 years	4th Decade 30-39 years	5th Decade 40-49 years	≥6th Decade ≥50 years
					
Environmental/Psychosocial Factors					
Life events	School Trade School/College Employment Parent/guardian loss	Trade School/College Employment Partnerships Children Parent/guardian loss	Employment Partnerships Children Parent/guardian loss	Employment Partnerships Parent/guardian loss	Employment/Retirement Partnerships
Self-management	Parental/caregiver involvement wanes	Self-management			Self-management May need assistance
Disclosure	Disclosure (to self) Disclosure to others	Disclosure of status to partners, children, friends, others			
Stigma	Internal and external stigma				

Zinyemba TP et al. J Econ Surveys 2019; **Yusuf** and Agwu. Expert Review of Anti-Infective Therapy. Sep 2020

Life course perspective for adolescents with HIV

	2nd Decade 10-19 years	3rd Decade 20-29 years	4th Decade 30-39 years	5th Decade 40-49 years	≥6th Decade ≥50 years
					
Treatment and Treatment-related Factors					
Antiretroviral treatment	Simple regimens* Increased responsibility of ART	Simple regimen Increased complex regimens due to development of resistance Full responsiblilty of ART	Simple regimen Increased complex regimens due to development of resistance Full responsiblilty of ART		
Adherence	May wane with decreased parental/caregiver involvement, stigma and nondisclosure to peers	Adherence variable Increased risk of resistance			
Co-morbidities	OIs if nonadherent with immune compromise Non-AIDS comorbidities	Inflammation, accelerated ageing, increased risk of comorbidities	Inflammation, accelerated ageing, ↑ risk of comorbidities		
Care Delivery	Pediatric/Adolescent care; transition from pediatric to adolescent or adult care may occur	Transition to adult care	Adult Care		
Risk factors	Tobacco, substance use may commence, modifiable risk factors begin	Increased weight gain, engagement in modifiable risk factors			

Yusuf and Agwu 2021



How will adolescents with HIV infection be impacted?

Deeks SG 2013; Vance DE et al. Am J Nurs. 2010 March ; 110(3): 42–49; Chiappini E. etal. Aging. 2018.

JOHNS HOPKINS MEDICINE

Leading Cause of Death in the United States for Select Age Groups (2019)

Data Courtesy of CDC

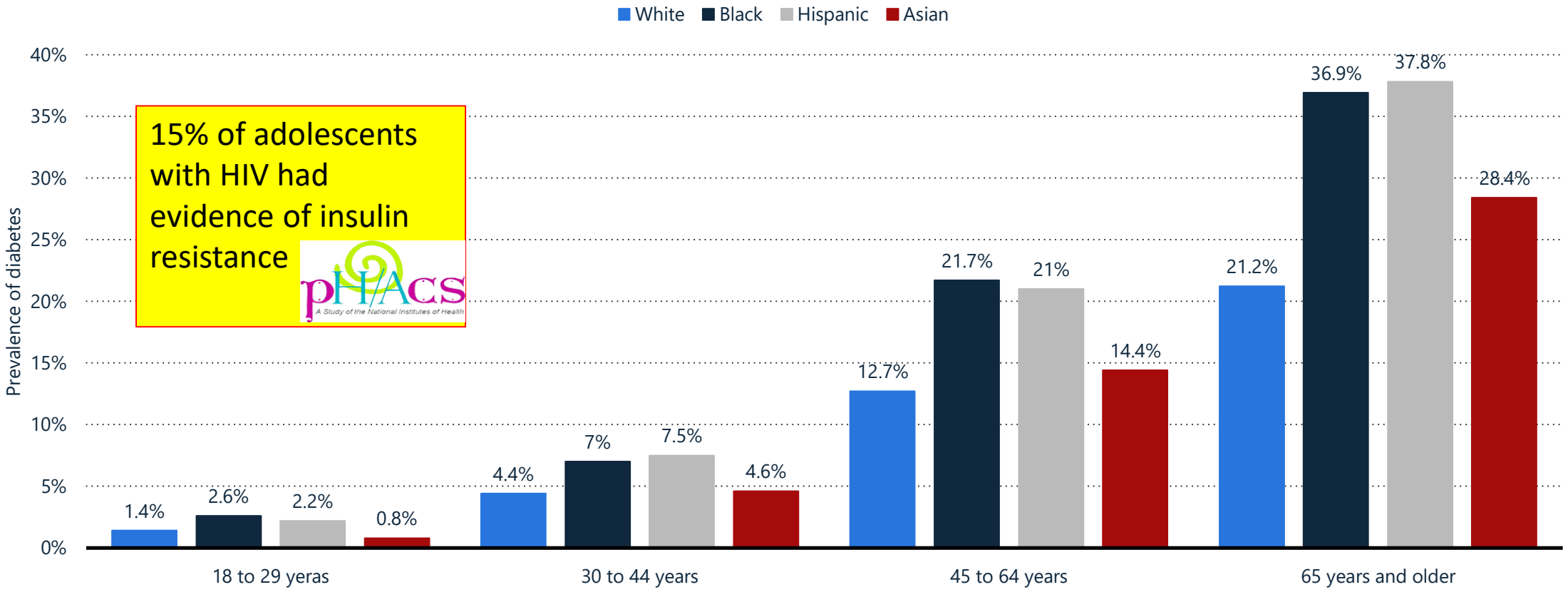
Rank	10-14	15-24	25-34	35-44	45-54	55-64	All Ages
1	Unintentional Injury 778	Unintentional Injury 11,755	Unintentional Injury 24,516	Unintentional Injury 24,070	Malignant Neoplasms 35,587	Malignant Neoplasms 111,765	Heart Disease 659,041
2	**Suicide 534**	**Suicide 5,954**	**Suicide 8,059**	Malignant Neoplasms 10,695	Heart Disease 31,138	Heart Disease 80,837	Malignant Neoplasms 599,601
3	Malignant Neoplasms 404	Homicide 4,774	Homicide 5,341	Heart Disease 10,499	Unintentional Injury 23,359	Unintentional Injury 24,892	Unintentional Injury 173,040
4	Homicide 191	Malignant Neoplasms 1,388	Malignant Neoplasms 3,577	**Suicide 7,525**	Liver Disease 8,098	CLRD 18,743	CLRD 156,979
5	Congenital Anomalies 189	Heart Disease 872	Heart Disease 3,495	Homicide 3,446	**Suicide 8,012**	Diabetes Mellitus 15,508	Cerebro-vascular 150,005
6	Heart Disease 87	Congenital Anomalies 390	Liver Disease 1,112	Liver Disease 3,417	Diabetes Mellitus 6,348	Liver Disease 14,385	Alzheimer's Disease 121,499
7	CLRD 81	Diabetes Mellitus 248	Diabetes Mellitus 887	Diabetes Mellitus 2,228	Cerebro-vascular 5,153	Cerebro-vascular 12,931	Diabetes Mellitus 87,647
8	Influenza & Pneumonia 71	Influenza & Pneumonia 175	Cerebro-vascular 585	Cerebro-vascular 1,741	CLRD 3,592	**Suicide 8,238**	Nephritis 51,565
9	Cerebro-vascular 48	CLRD 168	Complicated Pregnancy 532	Influenza & Pneumonia 951	Nephritis 2,269	Nephritis 5,857	Influenza & Pneumonia 49,783
10	Benign Neoplasms 35	Cerebro-vascular 158	HIV 486	Septicemia 812	Septicemia 2,176	Septicemia 5,672	**Suicide 47,511**

CLRD: Chronic Lower Respiratory Disease

Note: Suicide is not among the ten leading causes of death among children in the 0-9 year age group nor in adults in the age group 65 years and older.

CDC

Percentage of adults in the U.S. with diabetes as of 2016, by age and ethnicity



Note(s): United States; January 2 to December 30, 2016; 18 years and older; 177,192 respondents; Full or part time workers
Further information regarding this statistic can be found on page 8.
Source(s): Gallup (Gallup-Sharecare Well-Being Index); Sharecare; ID 790778

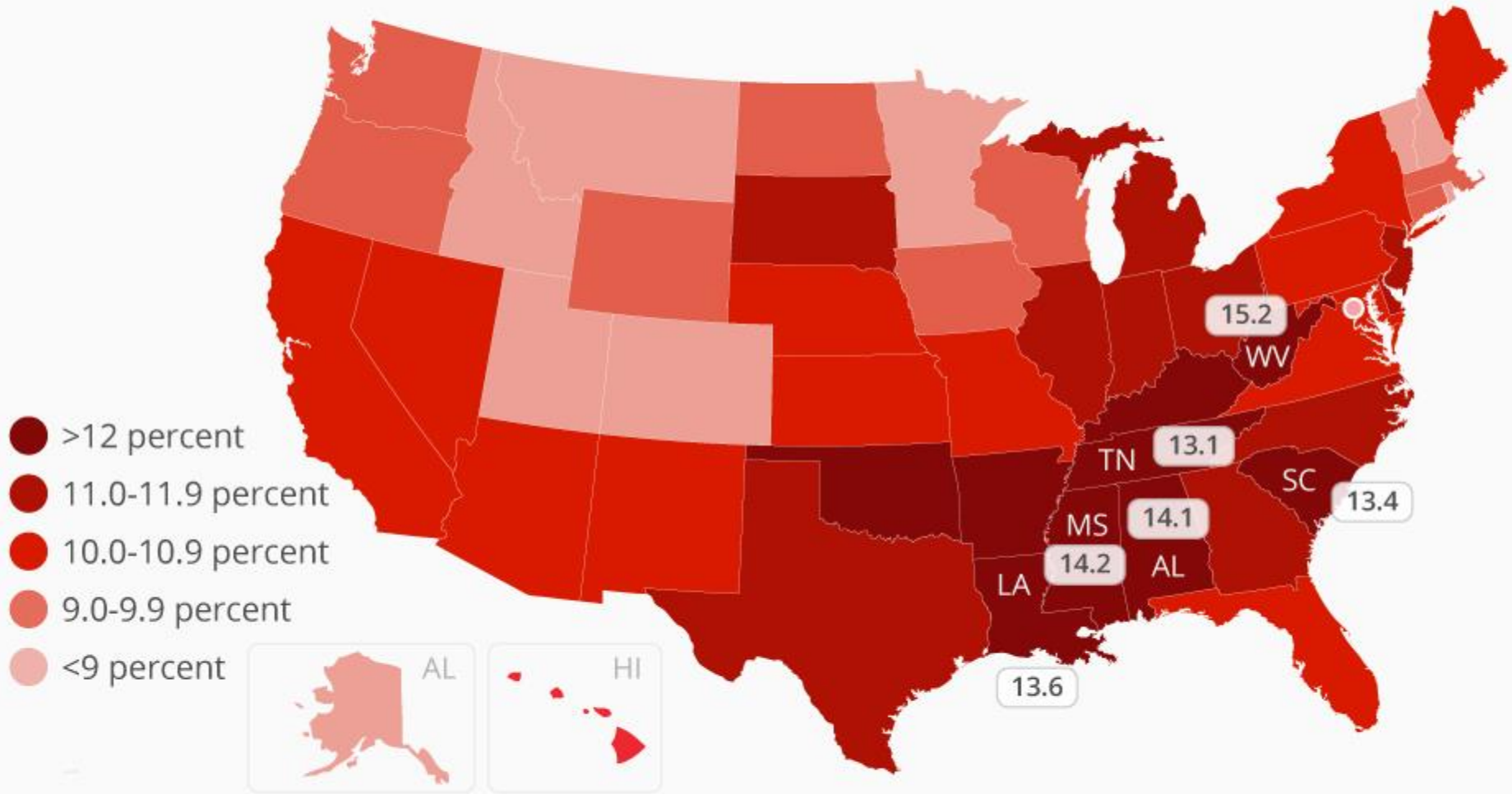
statista

Geffner ME. Horm Res Paediatr 2011; 76: 386-91

JOHNS HOPKINS MEDICINE

Where Diabetes is Most Prevalent in the U.S.

Percent of adults who have ever been told by a doctor that they have diabetes (2017*)



Includes pregnancy-related diabetes, percentages are weighted to reflect population characteristics (e.g. average age)
* latest on record

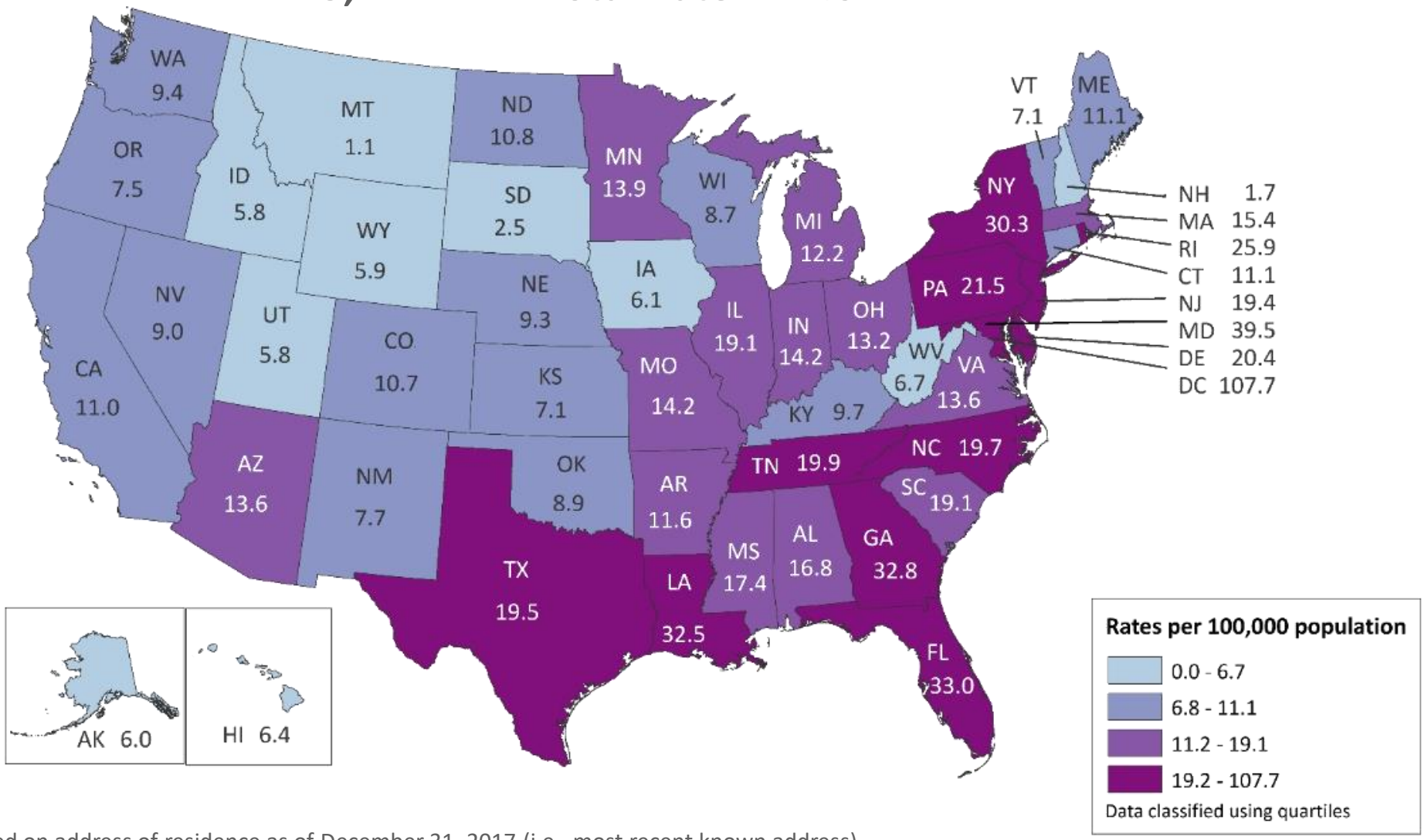
Sources: Kaiser Family Foundation, CDC

statista

Rates of Adolescents Aged 13–19 Years Living with Diagnosed HIV Infection

Year-end 2017—United States and 6 Dependent Areas

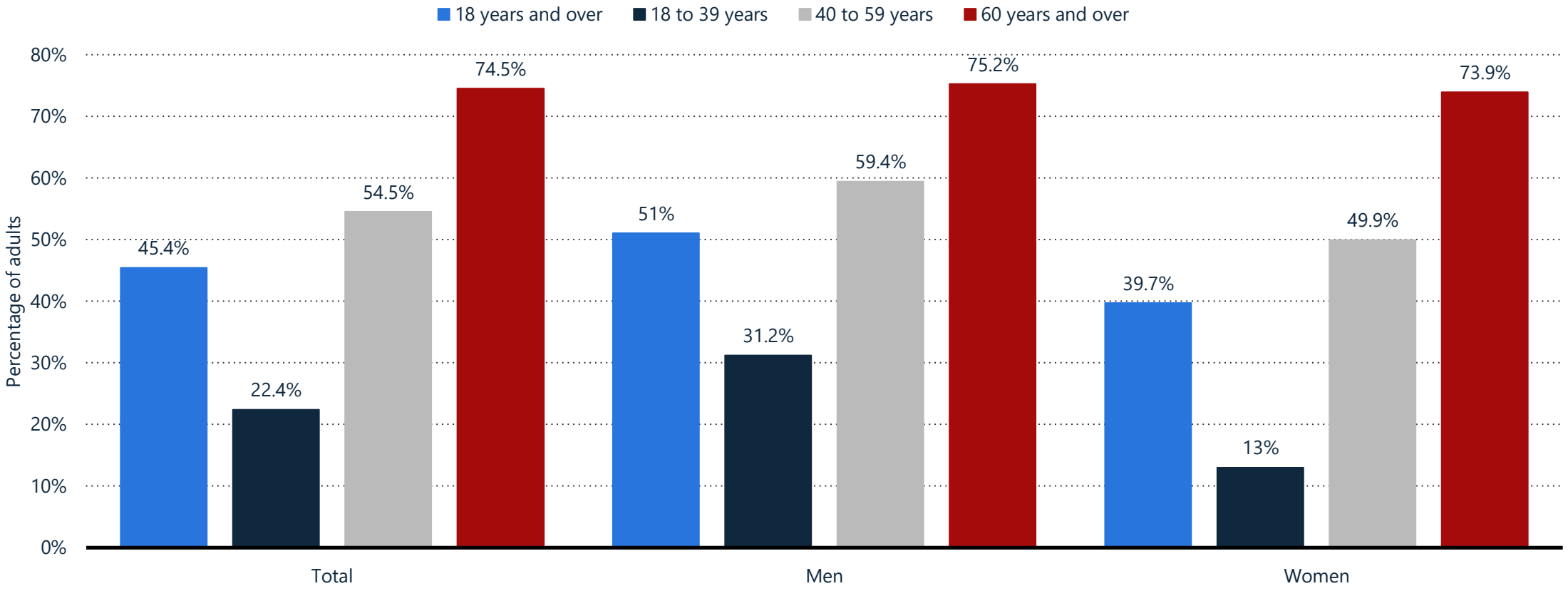
N = 5,222 **Total Rate = 17.6**



American Samoa	0.0
Guam	5.0
Northern Mariana Islands	0.0
Puerto Rico	14.6
Republic of Palau	0.0
U.S. Virgin Islands	34.3

Note. Data are based on address of residence as of December 31, 2017 (i.e., most recent known address).

Prevalence of hypertension among adults in the U.S. in 2017 and 2018, by age and gender

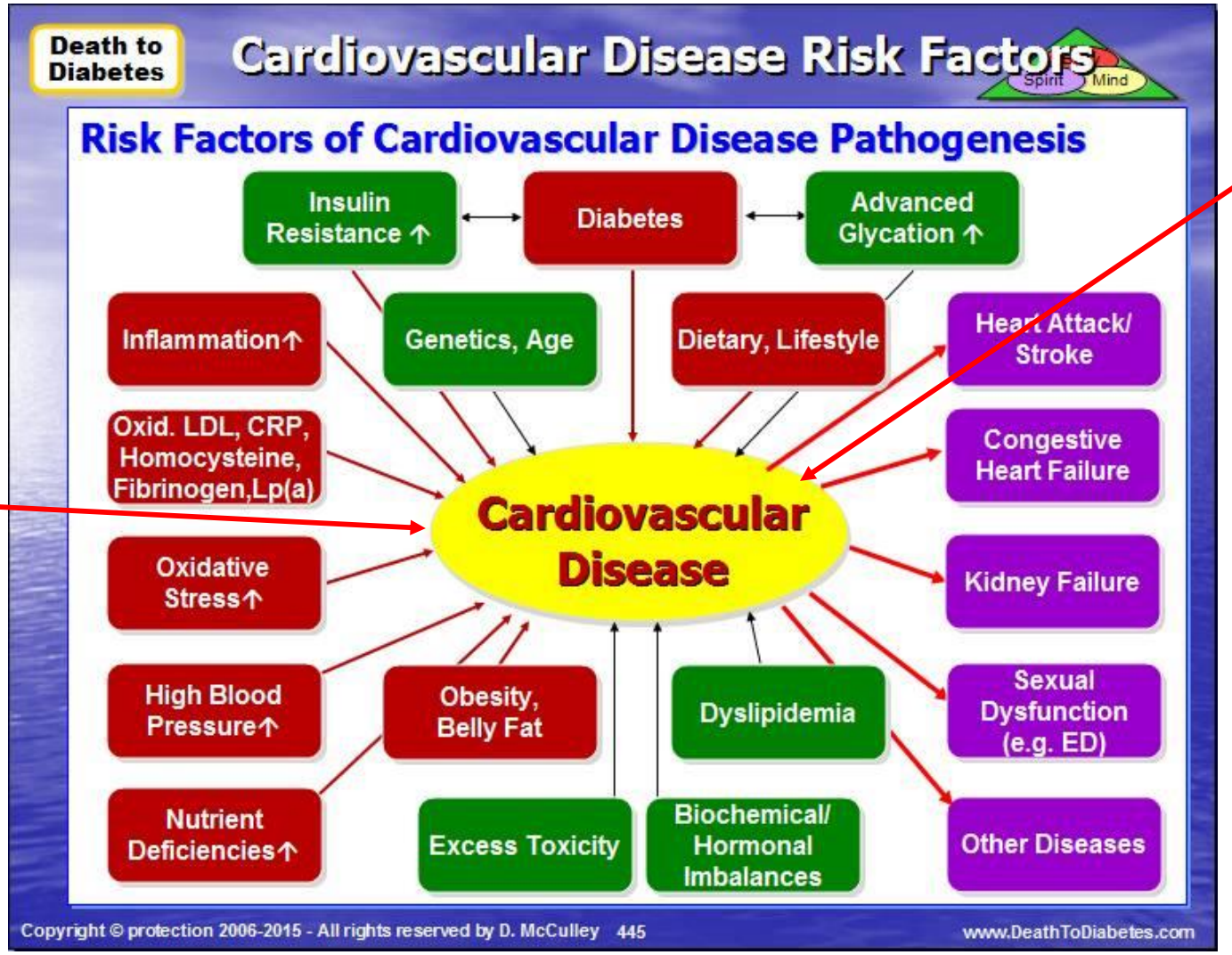


Adolescent boys (15-19%); adolescent girls (7-12%) Flynn JT et al. Pediatrics 2017
Among HIV+ youth ??20% Sainz et al PIDJ 2016

Note(s): United States; 2017 and 2018; 18 years and older
Further information regarding this statistic can be found on page 8.
Source(s): NCHS (National Health and Nutrition Examination Survey); CDC; ID 778065

HIV

ART?


Death to Diabetes
Cardiovascular Disease Risk Factors
Spirit
Mind
Risk Factors of Cardiovascular Disease Pathogenesis
Insulin Resistance ↑
Diabetes
Advanced Glycation ↑
Inflammation↑
Genetics, Age
Dietary, Lifestyle
Heart Attack/ Stroke
Oxid. LDL, CRP, Homocysteine, Fibrinogen,Lp(a)
Congestive Heart Failure
Cardiovascular Disease
Oxidative Stress↑
Kidney Failure
High Blood Pressure↑
Obesity, Belly Fat
Dyslipidemia
Sexual Dysfunction (e.g. ED)
Nutrient Deficiencies↑
Excess Toxicity
Biochemical/ Hormonal Imbalances
Other Diseases
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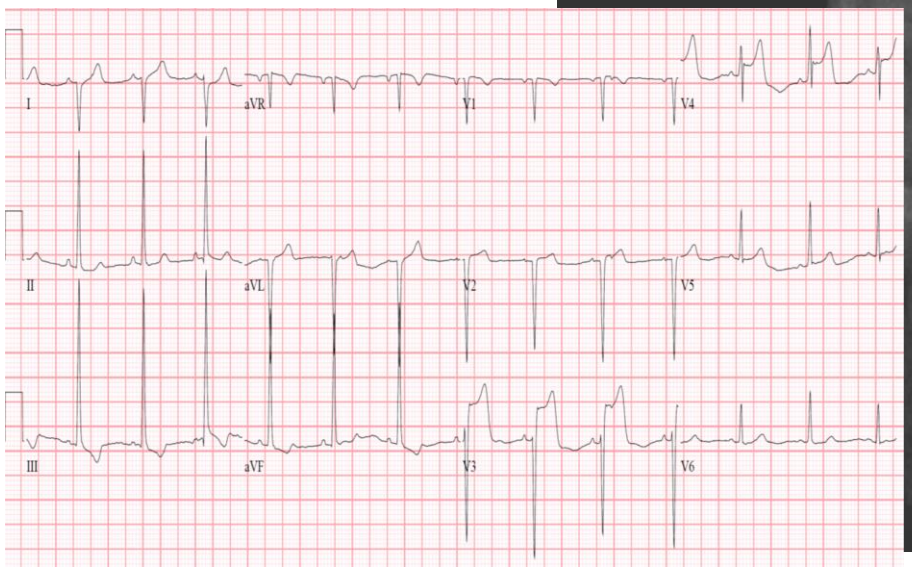
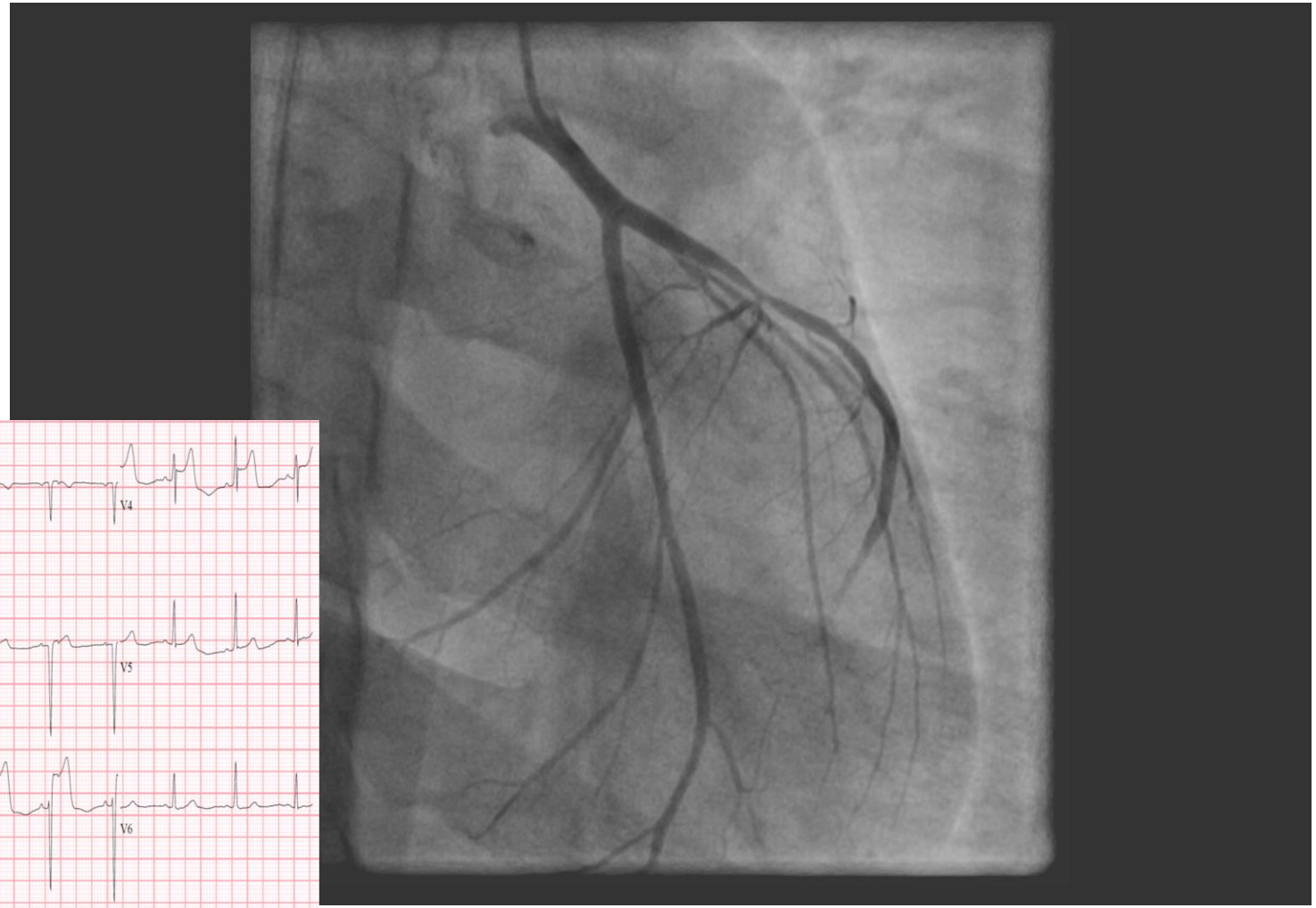
www.DeathToDiabetes.com

23 year old with HIV and acute chest pain





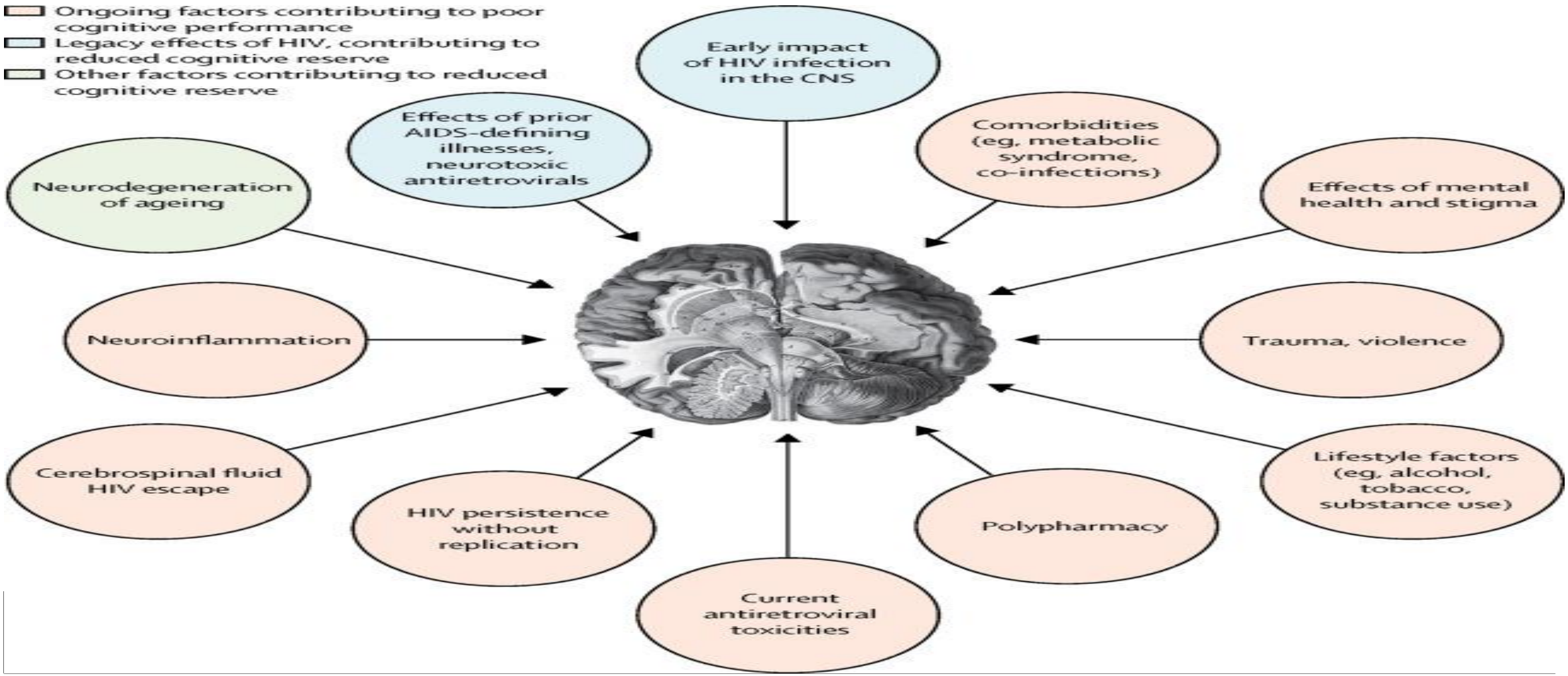
Griffith OFID 2018

CVD Data for Youth with HIV

- **Studies of children and youths in non-HIV disease states (diabetes, obesity) link arterial stiffness and thickness to hypertension & increased left ventricular mass**
- **Limited data on youth with perinatal infection**
  - Mixed results, study challenges
  - ↑ arterial thickness (carotid intimal medial thickness) in HIV+ vs. HIV-
  - ↑ arterial stiffness (pulse wave velocity) & ↓ flow-mediated dilatation in HIV+ vs. HIV-
  - ↑ inflammatory markers in HIV+ vs. HIV-→ associated with arterial thickness, stiffness, and flow-mediated dilatation
  - ↑ inflammatory markers despite longstanding virologic suppression
  - AYA with HIV have higher markers of cardiopulmonary dysfunction
    - Up to 28% show evidence of early cardiovascular dysfunction
    - Biomarkers of cardiomyocyte stress and injury (high sensitivity cardiac troponin-T [hs-cTnT] and N-terminal-pro-brain natriuretic peptide [NT-proBNP]) are elevated compared to uninfected adolescents after adjusting for adherence to ART,
    - Inflammation associated with poorer left ventricular function and increased stress in the ventricular walls

Miller TI, et al. HIV Med. 2012 13(5): 264-75; Sainz T et al Atherosclerosis 2014, Ross et al, Persaud D JAMA Peds 2014, Yusuf 2020

Mental health in adolescents born with HIV



Phillips Pediatrics 2016; Malee AIDS Care 2011; Scharko AIDS Care 2006; Earnshaw AIDS & Behavior 2018; Well Project; Winston A et al Lancet HIV 2020

Sexual and reproductive health for adults born with HIV

	2nd Decade 10-19 years	3rd Decade 20-29 years	4th Decade 30-39 years	5th Decade 40-49 years	≥6th Decade ≥50 years
					
Sexual and Reproductive Health					
Sex/reproductive	Sexual and gender identify evolving; Sexual activity often commences Risk reduction	Secondary Prevention Child bearing Risk reduction	Secondary Prevention Child bearing Risk reduction	Secondary Prevention Risk reduction	

Phillips Pediatrics 2016; Malee AIDS Care 2011; Scharko AIDS Care 2006; Earnshaw AIDS & Behavior 2018; Yusuf 2020

STI Rates among adolescents

Rates of chlamydia, gonorrhea, and primary & secondary syphilis ↑ for both sexes in 15–24 year olds

Chlamydia: highest among women 15–24 years; males 15–24 years ↑ 29% (2013–2017), while the rate in females ↑ 9%

Gonorrhea: males 15–24 years ↑ 52%, while the rate in females increased 24%

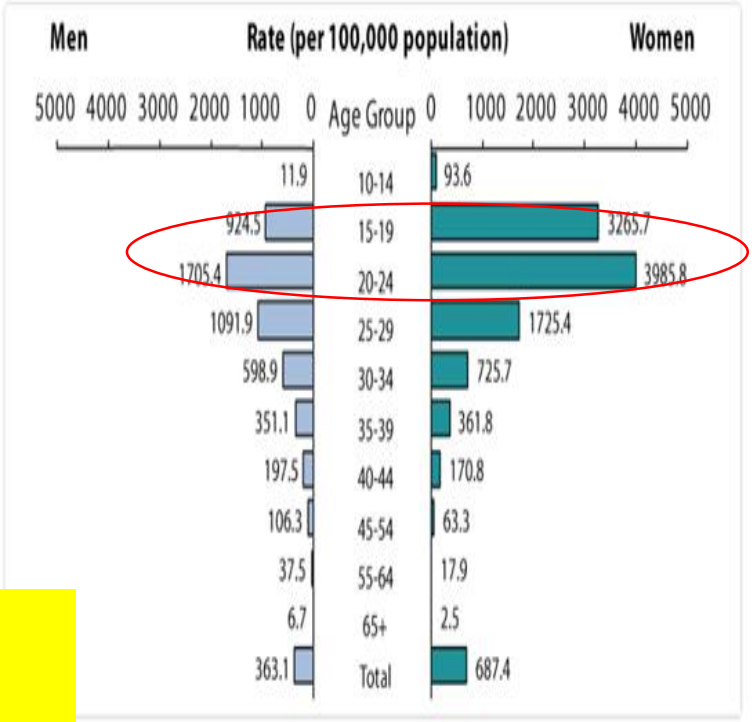
Reasons for increases include:

- ↑ incidence
- ↑ screening among young men
- ↑ extragenital screening

HIV positive adolescents:

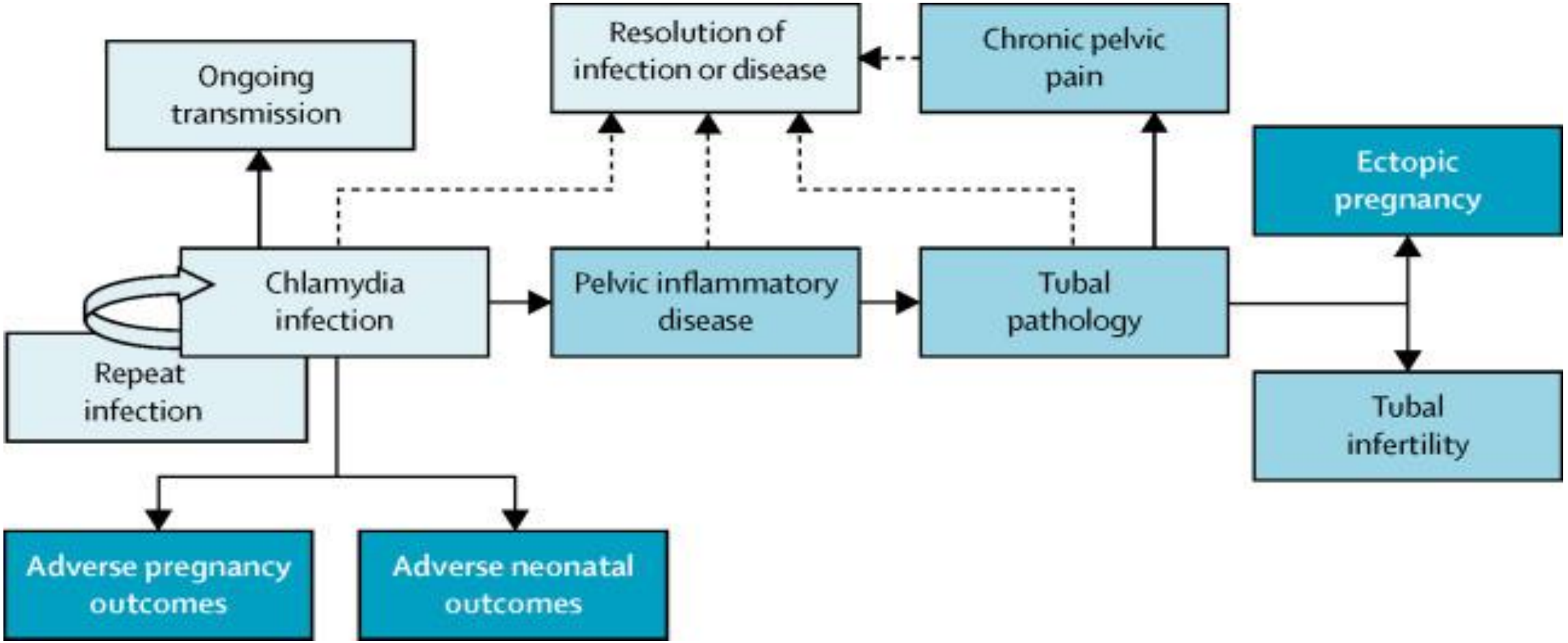
- Perinatally acquired: ↑ likelihood to use condoms (60% use condoms inconsistently); 30% have >1 concurrent partner
- Non-perinatally acquired: continued sexual activity, inconsistent condom use
- Pregnancy desires unchanged

Figure 5. Chlamydia – Rates of Reported Cases by Age Group and Sex, United States, 2017

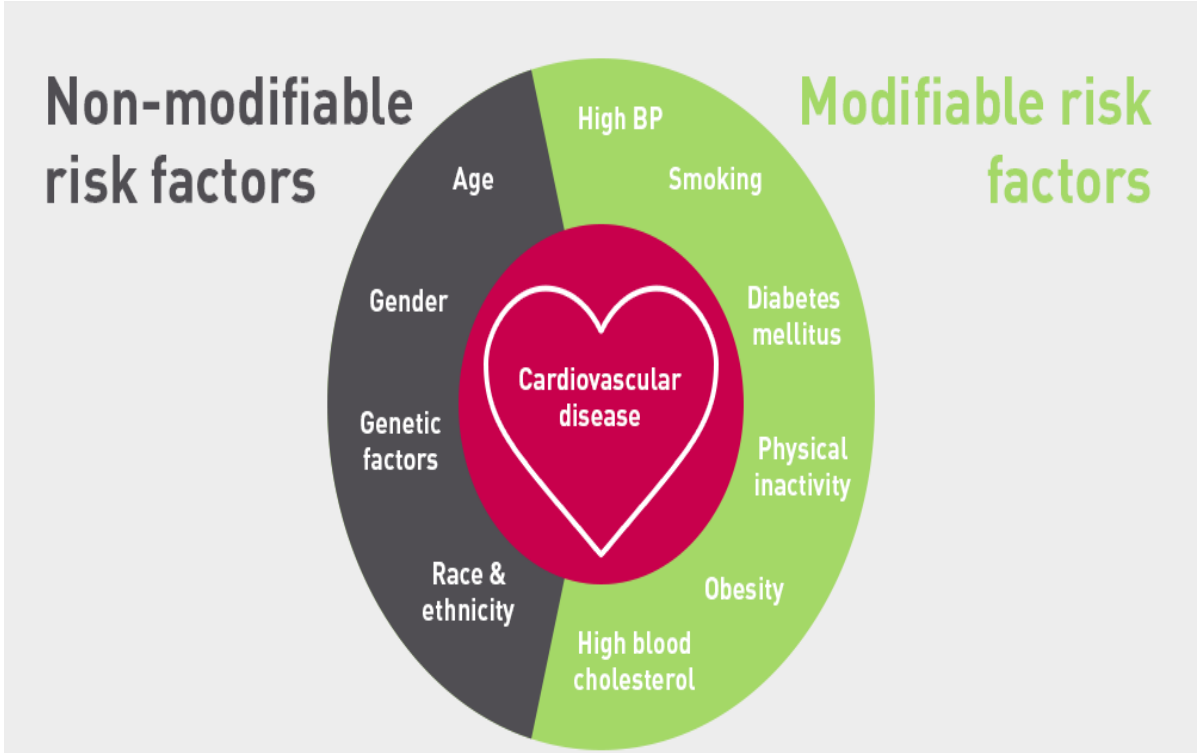


Judd et al PLoS One 2018; Ankunda Pan Afr Med 2016; Koenig JAIDS 2010; CDC

Comorbidities and Sequelae Resulting from STIs



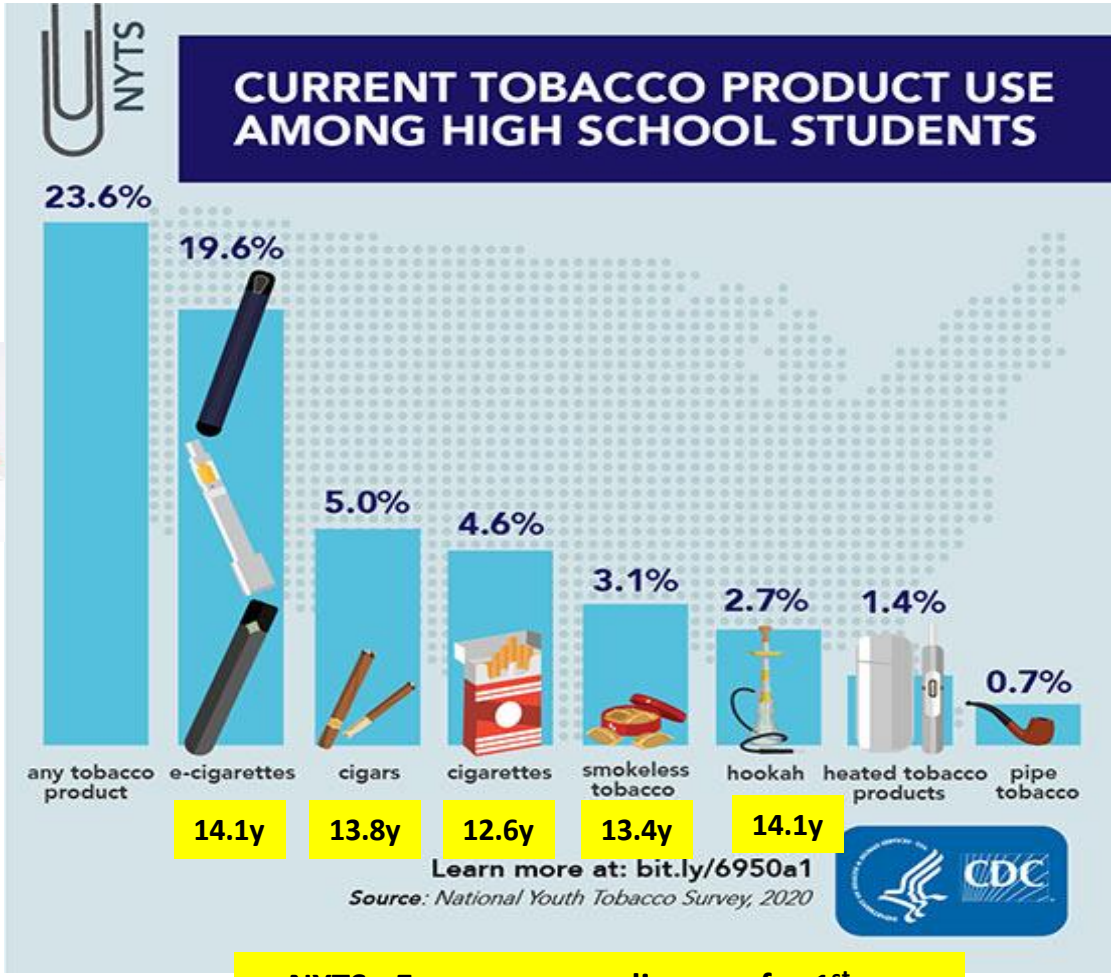
Unemo et al. Lancet ID 2017. 17(8): E235-79



Non-modifiable	Modifiable	Lifestyle	Social
• Age • Gender • Family history of CVD • Ethnicity • Genetic evidence • Previous history of CVD	• Blood pressure • Total cholesterol • HDL cholesterol • Smoking • Blood sugar/diabetes • BMI • Markers of chronic inflammation	• Smoking • Diet • Exercise • Stress	• Income • Social deprivation • Environment

Tobacco use among adolescents

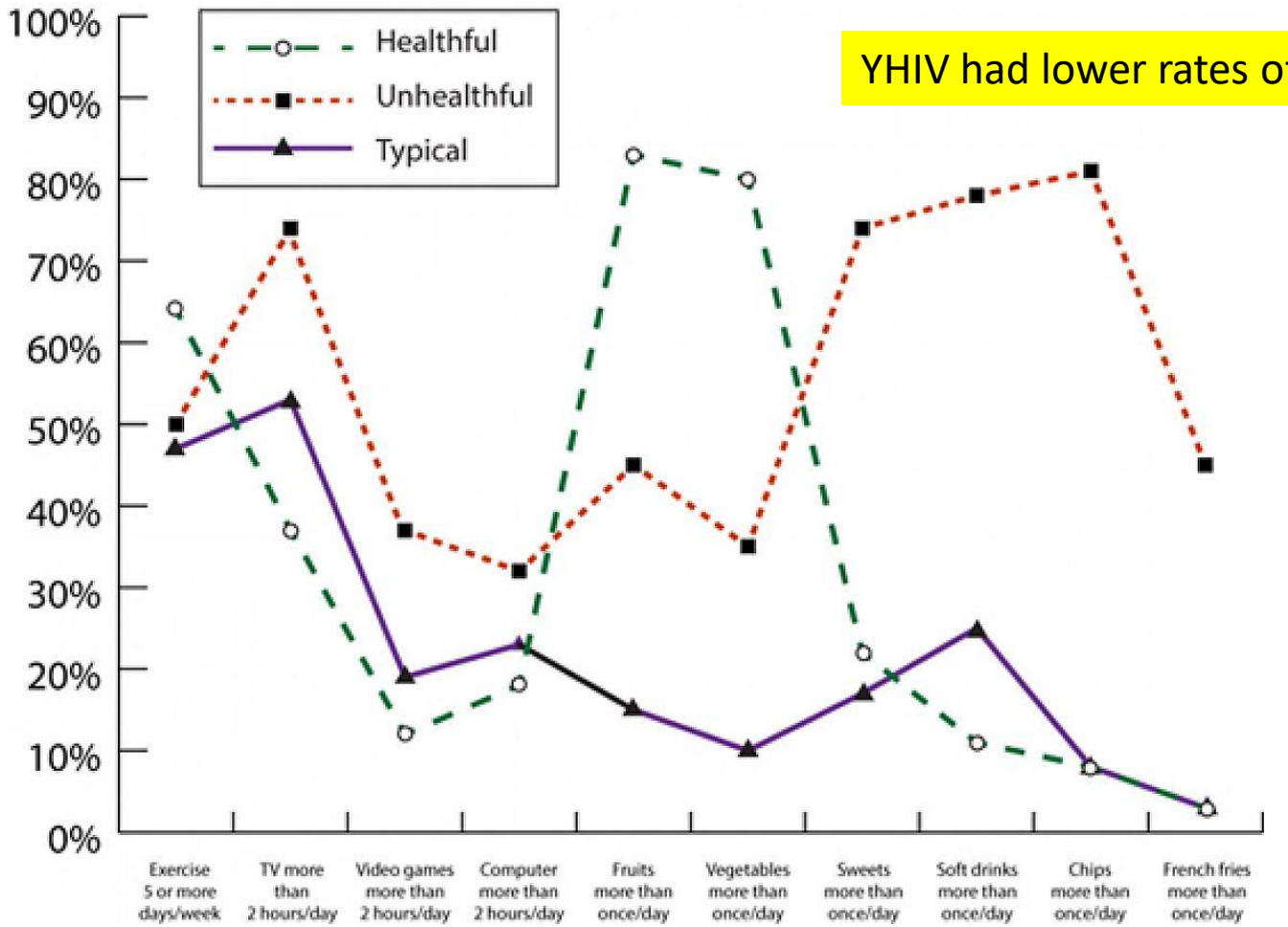
- 7% of middle schoolers and 23% of high schoolers report current use of a tobacco product
- Younger age at start associated with ↑ nicotine dependence
- Cigarillos use has markedly ↑ among adolescents
- YHIV: 24% daily/almost daily tob (ATN)
  - Associated with greater AIDS-related morbidity/mortality
  - Mixed association with viral load



NYTS: Ever-users, median age for 1st use

Nasim et al. Nicotine & Tobacco Research 2016; https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm, Sharapova BMJ 2018

Physical activity and lifestyle among adolescents

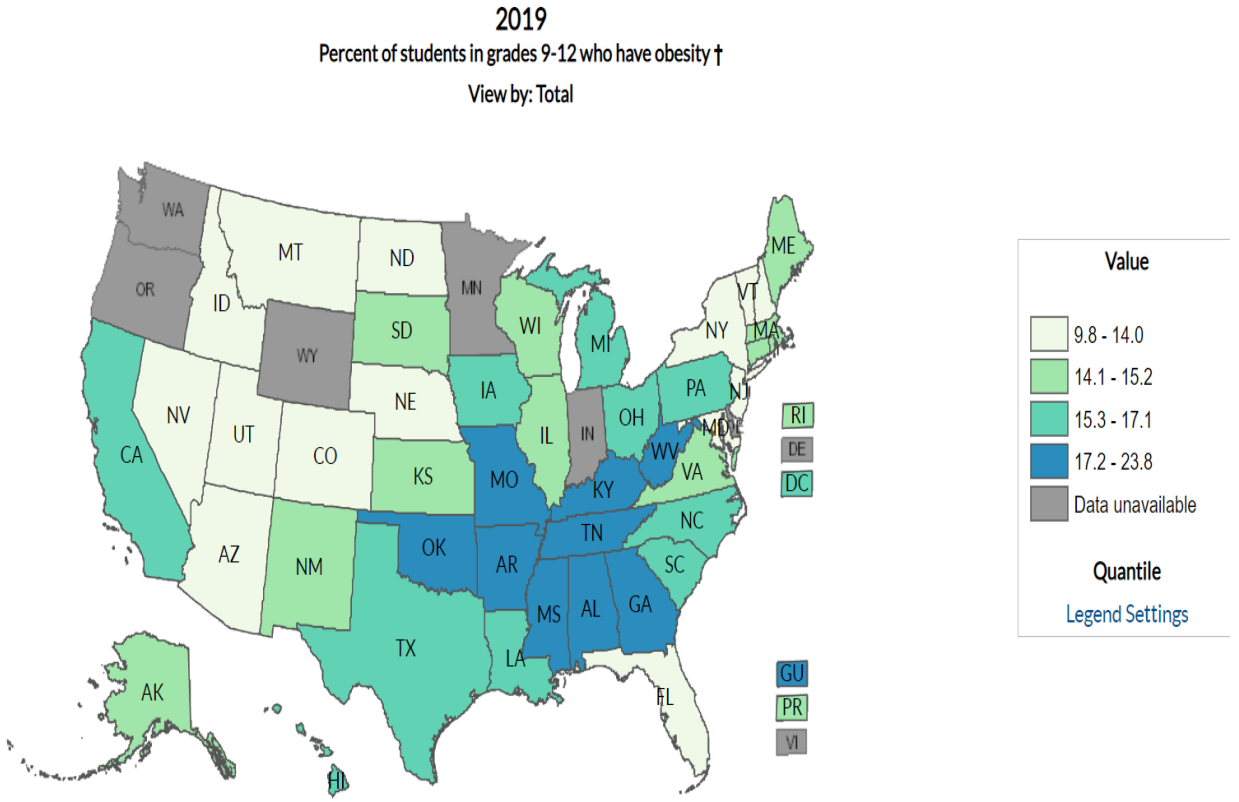


YHIV had lower rates of physical activity than HEU (PHACS)

https://www.nih.gov/news-events/news-releases/only-half-us-youth-meet-physical-activity-standards-nih-study-shows; Dirajilal-Fargo et al. JAIDS 2021

Obesity

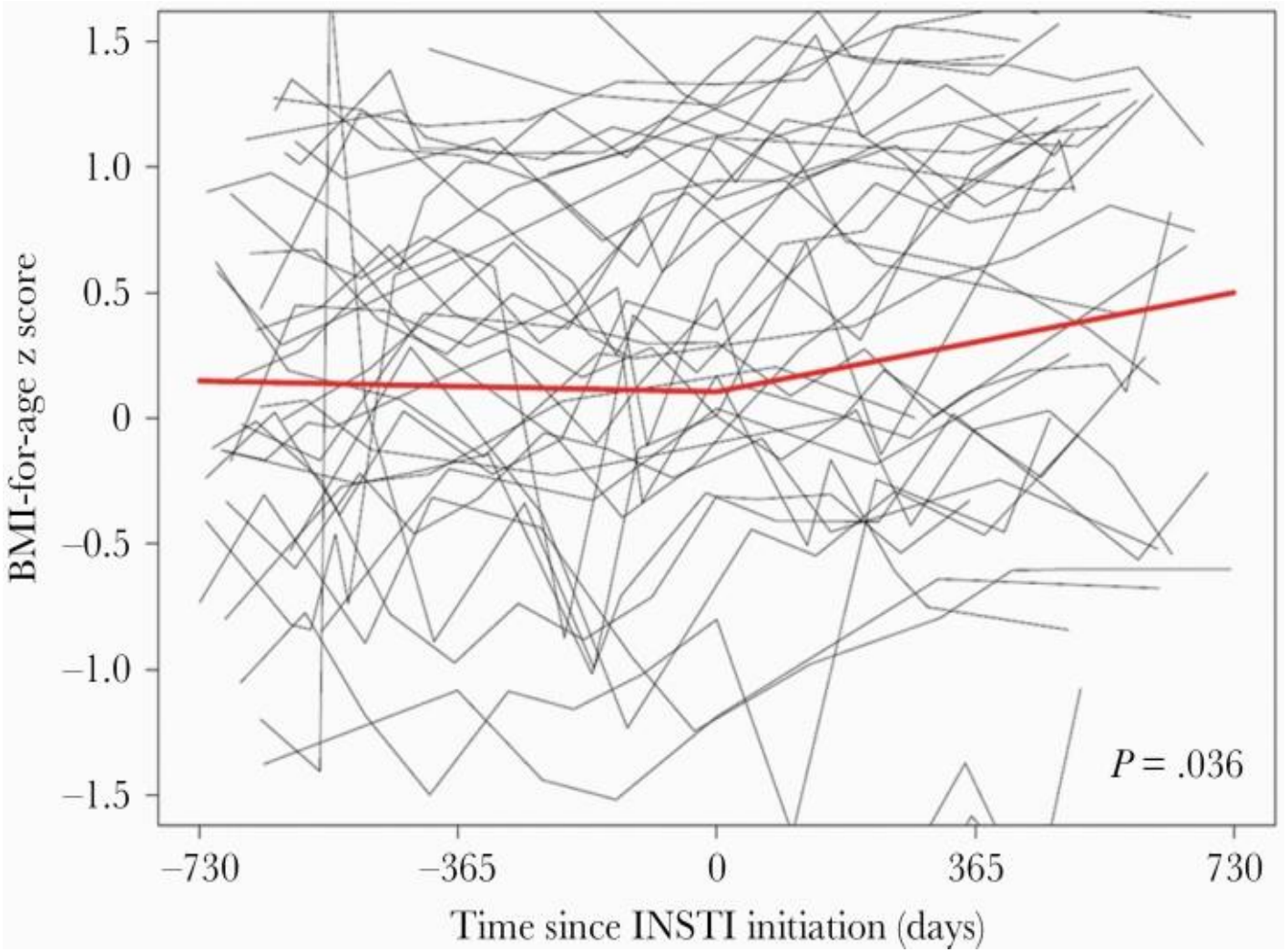
- 21% of 12-19 year olds are obese
  - Hispanic (26%)
  - non-Hispanic Black (24%)
  - non-Hispanic White (16%)
- 40-52% of HIV-positive youth overweight/obese



Obesity: ≥95th percentile BMI

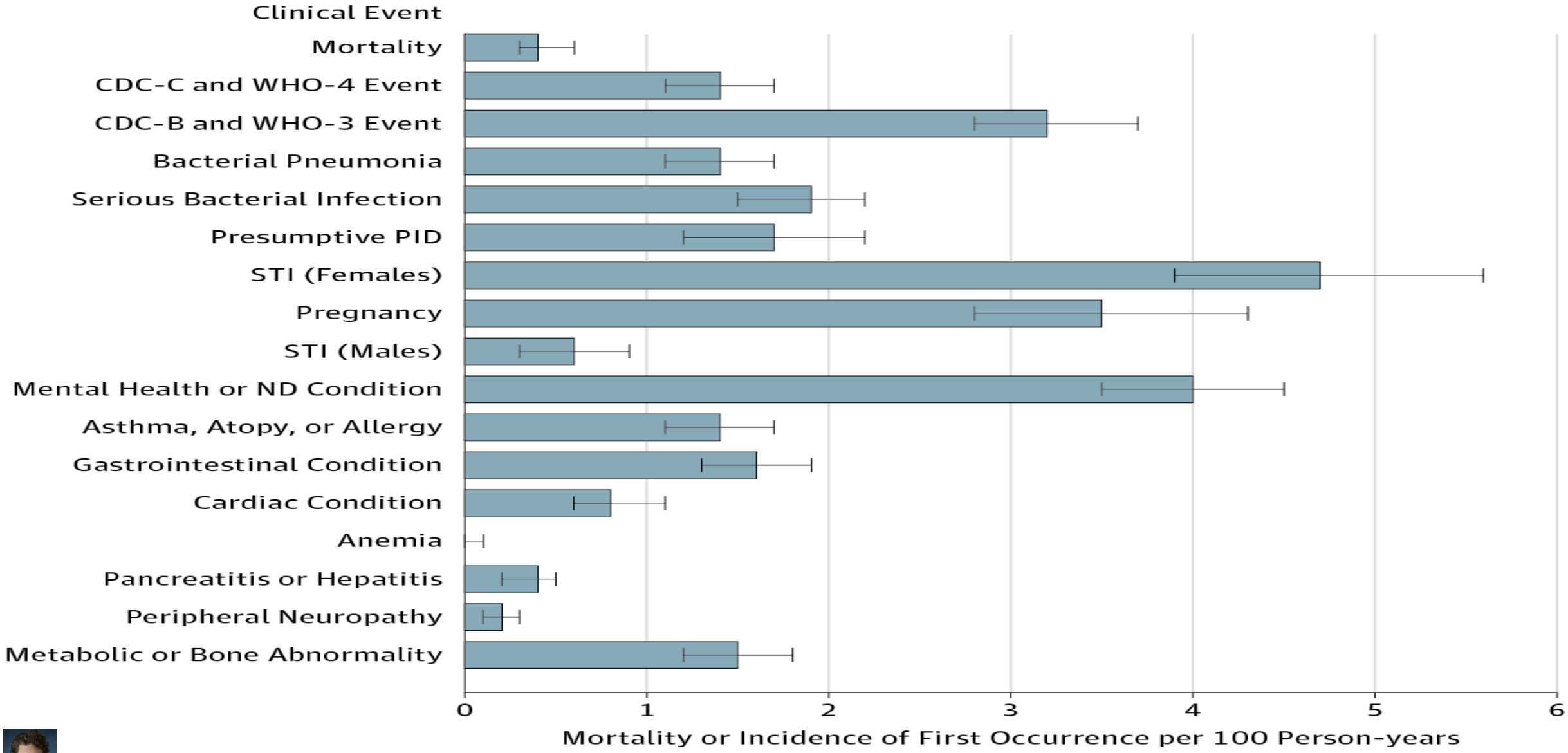
CDC, Youth Risk Behavior Survey 2019; Kruzich LA. J Acad of Nutri and Diet 2004; Mulligan K CID 2010

Weight again among adolescents with HIV



Li et al. JPIDS 2020; Koay et al OFID 2021

Long-term morbidity of HIV +/- ART



Griffith D et al. OFID 2017; Hazra R et al.; Izbudak, Agwu J Neurorad 2013;, **Venkataramani** 2012; Eckard et al Curr HIV/AIDS 2016; **Neilan** et al JAMA Peds 2017

What can you do?

- Take a good history
- Assess risk factors
  - Tobacco
  - Substances
  - Sex
  - Activities
  - Diet
  - Helmets, firearms
- Detailed family history
- Physical examination

Leading Cause of Death in the United States for Select Age Groups (2019)
Data Courtesy of CDC

Rank	10-14	15-24	25-34	35-44	45-54	55-64	All Ages
1	Unintentional Injury 778	Unintentional Injury 11,755	Unintentional Injury 24,516	Unintentional Injury 24,070	Malignant Neoplasms 35,587	Malignant Neoplasms 111,765	Heart Disease 659,041
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CLRD: Chronic Lower Respiratory Disease

Note: Suicide is not among the ten leading causes of death among children in the 0-9 year age group nor in adults in the age group 65 years and older.

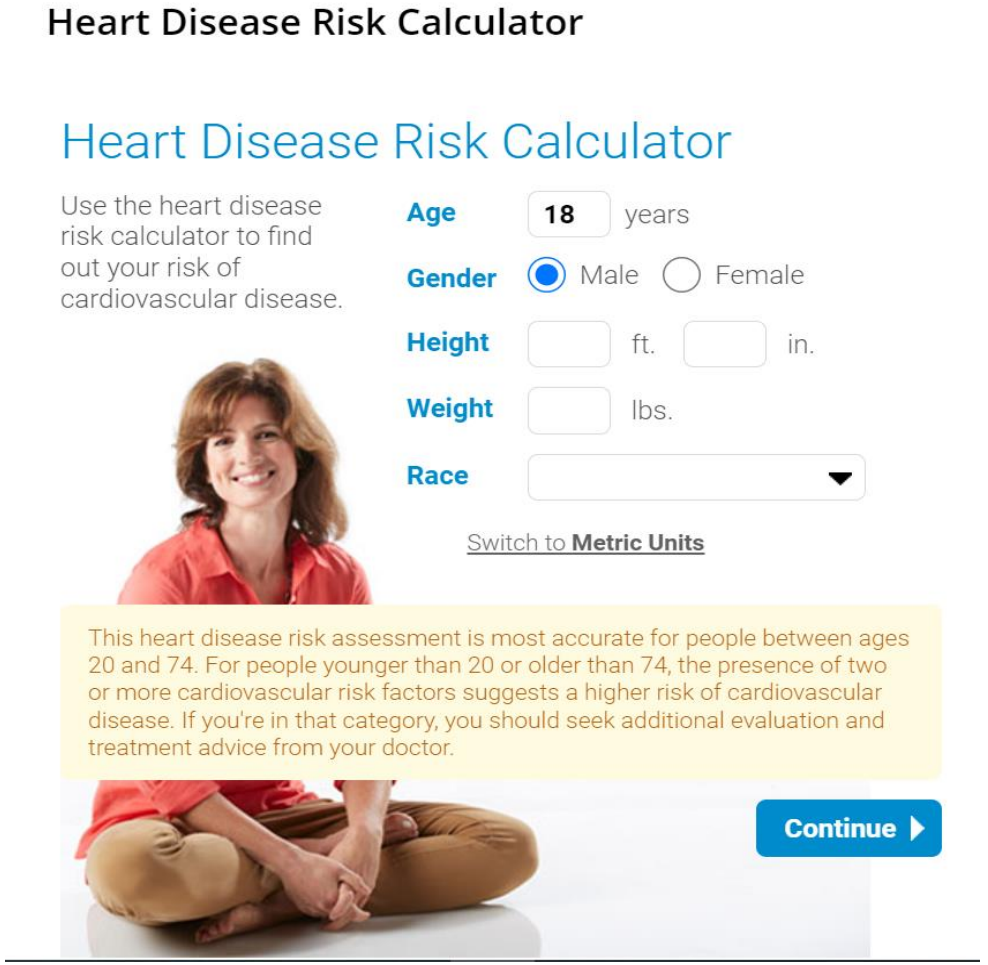
What can you do?

- **Education** (patient and staff)
- **Counseling**
  - Nutrition
  - Exercise
  - Smoking (cigarettes, vape, cigarillos, e-cigarettes))
  - Substance, ETOH use
  - Sex
  - Etc
- **Screening:** BP, lipids (fasting/non-fasting), glucose, weight

USPSTF

Risk calculators for adolescents?

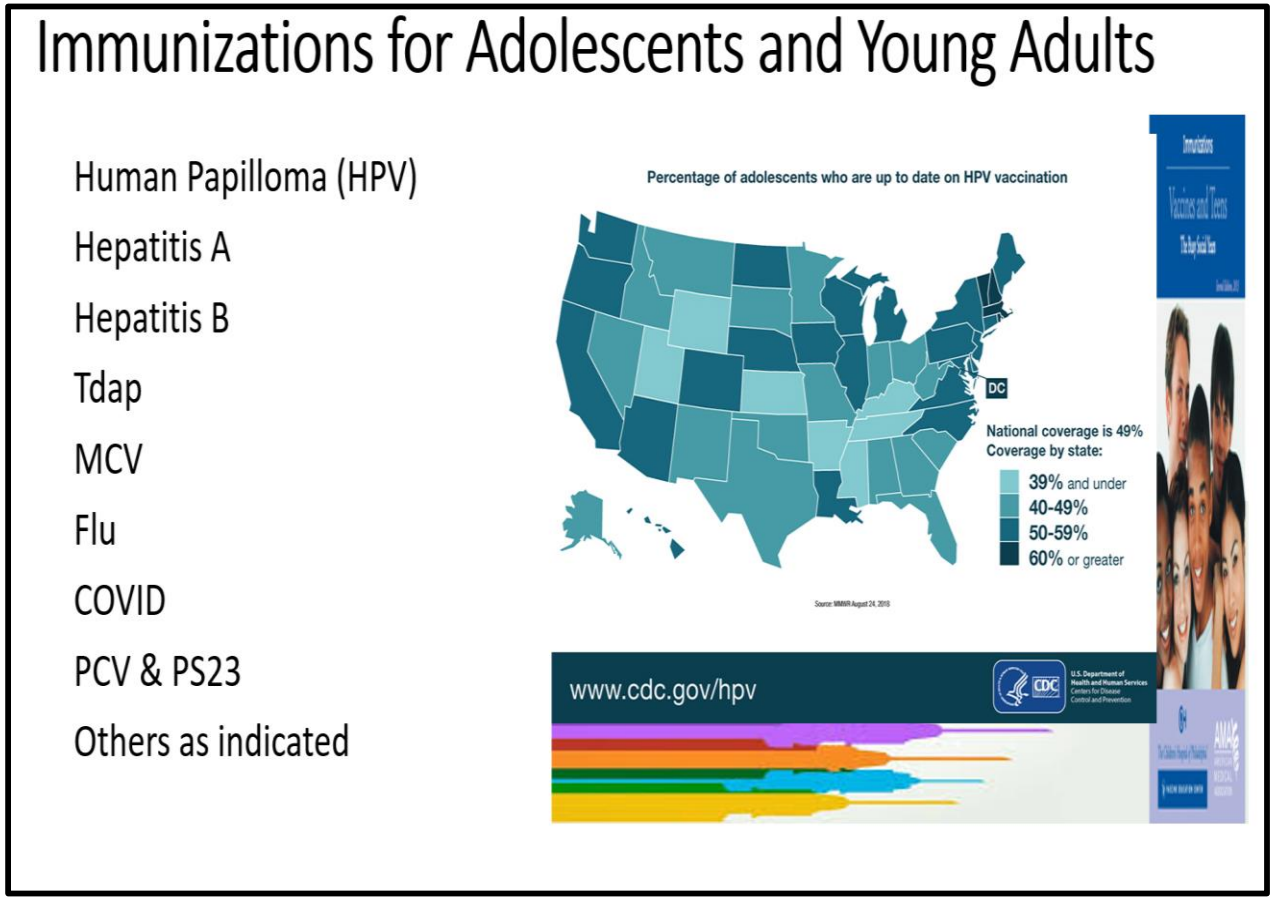
- ASCVD Heart Risk Calculator (age 40-79)
- If you know your lipids information and you are <60, the Framingham Heart Study General Cardiovascular Disease 30-Year Lipid-Based Risk Score Calculator is used. FOR AGES 30-79
- If you don't know your lipids information and you are <60, the Framingham Heart Study General Cardiovascular Disease 30-Year BMI-Based Risk Score Calculator is used. FOR AGES 30-79
- If you know your lipids information and you are ≥60 or older, the ACC/AHA Pooled Cohort Equations CV Risk Calculator is used.
- If you don't know your lipids information and you ≥ 60 or older, the Framingham Heart Study Cardiovascular Disease 10-Year BMI-Based Risk Score Calculator is used.



http://www.cvriskcalculator.com/; https://www.mayoclinichealthsystem.org/locations/menomonie/services-and-treatments/cardiology/heart-disease-risk-calculator

What can you do?

- **Actions:**
  - Smoking cessation
  - Lifestyle modification
  - Treatment
    - HTN (<130/80 goal) or <90th percentile
    - Hyperlipidemia: ?? (benefit for older youth with clear abnormal)
  - Weight loss
  - hyperlipidemia
  - Substance use treatment
  - STI counseling, screening, and treatment; family planning
  - Immunizations



USPSTF

Conclusion

- Adolescents with early-acquired HIV are surviving into adulthood
- Providers must be aware of their unique milieu and potential comorbidities to optimize care and outcomes
- Important to screen for and address comorbidities with prevention and early treatment

Acknowledgements

The Youth!!

ACE

Bartlett team

IPC/PAHAP

WICY team

JHU HIV Clinical Research team (IMPAACT, ATN, Cure, Tech2Check)

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National Institute of Allergy and Infectious Diseases

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

CENTER FOR AIDS RESEARCH
JOHNS HOPKINS UNIVERSITY

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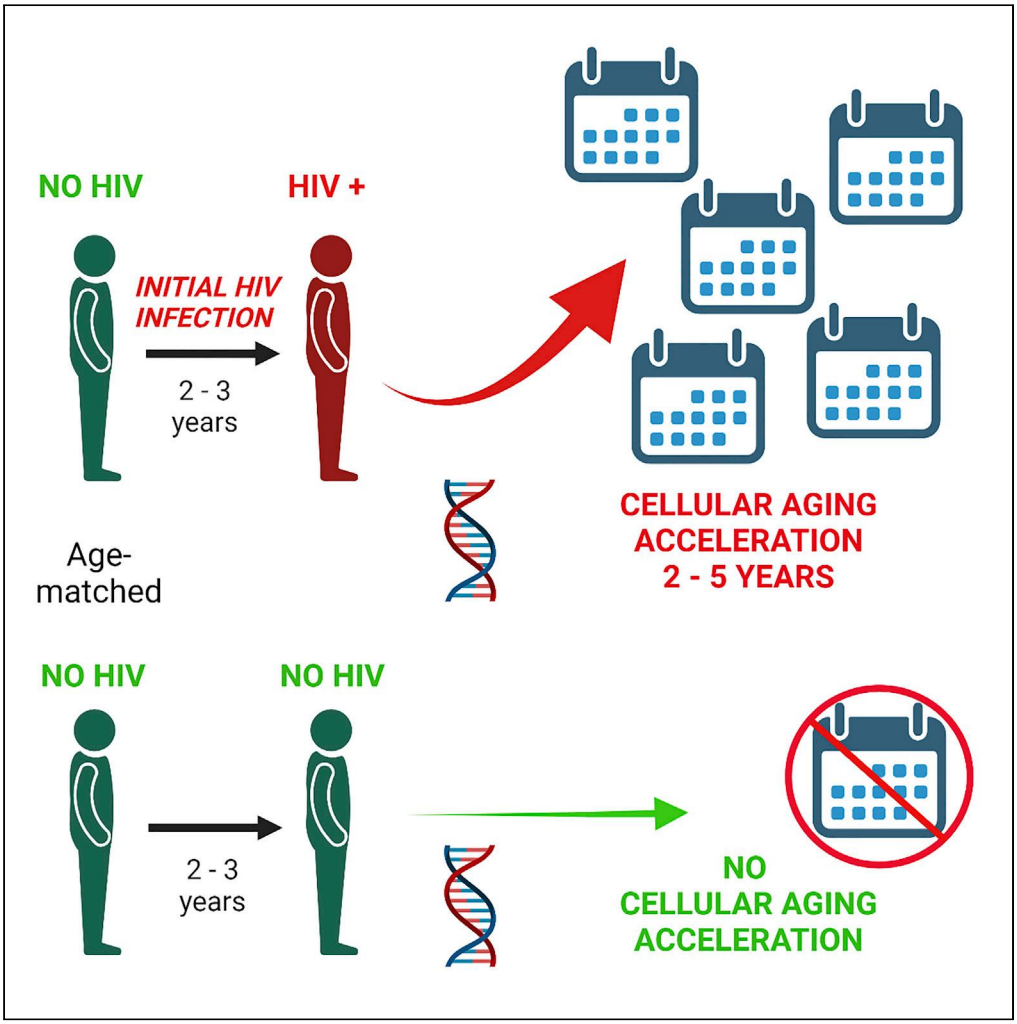
Article

Accelerated aging with HIV begins at the time of initial HIV infection



Elizabeth Crabb Breen, Mary E. Sehl, Roger Shih, ..., Otoniel Martínez-Maza, Christina M. Ramirez, Beth D. Jamieson

bjamieso@ucla.edu

Highlights

Accelerated epigenetic aging begins within three years after initial HIV infection

No epigenetic aging was observed in age-matched men over the same time period

T cell changes after HIV infection did not account for all epigenetic changes

Initial HIV infection is associated with significant genomic methylation changes

Breen et al., iScience 25, 104488
July 15, 2022
https://doi.org/10.1016/j.isci.2022.104488

iScience

CellPress
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Article

Accelerated aging with HIV begins at the time of initial HIV infection

Elizabeth Crabb Breen,[1] Mary E. Sehl,[2] Roger Shih,[2] Peter Langfelder,[3,4] Ruibin Wang,[5,13] Steve Horvath,[6,7] Jay H. Bream,[8] Priya Duggal,[5] Jeremy Martinson,[9] Steven M. Wolinsky,[10] Otoniel Martínez-Maza,[11] Christina M. Ramirez,[12] and Beth D. Jamieson[2,14,*]

SUMMARY

Living with HIV infection is associated with early onset of aging-related chronic conditions, sometimes described as accelerated aging. Epigenetic DNA methylation patterns can evaluate acceleration of biological age relative to chronological age. The impact of initial HIV infection on five epigenetic measures of aging was examined before and approximately 3 years after HIV infection in the same individuals (n=102). Significant epigenetic age acceleration (median 1.9–4.8 years) and estimated telomere length shortening (all $p \leq 0.001$) were observed from pre-to post-HIV infection, and remained significant in three epigenetic measures after controlling for T cell changes. No acceleration was seen in age- and time interval-matched HIV-uninfected controls. Changes in genome-wide co-methylation clusters were also significantly associated with initial HIV infection ($p \leq 2.0 \times 10^{-4}$). These longitudinal observations clearly demonstrate an early and substantial impact of HIV infection on the epigenetic aging process, and suggest a role for HIV itself in the earlier onset of clinical aging.

INTRODUCTION

Despite a significant increase in life expectancy(Marcus et al., 2016; Wandeler et al., 2016; Teeraananchai et al., 2017), there is mounting evidence that living long-term with Human Immunodeficiency Virus (HIV) and antiretroviral therapy, even when clinically well-controlled, is associated with an earlier than expected onset of chronic conditions such as heart and kidney disease, frailty, and neurocognitive difficulties (Currier et al., 2003; Obel et al., 2007; Lucas et al., 2008; Desquilbet et al., 2007; Sacktor et al., 2002; Schouten et al., 2011). It has been suggested that this represents premature or accelerated aging, but consensus on this point has been hampered by a lack of agreement on, or methods by which to define, what constitutes normal aging (High et al., 2012).

In recent years, there has been tremendous interest in assessing the process of human aging at a subcellular level by examining patterns of DNA methylation (DNAm) in various cell types and tissues. This approach was pioneered by the "epigenetic clock" developed by Horvath (Horvath, 2013), which uses methylation patterns from a carefully-curated set of 353 methylation sites found in genomic DNA (known as CpGs), to predict an epigenetic or biological age that is closely correlated to chronologic age across different normal tissues in human and non-human primate species. The original Horvath clock (Pan-Tissue Clock) has been validated in a wide range of human tissues and cell types throughout the body, including peripheral blood mononuclear cells (PBMC) (Horvath, 2013). Horvath then developed acceleration measures including the intuitive "age acceleration difference," which is calculated by subtracting the individual's chronologic age from his or her epigenetic age, and therefore, equals the number of years that a person's epigenetic age differs from their chronologic age. If the epigenetic age is older (a positive value using the age acceleration difference), this is viewed as an indicator of accelerated biological aging relative to chronologic age. Furthermore, an age-adjusted "age acceleration residual" (AAR), can be calculated from a linear regression model between the Horvath DNAm age and chronologic age, with greater values indicating accelerated biological aging. Another epigenetic clock was developed by Hannum (Hannum et al., 2013), and used to construct a calculated age-adjusted residual known as "extrinsic epigenetic age acceleration" (EEAA), which is positively correlated with senescent T lymphocytes and negatively correlated with naive T lymphocytes (Chen et al., 2016). In recent years, additional epigenetic measures

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Continued

have been developed utilizing various approaches to identify clusters of CpGs that yield "clocks" that predict differences relative to not only lifespan (years of life, "Grim epigenetic age acceleration" [GEAA]), but also healthspan (years of healthy life, "phenotypic epigenetic age acceleration" [PEAA]) (Levine et al., 2018; Lu et al., 2019a), or that estimate telomere length (TL) on chromosomes(Lu et al., 2019b), a well-documented cellular indicator of aging which becomes shorter with age. These DNA methylation-based measures (described in more detail in Table S1) provide tools by which aging at the cellular level can be evaluated in an objective manner.

In persons with HIV (PWH), some of these epigenetic approaches have been utilized to explore the possibility of accelerated biological aging in both untreated and treated HIV infection. However, epigenetic and telomere length studies thus far examining HIV infection and accelerated aging have largely been cross-sectional, comparing persons with established or chronic HIV infection to HIV-uninfected persons of the same chronologic age(Horvath and Levine, 2015; Rickabaugh et al., 2015; Gross et al., 2016; Zanet et al., 2014), rather than in longitudinal studies of the same persons over the course of initial HIV infection. These cross-sectional studies have demonstrated significant age acceleration in PWH compared to uninfected controls, utilizing a variety of approaches, including calculating the Horvath AAR, or a different calculation based on a consensus of the Horvath and Hannum epigenetic clocks, by directly measuring TL, or conducting a broad survey of genome-wide CpG sites known as Weighted Gene Correlation Network Analysis (WGCNA). In one small study of 31 intravenous drug users before and after HIV seroconversion, nearly all of whom were co-infected with Hepatitis C Virus (HCV), TL was shortened dramatically after HIV infection, but age acceleration as measured by AAR was only shown to positively correlate with time since the pre-HIV sample (Leung et al., 2017). There were no comparisons over the same time period to control subjects who were not HIV and/or HCV-infected, and no truly longitudinal analyses were reported evaluating the within-person change in AAR from pre-to post-HIV seroconversion. These studies leave open for investigation the potential contribution of lifestyle and other factors besides HIV to accelerated aging. There remains a clear need to evaluate the role of HIV infection in true longitudinal studies, especially the impact of initial acute HIV infection versus other potential variables, in accelerated biological aging utilizing an appropriate control group.

In the first ever study of this size and design, we have examined epigenetic aging over the course of initial HIV infection in more than one hundred persons, with five epigenetic measures of biological aging within six months or less before HIV infection, and again in the same persons shortly after initial HIV infection. In comparison, we evaluated the same epigenetic measures over matched time intervals in persons of the same chronologic age who did not become HIV-infected over the course of this study. The persons who became HIV-infected and those who remained uninfected were all drawn from the same population of men at-risk for HIV (men who have sex with men), and all had extensive information on other factors that might contribute to accelerated aging, regardless of HIV status. In addition to the five specific epigenetic measures, we conducted a genome-wide survey of methylation changes over the course of initial HIV infection.

To our knowledge, this is the first truly longitudinal case/control study to analyze the impact of initial HIV infection on epigenetic age, utilizing multiple DNAm-based measures and comparing the results to well-matched controls aging in the absence of HIV. In conjunction with the wealth of other clinical and demographic data available, we tested our hypothesis that initial HIV infection, and specifically the HIV viral load, would be major contributing factors to early accelerated epigenetic aging, as characterized by multiple DNAm patterns which develop in the first years of living with HIV. Likewise, we believe that this is the first longitudinal examination of genome-wide DNAm changes associated with initial HIV infection.

RESULTS

Demographics

Participants from the Multicenter AIDS Cohort Study (MACS) who were included in the current substudy of initial HIV infection were predominantly white, non-Hispanic, college-educated men who have sex with men (Table 1), similar to the overall MACS demographics at the initiation of the study in the 1980s(Kaslow et al., 1987). There were slightly more non-white men among the persistently HIV-seronegative (SN) participants (26/102) compared to the participants who became HIV-infected and seroconverted (SC; 13/102, $p = 0.02$), which is consistent with the larger MACS biomarker study from which the participants for this substudy were drawn (Wada et al., 2015). The SN and SC groups did not differ significantly by Hispanic ethnicity or level

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Table 1. Demographics and characteristics of HIV seroconverter (SC) and matched HIV seronegative (SN) participants from the Multicenter AIDS Cohort Study (MACS)

Participants		SC[a], n (%) or mean (SD)		SN[b], n (%) or mean (SD)	
White Race		89 (87.3%)		76 (74.5%)	
Non-Hispanic Ethnicity		95 (93.1%)		92 (90.2%)	
≥1 year of College Education		91 (89.2%)		86 (84.3%)	
Visit A to Visit B, years		2.9 (0.5)		2.7 (0.7)	
At each visit	Visit A	Visit B	Visit A	Visit B	
Age, years	35.7 (8.2)	38.5 (8.0)	36.3 (8.4)	39.0 (8.1)	
Hepatitis C Virus RNA-positive	2 (2.0%)	3 (2.9%)	2 (2.0%)	3 (2.9%)	
Hepatitis B Virus surface antigen-positive	2 (2.0%)	1 (1.0%)	2 (2.0%), n=99	3 (2.9%), n=100	
Cytomegalovirus antibody-positive	90 (100%), n=90	N/A	64 (97%), n=66	N/A	
Body Mass Index, kg/m^2	24.1 (3.1)	24.7 (3.3), n=97	25.2 (5.7), n=100	25.8 (4.2), n=97	
Smoking, cumulative pack years	12.0 (15.4), n=101	13.1 (16.5), n=98	7.8 (13.3)	8.3 (13.8), n=101	
Absolute CD4 T cell count, cells/mm^3	1087 (384), n=93	616 (241), n=100	1004 (428), n=97	1000 (365), n=93	
Plasma HIV Viral Load[c], copies/mL	N/A	49,757 (121,315)	N/A	N/A	
Estimated time since HIV infection[d], years	N/A	2.2 (0.5)	N/A	N/A	

[a]n=102 SC at Visit A and Visit B unless indicated otherwise
[b]n=101 SN at Visit A, n=102 at Visit B unless indicated otherwise
[c]For 10 SC missing HIV Viral Load (VL) at Visit B, HIV VL from the closest MACS study visit 3-6 months prior to Visit B was used
[d]Date of HIV infection estimated as midpoint between last MACS study visit that was HIV seronegative and HIV VL undetectable (if VL data were available) and the first MACS study visit with either HIV-positive serostatus or detectable HIV VL, whichever came first

of education (minimum p values > 0.3). Mean age in SC and SN at Visit B (post-HIV infection or equivalent visit) was 39.0 and 38.5 years, respectively, reflecting the matching criteria (range 22–72 years across all participants). Likewise, because of matching criteria, the percentage of SC and SN with HCV infection were similar and small (2–3%), and both groups had low rates of active Hepatitis B Virus (HBV) infection at both visits (1–3%). As expected, based on reports of ≥90% Cytomegalovirus (CMV) seroprevalence among homosexual men(Drew et al., 1981; Nerurkar et al., 1987), the MACS men in this substudy for whom CMV serostatus data were available showed very high CMV seropositivity (97–100%) at Visit A, when both SC and SN were HIV-uninfected. Consistent with a previous MACS report among HIV-seropositive participants(Akhtar-Khaleel et al., 2016), SC had more cumulative pack-years of smoking than SN (p = 0.03 by Visit B).

By design, the mean time intervals between peripheral blood mononuclear cell (PBMC) samples at Visits A and B were very similar in SC (2.9 years, range 1.3–3.7), and SN (2.7 years, range 0.9–4.0). Mean absolute CD4 T cell counts were stable in SN from Visit A to B at approximately 1000 cells/mm^3, and similar to the mean CD4 counts seen in SC at the pre-HIV infection visit (Visit A, 1087 cells/mm^3, p = 0.2). As expected, after initial HIV infection, the SC showed dramatically lower mean CD4 T cells at Visit B (mean = 616 cells/mm^3, p < 0.001), but also had a wide range (73–1210 cells/mm^3).

Among SC, the mean time interval between estimated date of HIV infection and the post-HIV infection PBMC sample at Visit B was 2.2 years (range 0.7–3.3 years). The calendar dates of estimated HIV infection ranged from 1985–2006, with 86% of the infection dates before 1995; regardless of calendar time, all SC post-HIV infection samples were before the initiation of highly active antiretroviral therapy (HAART) (Castillo-Mancilla et al., 2016). Mean plasma HIV viral load (VL) in SC at or immediately preceding Visit B was 49,757 copies/mL (median 14,084 copies/mL), ranging from a single individual with <50 copies/mL up to 948,000 copies/mL.

Multiple epigenetic age acceleration measures differ significantly after initial HIV infection

At Visit A, when all participants were HIV-uninfected, both the SC and SN groups had median epigenetic ages that differed from chronologic age by 1 year or less, as calculated by the Age Acceleration Residual (AAR, Figure 1A). When comparing the SC (before they became HIV-infected) and matched SN (those who

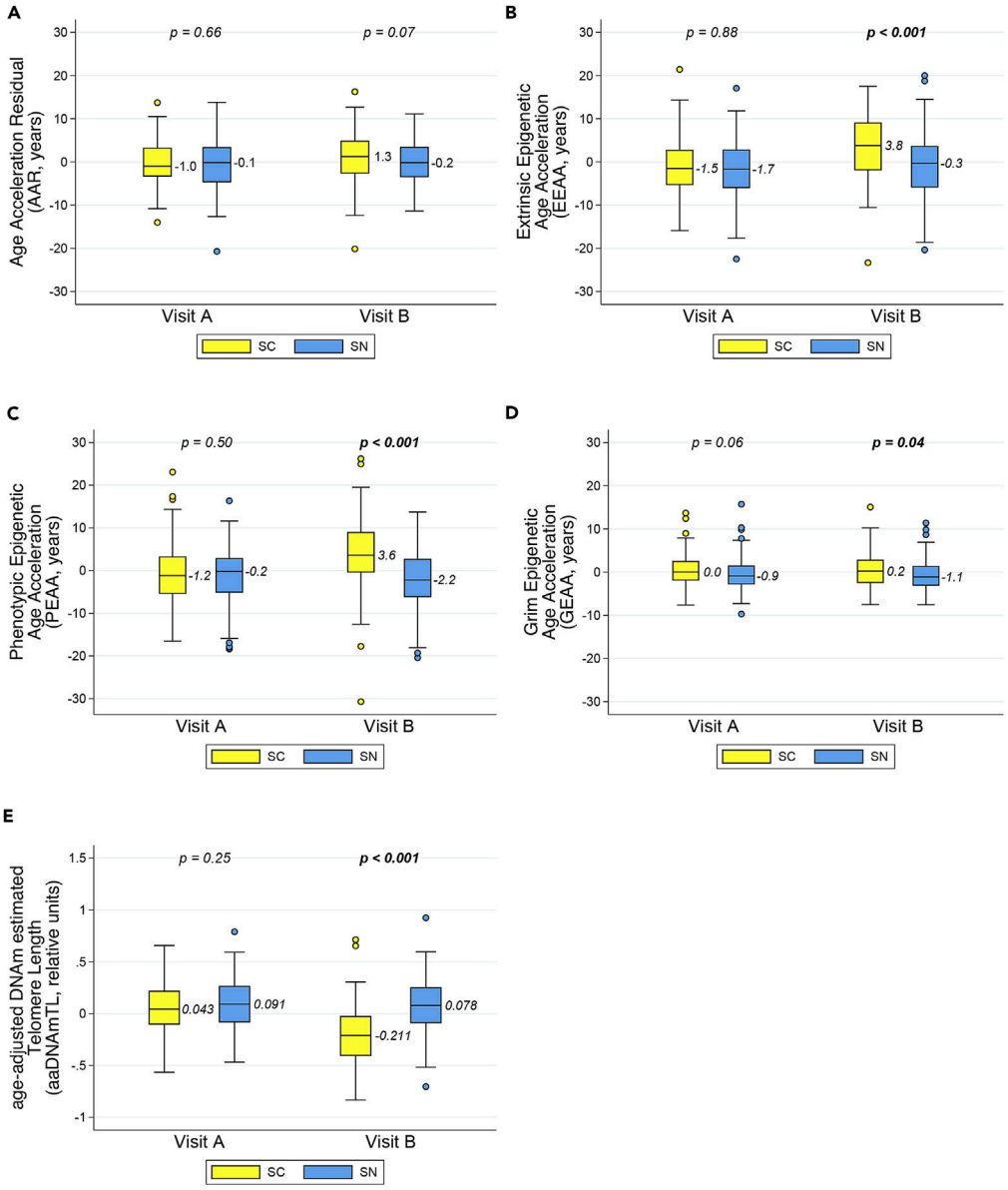

Figure 1. Multiple epigenetic measures in peripheral blood mononuclear cells (PBMC) demonstrate significant differences in biological aging after initial HIV infection, compared to age-matched HIV-uninfected persons

Longitudinal PBMC samples from men before (Visit A) and after (Visit B) documented HIV infection and seroconversion (SC), and from matched (chronologic age, Hepatitis C status, and time interval) persistently HIV seronegative men (SN), were evaluated for biological aging by five different age-adjusted epigenetic measures: (A) Age Acceleration Residual (AAR), (B) Extrinsic Epigenetic Age Acceleration (EEAA), (C) Phenotypic Epigenetic Age Acceleration (PEAA), (D) Grim Epigenetic Age Acceleration (GEAA), and (E) age-adjusted DNA methylation-based estimate of telomere length (aaDNAmTL) (see also Table S1). The first four are epigenetic "clocks" which increase with aging whereas estimated TL shortens (decreases) with aging. Each panel shows box and whisker plots (heavy line = median, box = 25^{th}-75^{th} percentile, whiskers = 5^{th}-95^{th} percentile) for SC (yellow) and SN (blue) participants at Visit A and Visit B; p values are for comparison of SN vs. SC at each visit by t-tests. 102 matched SC/SN pairs were evaluated; one SN participant was missing a PBMC sample at Visit A.

remain HIV-uninfected) to each other at Visit A, there were no statistically significant differences between the two groups in the AAR, Extrinsic Epigenetic Age Acceleration (EEAA), and Phenotypic Epigenetic Age Acceleration (PEAA) clocks (all p > 0.50, Figures 1A–1C). The Grim Epigenetic Age Acceleration (GEAA) clock demonstrated a small difference bordering on statistical significance (p = 0.06; Figure 1D), with

the SC group being slightly epigenetically older than the SN group. Age-adjusted DNA methylation-based estimates of telomere length (aaDNAmTL) were similar in the SC and SN at Visit A ($p = 0.25$, Figure 1E).

At Visit B, following initial HIV infection in the SC, SC showed dramatically significant differences in epigenetic age acceleration (greater EEAA, PEAA) and estimated telomere length (shorter aaDNAmTL) compared to matched HIV-uninfected SN (all p values < 0.001), and continued to be slightly more accelerated in GEAA ($p = 0.04$) (Figures 1B–1E). Median AAR was greater in SC compared to SN, but the differences were marginally non-significant ($p = 0.07$, Figure 1A).

When epigenetic changes were evaluated within each persistently HIV-uninfected (SN) individual over the time interval between Visits A and B (just under 3 years on average), no significant changes were seen in any of the epigenetic clocks (−0.6 to 0.1 years median change, $p \geq 0.16$) or in the aaDNAmTL (median difference −0.015 relative units, $p = 0.70$) (Figures 2A–2E). This lack of demonstrable age acceleration over approximately three years in multiple measures of epigenetic aging is consistent with previous reports based on the original Horvath clock, indicating the resolution of that epigenetic clock is between 3 and 4 years(Horvath, 2013).

In sharp contrast, over matched time intervals between Visits A and B among SC experiencing initial HIV infection, AAR, EEAA, and PEAA clocks showed 1.9, 4.8, and 4.8 median years age acceleration at Visit B, respectively (all $p \leq 0.001$, Figures 2A–2C). Likewise, aaDNAmTL showed significant shortening, with a median estimated change of −0.264 relative units from Visit A to Visit B ($p < 0.001$, Figure 2E), which is 17.6-fold greater than the median estimated change seen in SN. GEAA in SC showed very little change (−0.3 year median difference, $p = 0.57$) which was the same as in the SN (−0.3 year, $p = 0.16$, Figure 2D).

Initial HIV infection remains associated with older EEAA and PEAA ages, and shorter estimated aaDNAmTL, even after taking demographic factors and T cell changes into account

Mixed model analyses on all participants at both visits, taking demographic characteristics into account, demonstrated that becoming infected with HIV between Visits A and B contributed to epigenetic aging as measured by EEAA, PEAA and aaDNAmTL (all $p < 0.001$), with no significant contribution to these three measures made by HBV status, body mass index (BMI), or smoking (all $p \geq 0.18$, Table 2). Study visit (A or B) alone strongly contributed to the chronologic age-adjusted epigenetic values over time for AAR, EEAA, PEAA, and aaDNAmTL (all $p \leq 0.001$) but not GEAA (Table 2). However, when examining the interaction of the study visit and HIV serostatus group (i.e., SC or SN), which describes the change in HIV infection status from HIV-uninfected to HIV-infected in the SC group compared to the persistently HIV-uninfected SN group, initial HIV infection was clearly the driving force behind the epigenetic values seen at the two visits for EEAA, PEAA, and aaDNAmTL. AAR, even though it changed significantly as a function of study visit, had no associations with any of the other co-variates, including HIV serostatus group or the study visit*HIV serostatus group interaction (all $p \geq 0.16$). Race was not a significant contributor for AAR, EEAA, or PEAA, but was strongly significant for GEAA ($p \leq 0.001$) and weakly significant for aaDNAmTL ($p = 0.03$). Further exploration of GEAA revealed that this effect was driven by the small subpopulation of non-white participants (n = 39 non-whites out of 203 total participants), especially in the SC group (13 non-whites out of 102 SC, 3.1 years age acceleration because of non-white race alone, $p = 0.01$, data not shown). For aaDNAmTL, white and non-white participants differed slightly in mean estimated aaDNAmTL at Visit A ($p = 0.03$), but they did not differ significantly at Visit B ($p = 0.10$, data not shown). However, the aaDNAmTL values among the 39 non-white participants at Visit A were not normally distributed. Although it is of great interest, because of the limitations of statistical power as a result of small numbers of non-white individuals, it was not feasible to explore any additional relationships between race and either GEAA or aaDNAmTL. As expected, smoking history was strongly associated with GEAA, because of the incorporation of smoking-related biomarkers into this particular epigenetic clock (Table S1). Results from the mixed model fixed effects analyses for individual co-variates for all five epigenetic measures are shown in Table S2, and were consistent with models taking all co-variates into account.

Separately from the mixed models, pairwise correlations among the four epigenetic clocks and the estimated aaDNAmTL were evaluated (Table S3). When including all participants at Visit A (all HIV-uninfected, n = 203), every pairwise correlation among all the measures was highly significant ($p \leq 0.003$). This was not surprising because all were intended to examine epigenetic or biological aging, even though they were developed separately, each using a different curated set of CpG methylation sites. When evaluating the

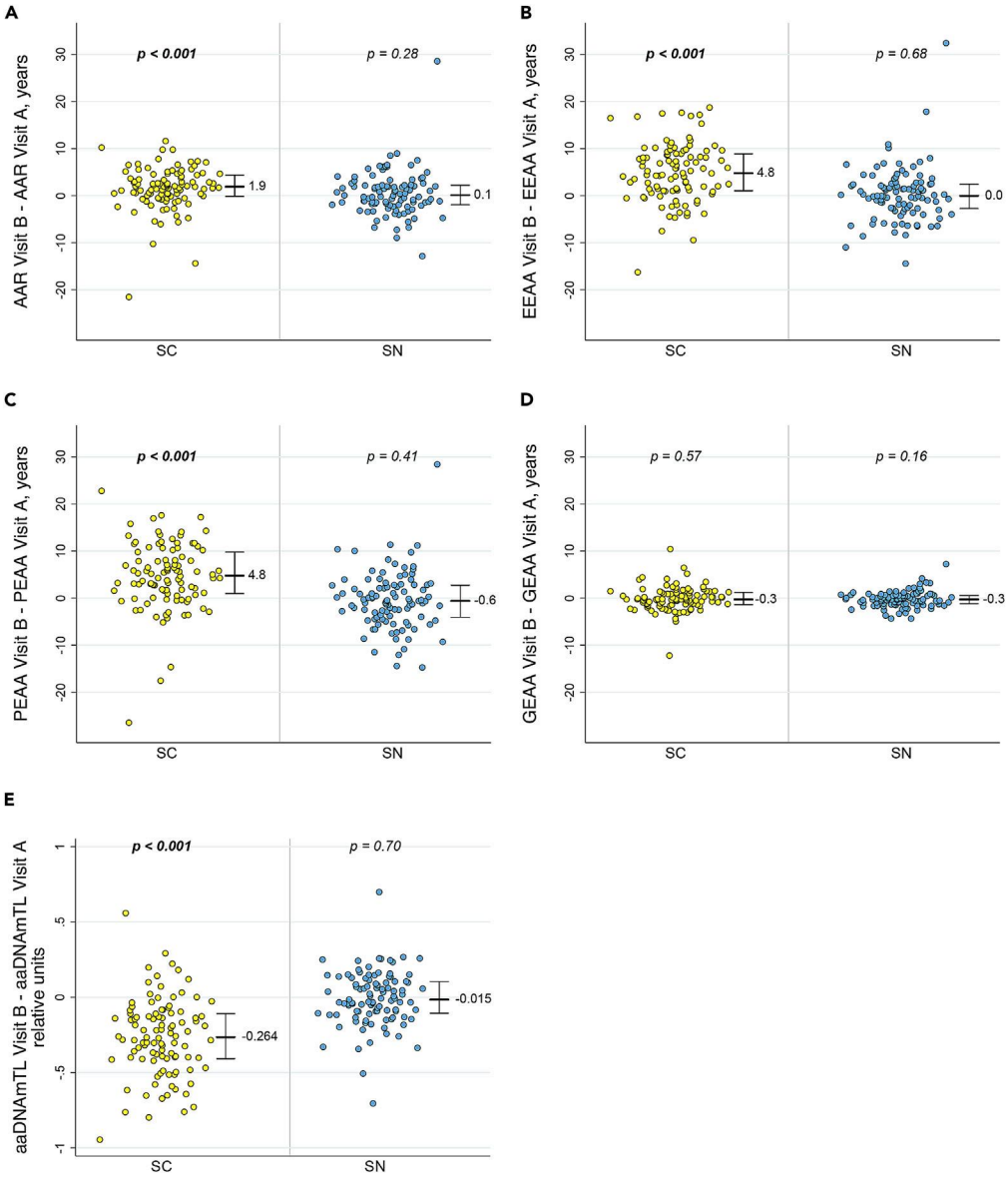

Figure 2. Significant accelerations in multiple epigenetic measures of aging occur in men over the course of initial HIV infection, but not in matched men who remain HIV-uninfected

Dot plots of HIV seroconverter (SC, n = 102) and persistently HIV seronegative (SN, n = 101) participants show the epigenetic change from the pre-HIV infection or equivalent visit (Visit A) to the post-HIV infection or equivalent visit (Visit B) within each participant as measured by (A) AAR, B) EEAA, (C) PEAA, (D) GEAA, and (E) aaDNAmTL. Heavy bar and numerical value = median change, whiskers = 25^{th}-75^{th} percentiles, p values = t-test for change within each participant group for differences from zero.

correlations in SC and SN groups separately at Visit B (n = 102 each group), all measures remained significantly correlated except GEAA, which was no longer correlated with AAR in the HIV-infected SC, and was correlated only with PEAA in the uninfected SN.

As noted in Table 1, the SC group showed a large decrease in mean absolute CD4 T cell numbers at Visit B, as expected following HIV infection. Therefore, it was appropriate to develop another set of mixed models that could account for potential differences in the cell composition of each sample. Multiple methods have been developed for utilizing DNAm data to estimate the proportion of different cell types in blood samples, including those of Houseman(Houseman et al., 2012), and of Salas(Salas et al., 2018), which draws

Table 2. Potential contribution of demographic and behavioral co-variates to epigenetic measures over time, using mixed effects models

Potential Contributors to Epigenetic Measures	F value (p *value*)[a]				
	AAR	EEAA	PEAA	GEAA	aaDNAmTL
Study Visit, Visit A vs B	11.00 (*0.001*)	38.85 (*<0.001*)	21.01 (*<0.001*)	1.56 (*0.21*)	75.13 (*<0.001*)
HIV Serostatus Group, SC vs SN[b]	1.99 (*0.16*)	5.29 (*0.02*)	10.22 (*0.002*)	3.39 (*0.07*)	15.14 (*<0.001*)
Study Visit*HIV Serostatus Group	1.66 (*0.20*)	29.68 (*<0.001*)	26.23 (*<0.001*)	0.00 (*0.96*)	63.44 (*<0.001*)
Race, non-white vs white	0.36 (*0.55*)	1.70 (*0.19*)	3.37 (*0.07*)	30.38 (*<0.001*)	4.52 (*0.03*)
Hepatitis B Status, HBsAg – vs + [c]	1.22 (*0.27*)	0.19 (*0.66*)	0.14 (*0.71*)	0.10 (*0.75*)	0.70 (*0.40*)
BMI, kg/m^2	0.02 (*0.89*)	0.17 (*0.68*)	0.10 (*0.75*)	0.79 (*0.38*)	0.15 (*0.70*)
Smoking, cumulative pack years	0.01 (*0.93*	0.03 (*0.87*)	1.79 (*0.18*)	47.15 (*<0.001*)	1.5 (*0.22*)

AAR = Age-Acceleration Residual, EEAA = Extrinsic Epigenetic Age Acceleration, PEAA = Phenotypic Epigenetic Age Acceleration, aaDNAmTL = age-adjusted DNA methylation-based estimate of Telomere Length, HBsAg = Hepatitis B surface Antigen, BMI = Body Mass Index.

[a]F values and Pr > F p values (p values in italics, bold if < 0.05) from mixed models incorporating all potential co-variates for all participants at both visits (n = 387 out of 407 total observations due to missing data for some co-variates) in a single model (see also Table S2).

[b]HIV serostatus groups classified as SC (became HIV-infected and seroconverted between Visits A and B) vs SN (persistently HIV-uninfected and seronegative at Visits A and B).

[c]Hepatitis B virus status classified by current HBsAg at visit, negative vs positive.

at least in part on Houseman's method. To be consistent with the approach that was utilized to calculate values for the epigenetic measures on study samples, the same software platform http://dnamage.genetics.ucla.eduwas initially utilized to impute cell proportions for each sample, which is based on Houseman's method(Horvath et al., 2016; Horvath and Levine, 2015). However, these imputed proportions might suffer from the underestimation of CD4 and/or overestimation of CD8 T cells that was recently described among HIV-infected subjects when using the Houseman method(Shu et al., 2020). As an alternative, direct measures of absolute numbers of CD4 and CD8 T cells were available from the MWCCS database, and measurements of selected T cell subsets by flow cytometry were performed at UCLA on a portion of each of the thawed viable PBMC samples from which DNA had been extracted for DNAm analyses. Therefore, the absolute numbers of total CD4 and CD8 T cells, and of naïve, activated, and senescent CD4 and CD8 T cell subsets, which are likely to be more reliable than imputed proportions, were available for use in analyses for most participants at both visits (Table 3). As expected, there were no differences in any of the mean absolute T cell counts between the SC and SN group at Visit A (all HIV-uninfected), but significant differences at Visit B in 6 out of the 8 T cell subsets (all but activated and senescent CD4 T cells). Similarly, mean within-person changes in absolute T cell numbers from Visit A to Visit B showed no changes in SN, and highly significant changes in the same 6 T cell subsets in SC (Table S4). Correlations between absolute counts of different T cell subsets, and between each T cell subset and the five epigenetic measures, are shown in Tables S5–S7.

Utilizing different combinations of T cell subsets, as described in the STAR Methods, a consensus model was identified with the best fit across all five of the epigenetic measures. This model included natural log-transformed absolute T cell counts for total CD4, total CD8, naïve CD4, activated CD8, and senescent CD8, and was utilized to analyze the possible contributions of changes over time in cell numbers, as well as changes in HIV infection status, to the observed values for each epigenetic measure (Table 4, Table S8). Significant associations were observed between T cell subset counts and one or more of the epigenetic measures, and all measures but AAR were significantly associated independently with study visit and with HIV serostatus group (Table 4). However, even when controlling for five T cell subsets, the same three epigenetic measures that were significant in the original mixed model, EEAA, PEAA, and estimated aaDNAmTL, still showed a statistically significant relationship to the interaction of study visit*HIV serostatus group (mixed effects models, p = 0.03, 0.04, <0.001, respectively), thus confirming initial HIV infection that occurs between Visit A and Visit B, but only in the SC group, as contributing to epigenetic age acceleration by these measures. As further confirmation, the frequencies of T cell subsets within the lymphocyte population were calculated using the flow cytometry measurements directly made on the PBMC samples, at Visits A and B for SC and SN groups (Table S9), and the consensus mixed model was repeated for each of

Table 3. Mean absolute T cell counts of the SC and SN groups, at Visits A and B

	Visit A[b], Mean (SE) n			Visit B[c], Mean (SE) n		
T cell population[a]	SC	SN	*p value*[d]	SC	SN	*p value*[d]
CD4 T cells, cells/mm^3	1088 (384) n = 93	1004 (428) n = 97	*0.16*	616 (240) n = 101	1000 (365) n = 93	*< 0.001*
CD8 T cells, cells/mm^3	630 (252) n = 93	598 (287) n = 97	*0.42*	890 (402) n = 101	617 (295) n = 93	*< 0.001*
Naive (CD45RA$^+$CCR7$^+$) CD4 T cells, cells/mm^3	404 (193) n = 92	406 (293) n = 96	*0.95*	244 (140) n = 101	383 (231) n = 92	*< 0.001*
Naive (CD45RA$^+$CCR7$^+$) CD8 T cells, cells/mm^3	219 (116) n = 92	212 (130) n = 96	*0.72*	138 (82) n = 101	214 (113) n = 92	*< 0.001*
Activated (HLA-DR$^+$CD38$^+$) CD4 T cells, cells/mm^3	28 (13) n = 90	27 (19) n = 95	*0.63*	32 (17) n = 99	28 (18) n = 90	*0.14*
Activated (HLA-DR$^+$CD38$^+$) CD8 T cells, cells/mm^3	25 (16) n = 90	23 (20) n = 95	*0.40*	180 (149) n = 99	26 (30) n = 90	*< 0.001*
Senescent (CD28$^-$CD57$^+$) CD4 T cells, cells/mm^3	45 (55) n = 92	33 (42) n = 96	*0.10*	39 (50) n = 101	33 (37) n = 92	*0.34*
Senescent (CD28$^-$CD57$^+$) CD8 T cells, cells/mm^3	108 (81) n = 92	104 (88) n = 96	*0.79*	140 (115) n = 101	105 (105) n = 92	*0.03*

[a]Absolute CD4 and CD8 T cell counts obtained from MWCCS database, and were determined by standardized flow cytometry at the time of original blood sample collection; T cell subsets determined by multicolor flow cytometry at the time of thawing of viable PBMC aliquots as described in the STAR Methods, and absolute T cell subset counts calculated from total CD4 and CD8 counts (see also Table S4).
[b]All participants HIV-uninfected at Visit A, matched on age and hepatitis C status.
[c]SC recently HIV-infected, SN persistently HIV-uninfected at matched time intervals at Visit B.
[d]p values are for comparison of SC vs. SN at each visit by t-tests (p values in italics, bold if < 0.05).

the five epigenetic measures (Table S10). Similar to the results with absolute cell counts, significant associations were observed between T cell subset percentages and one or more of the epigenetic measures, and independently with study visit and HIV serostatus group. Most importantly, consistent with the original mixed models (Table 2) and the models taking absolute cell numbers into account (Table 4), EEAA, PEAA, and estimated aaDNAmTL remained significantly associated with the study visit*HIV serostatus group interaction that describes initial HIV infection, even after controlling for changes in percentages of T cell subsets (p = 0.04, 0.01, <0.001, respectively, Table S10).

Plasma HIV viral load correlates with EEAA and PEAA clocks, and estimated aaDNAmTL at the post-HIV infection visit

The persistent significant associations between three of the epigenetic measures and the study visit*HIV serostatus group interaction, representing the HIV infection event in the SC group, even after accounting for demographic factors or T cell changes, suggests a role for HIV itself in contributing to accelerated biological aging. Regression analyses were performed to determine if the amount of circulating HIV present post-infection, i.e., the plasma HIV viral load (VL), was correlated with the magnitude of any of the epigenetic measures at Visit B. Consistent with the mixed models, greater epigenetic age acceleration, as measured by higher EEAA and PEAA (both p = 0.002), and shorter estimated telomere length, as measured by aaDNAmTL (p = 0.025), were significantly associated with higher HIV VL post-HIV infection whereas neither AAR nor GEAA were correlated with HIV VL (Figures S1A–S1E). For every $\log_{10}$ increase in HIV VL, EEAA and PEEA increased 2.6 and 3.1 years, respectively. For every $\log_{10}$ increase in HIV VL, aaDNAmTL shortened by 0.075 relative units (28% of the median change in SC from Visit A to B). As expected, following initial HIV infection, HIV VL and absolute CD4 T cell counts were inversely correlated at Visit B (correlation coefficient = −0.26; p = 0.01). Because HIV VL and absolute CD4 counts were not independent and exhibited high correlation, when both HIV VL and CD4 were included in the analyses, neither co-variate showed a significant association with any of the epigenetic measures, which can occur with multicollinearity (all p values > 0.05, data not shown).

Genome-wide methylation of CpGs changes significantly with initial HIV infection

Weighted Gene Correlation Network Analysis (WGCNA) (Langfelder and Horvath, 2008) was utilized to identify clusters of CpGs that are correlated with each other across all of the samples analyzed

Table 4. Potential contribution of absolute T cell counts to epigenetic measures over time, using mixed effects models

Potential Contributors to Epigenetic Measures	F value (p *value*)[a]				
	AAR	EEAA	PEAA	GEAA	aaDNAmTL
Study Visit, Visit A vs B	0.49 *(0.48)*	9.12 *(0.003)*	4.86 *(0.03)*	5.18 *(0.02)*	11.98 *(<0.001)*
HIV Serostatus Group, SC vs SN[b]	3.52 *(0.06)*	9.77 *(0.002)*	16.07 *(<0.001)*	5.62 *(0.02)*	37.97 *(<0.001)*
Study Visit*HIV Serostatus Group	0.14 *(0.71)*	4.90 *(0.03)*	4.09 *(0.04)*	0.68 *(0.41)*	15.40 *(<0.001)*
CD4 T cells[c], ln cells/mm^3	2.51 *(0.11)*	7.18 *(0.008)*	5.56 *(0.02)*	4.85 *(0.03)*	15.28 *(<0.001)*
CD8 T cells, ln cells/mm^3	0.02 *(0.89)*	4.59 *(0.03)*	1.24 *(0.27)*	0.98 *(0.32)*	5.63 *(0.02)*
Naive ($CD45RA^+CCR7^+$) CD4 T cells, ln cells/mm^3	7.41 *(0.007)*	21.3 *(<0.001)*	14.89 *(<0.001)*	1.06 *(0.30)*	18.63 *(<0.001)*
Activated ($HLA\text{-}DR^+CD38^+$) CD8 T cells, ln cells/mm^3	6.59 *(0.01)*	1.94 *(0.17)*	2.68 *(0.10)*	0.02 *(0.90)*	1.80 *(0.18)*
Senescent ($CD28^-CD57^+$) CD8 T cells, ln cells/mm^3	16.71 *(<0.001)*	15.95 *(<0.001)*	5.50 *(0.02)*	0.95 *(0.33)*	25.61 *(<0.001)*

AAR = Age-Acceleration Residual, EEAA = Extrinsic Epigenetic Age Acceleration, PEAA = Phenotypic Epigenetic Age Acceleration, aaDNAmTL = age-adjusted DNA methylation-based estimate of telomere length.

[a]F values and Pr > F p values (p values in italics, bold if < 0.05) from mixed models incorporating all potential co-variates for all participants at both visits (n = 374 out of 407 total observations due to missing data for some co-variates) in a single model (see also Table S8).

[b]HIV serostatus groups classified as SC (became HIV-infected and seroconverted between Visits A and B) vs SN (persistently HIV-uninfected and seronegative at Visits A and B).

[c]Absolute counts of T cell subsets as described in STAR Methods and Table S13; all cell counts natural log-transformed (ln) for analyses.

(co-methylation modules), using methylation levels measured at over 850,000 individual CpG methylation sites on the Infinium MethylationEPIC BeadChip. Sixty-seven co-methylation modules were identified, 18 of which showed statistically significant mean module eigenvector methylation differences from visit A to visit B in the SC group (i.e., over the course of initial HIV infection, p values $\leq 2.0 \times 10^{-4}$, Table 5), but none of the 67 modules showed significant differences between visits in the SN group (data not shown). For each CpG within each of the 18 HIV infection-associated modules, we calculated an intramodular connectivity measure (kME value) (Horvath and Dong, 2008) and chose the most stringent cutoff of 0.85 to identify genes within each module. The number of CpG sites with kME value $\geq$ 0.85 ranged from 1–36,000+ (Table 5). All individual CpG sites within these 18 modules are listed in Table S11 (Excel file). Enrichment analyses were performed using the EnrichR gene list enhancement tool(Kuleshov et al., 2016) to identify overrepresented biological pathways for those CpG sites with kME $\geq$0.85 within the 18 modules (Table S12, Excel file). These analyses highlighted large numbers of pathways, especially in modules 2 and 18, with many related to embryonic morphogenesis and cellular differentiation, or immune function and biosynthesis, respectively.

DISCUSSION

Although small longitudinal studies have examined accelerated aging in HIV seroconverters(Leung et al., 2017), and in perinatally HIV-infected youth many years after HIV infection(Shiau et al., 2021), and cross-sectional studies suggest that persons with HIV may be aging at a faster rate(Rickabaugh et al., 2015; Horvath and Levine, 2015; Gross et al., 2016), the study reported here is the largest, and the first with matched HIV-uninfected controls, to longitudinally follow individuals over the course of becoming infected with HIV, and to document epigenetic changes consistent with accelerated biological aging. We have utilized four well-validated epigenetic measures based on methylation patterns of genomic DNA, each of which calculates years of biological age acceleration relative to chronologic age (known as epigenetic "clocks"), and an age-adjusted DNA methylation-based estimate of the length of telomeres at the ends of chromosomes (which are known to shorten with repeated cell division and increasing age). Over a relatively short time frame (less than three years on average), during which age-matched HIV-uninfected men showed no significant changes or acceleration in any epigenetic measure of aging, men who became infected with HIV

Table 5. Weighted Gene Correlation Network Analysis (WGCNA) of genome-wide methylation of CpG sites that change significantly with initial HIV infection in the SC group

		Module eigenvector methylation[b]			
Co-methylation Module[a]	# of CpGs in Module	Visit A Mean (SD)	Visit B Mean (SD)	*p value*[c]	# (%) of CpGs with kME ≥ 0.85[d]
1	133,037	0.004 (0.017)	−0.006 (0.020)	$3.6x10^{-4}$	37,284 (28)
2	37,328	−0.015 (0.014)	−0.003 (0.017)	$5.5x10^{-8}$	8097 (21)
3	16,985	−0.008 (0.014)	0.003 (0.022)	$5.5x10^{-8}$	2300 (14)
4	9,775	0.012 (0.018)	−0.005 (0.021)	$5.8x10^{-9}$	1596 (16)
5	5,615	−0.022 (0.014)	0.004 (0.017)	$3.2x10^{-21}$	672 (12)
6	5,184	0.009 (0.017)	−0.002 (0.024)	$3.2x10^{-4}$	892 (17)
7	2,398	−0.006 (0.023)	0.005 (0.022)	$2.2x10^{-4}$	514 (21)
8	1,677	0.016 (0.016)	−0.004 (0.019)	$1.5x10^{-13}$	141 (8)
9	1,019	0.006 (0.019)	−0.005 (0.021)	$3.7x10^{-5}$	50 (5)
10	962	0.016 (0.016)	−0.005 (0.020)	$2.5x10^{-12}$	58 (6)
11	707	−0.013 (0.023)	−0.002 (0.022)	$6.0x10^{-4}$	22 (3)
12	222	−0.012 (0.025)	0.003 (0.015)	$1.8x10^{-6}$	1 (0.4)
13	215	−0.017 (0.027)	−0.005 (0.025)	$2.0x10^{-4}$	26 (12)
14	106	−0.009 (0.014)	0.010 (0.022)	$1.7x10^{-10}$	5 (4.7)
15	94	−0.005 (0.018)	0.015 (0.023)	$1.1x10^{-10}$	1 (1)
16	67	−0.015 (0.018)	−0.003 (0.020)	$2.8x10^{-6}$	1 (1.5)
17	44	−0.022 (0.021)	−0.002 (0.019)	$5.9x10^{-11}$	2 (5)
18	38	0.011 (0.007)	−0.003 (0.018)	$2.5x10^{-11}$	17 (45)

[a]Each Co-methylation Module is a cluster of CpG methylation sites within the 850,00 + sites evaluated on the Infinium MethylationEPIC BeadChip, identified by WGCNA to be correlated with each other; any one CpG site belongs to only one Module. Out of a total of 67 Modules identified by WGCNA utilizing all samples from all participants at both visits (n = 407 samples), 18 Modules shown are those that are significantly associated with the change in HIV status from visit A to visit B in the SC group (initial HIV infection). Modules 1–18 are numbered according to the number of CpGs (largest to smallest) contained in each Module. All CpGs in Modules 1–18 are listed in Table S11 (Excel file).

[b]Methylation levels are quantified by the beta value from the EPIC BeadChip assay, using the ratio of intensities between methylated and un-methylated alleles as described in the STAR Methods. In WGCNA, a representative methylation profile for each Module, known as the Module eigenvector, is defined as the first principal component in the Module methylation matrix. Mean and SD eigenvector methylation values shown for each Module are based on 102 HIV seroconverters (SC group) with observations at both Visits A and B.

[c]Italicized p values are from a non-parametric group comparison test (Kruskal-Wallis) comparing mean Module eigenvector methylation from Visit A (before HIV infection) to Visit B (after initial HIV infection); level of significance for Module association with HIV infection accounting for multiple comparisons is $p < 0.05/67$ or $< 7.5x10^{-4}$.

[d]kME is the intramodular connectivity measure for each CpG calculated from the WGCNA, and ≥0.85 is the threshold for a CpG to be considered a "hub" site, as described in the STAR Methods. All CpGs from Modules 1–18 with kME ≥0.85 were included in a pathways enrichment analysis (please see Table S12, Excel file), and Modules in bold (n = 5) contain at least one CpG in a gene that falls within biological pathways with significant p values after adjustment for multiple comparisons.

showed highly significant age acceleration in three out of four of the epigenetic clocks as well as accelerated estimated telomere shortening (Figure 2). In mixed models, taking demographic and clinical co-variates or absolute cell counts or percentages of five T cell subsets into account (Tables 2 and 4 and S10), age acceleration in two epigenetic clocks, EEAA and PEAA, and shortening in the DNAm-based estimate of TL remained significantly associated with initial HIV infection. This clearly demonstrates an early and substantial impact of HIV infection on the epigenetic aging process that begins in the first months and years of living with HIV. This result in multiple epigenetic measures is not simply due to the correlations observed between the measures, as each was developed separately. Rather, because all were constructed for the purpose of examining epigenetic or biological aging, it is not surprising that they are correlated to each other and that more than one of the epigenetic measures point to a role of initial HIV infection in age acceleration.

EEAA and PEAA consistently showed significant results associated with HIV infection, with a median biological age acceleration of 4.8 years in SC, after adjusting for chronologic age. EEAA was recently developed from the Hannum clock of 71 CpGs(Hannum et al., 2013) focusing on mortality, but was also specifically designed to be positively correlated with senescent (aged) T cells and negatively correlated with naïve T cells of the immune system (Chen et al., 2016). PEAA is also a recently-developed epigenetic clock, utilizing a phenotypic measure of mortality from 513 CpGs of Levine (Levine et al., 2018), and so predicts lifespan. In populations not infected with HIV, a one-year increase in epigenetic age acceleration as measured by EEAA and PEAA is associated with an increase in all-cause mortality risk of 4.0% and 4.5%, respectively(Chen et al., 2016; Levine et al., 2018), which would translate to approximately 20% or more increase in mortality risk with a five-year increase in epigenetic age acceleration. The 4.8 years of acceleration revealed by these two clocks shortly following initial HIV infection clearly indicates that becoming infected and living with HIV for only three years or less is already associated with approximately 20% increased risk for a shortened lifespan. AAR, which is an age-adjusted residual of the difference in years between biological and chronological age calculated from 353 CpGs by Horvath's original Pan-Tissue epigenetic clock (Horvath, 2013), showed a more modest median acceleration of biological aging of 1.9 years over the course of initial HIV infection, but was no longer significantly-associated with HIV infection when controlling for demographic factors or T cell subsets. This further illustrates that although AAR, EEAA, and PEAA values among the PBMC samples were strongly correlated, clocks incorporating information on naive and senescent cell composition such as EEAA, and "second-generation" clocks such as PEAA focused on mortality may be detecting differential effects of the impact of initial HIV infection.

The age-adjusted DNAm-based estimate of telomere length (aaDNAmTL) (Lu et al., 2019b), characterizes accelerated biological aging in the opposite direction of the epigenetic clocks, as telomeres become shorter with repeated cellular divisions, yielding a lower value and a negative direction of change over time. Similar to acceleration in the EEAA and PEAA epigenetic clocks, aaDNAmTL showed accelerated telomere shortening over the course of initial HIV infection in SC participants, but essentially no change in SN participants over the approximately three years evaluated in this study. Because age acceleration in the EEAA clock correlates with increases in the number of senescent T cells, which are terminally-differentiated aged cells no longer able to divide, and TL is similarly linked to cell division, the strong association of both of these measures of accelerated biological aging with initial HIV infection may be due, at least in part, to rapid changes in the cells of the immune system itself.

It is of interest to note that the GEAA epigenetic clock, which was developed based on 1030 CpGs of Lu (Lu et al., 2019a) and is also focused on mortality and lifespan, showed no differences over time regardless of changes in HIV infection status. This was the only epigenetic measure that approached statistical significance for differences between the SC group and the SN group at Visit A when all of the participants were still HIV-uninfected, and it continued to demonstrate a marginal difference between the two groups at the post-HIV infection Visit B. This suggests that there are factors included in this clock that predict mortality but are not impacted, at least during the first months and years, by changes picked up by other epigenetic measures that occur when an individual first becomes infected with HIV. GEAA was developed utilizing, among other markers, DNA methylation-based surrogate markers related to smoking pack-years. The small but persistent differences in the GEAA clock, with SC showing slightly more age acceleration than SN, is consistent with SC reporting more smoking (greater mean cumulative pack-years) than the SN group, even before HIV infection. It is possible, therefore, that the role of smoking in shaping DNA methylation patterns detected by the GEAA clock is relatively unaffected by the age acceleration indicated by the other epigenetic measures, which are more likely to reflect immune system changes and immunosenescence. This is supported by our observation that smoking history was not a significant contributing factor in mixed models to the age acceleration seen over the course of initial HIV infection in the AAR, PEAA, and EEAA clocks, nor the aaDNAmTL. Additional analyses are in progress, evaluating the risk conferred by accelerated epigenetic aging indicated by these DNAm measures for specific health outcomes and mortality in treated persons living long term with HIV.

The greater history of smoking among the SC group in this study is consistent with previous observations among MACS men, where greater prevalence of heavy alcohol consumption, and to a lesser degree, smoking, high-risk sexual behaviors, and moderate to heavy drug use, were associated with HIV seroconversion (Penkower et al., 1991). Therefore, smoking history could be viewed as a surrogate for greater risk-taking behaviors associated with becoming HIV-infected. Chronic alcohol consumption has been reported to

contribute to DNA hypomethylation (Zakhari, 2013), and so could be impacting genome-wide DNAm patterns included in one or more of the epigenetic measures evaluated here. Risk-taking behavior, including smoking, could be contributing to the marginally-significant difference between SC and SN groups observed only in GEAA, as described above. However, any possible epigenetic effects of smoking and other risky behavior(s) in the SC group before HIV infection were not detected by any of the other epigenetic clocks or the estimate of TL, as those measures showed no differences between SC and SN groups at Visit A.

High risk sexual behaviors that are associated with HIV seroconversion carry other health-related risks, such as infection with HCV, HBV, CMV, or other infectious agents, which in turn, could affect the aging process. Because of these concerns, SC and SN participants were matched on chronologic age and time interval between study visits as well as on HCV status, and HBV status was included as a co-variate in the demographic mixed model analyses. Consistent with other reports in homosexual men (Drew et al., 1981; Nerurkar et al., 1987), infection with CMV in these MACS participants was nearly universal at the first visit evaluated, when all men were HIV-uninfected. Therefore, CMV serostatus was not included among potential contributors to the epigenetic changes observed following initial HIV infection. Although it is possible that prevalent CMV infection could be synergizing with incident HIV infection in its effects on epigenetic aging, it was not possible to examine that question in this population. In a recent very small cross-sectional study(Corley et al., 2021), current serious illness with other viral infections such influenza or COVID-19 were similar on some and different on other epigenetic aging measures (PEAA, GrimAge, DNAmTL) compared to untreated persons living with HIV, with critically-ill COVID-19 patients showing the greatest increase in GrimAge. Genome-wide analyses in the same groups suggested that severe COVID19 may have a different global epigenetic "signature" than established HIV infection. Animal and human studies suggest HCV infection may impact genome-wide DNAm patterns as well as methylation states of key cellular pathways involved in carcinogenesis (Domovitz and Gal-Tanamy, 2021). Although it is likely that at least some of the epigenetic changes observed over the course of HIV infection may not be unique among viral infections, the current longitudinal study design offers a rare insight before and after initial infection with a virus that directly infects and impacts immune cells circulating in the blood.

When we did examine other potential contributors to the epigenetic measures at the two visits (Table2), the study visit itself, i.e., simply the differences between Visit A and B, was strongly associated with all of the epigenetic measures except GEAA. This parallels the within-person changes between visits illustrated by Figure 2, where only GEAA failed to reveal differences in the SC group. When the interaction between study visit and HIV serostatus group was analyzed, it became clear that for the EEAA and PEAA clocks plus the estimated aaDNAmTL (all $p < 0.001$), the association with study visit was because of the changes in the SC group, i.e., initial HIV infection, even when taking other co-variates into account. Active HBV infection and BMI did not associate with any of the epigenetic measures, and as discussed above, it was not surprising that only GEAA was associated with smoking history. This supports and further strengthens our observation that the processes involved in the initial HIV infection event itself appear to be driving accelerated aging as characterized by the EEAA, PEAA, and aaDNAmTL epigenetic measures. We did observe a small effect of race (non-white vs white) on the estimated aaDNAmTL before any of the participants in our substudy became HIV-infected, which is consistent with recent reports of longer measured telomere length in blacks compared to whites(Rewak et al., 2014). There was a highly significant effect of race on GEAA, which appeared to be driven by non-white participants in the SC group, of which there were only 13 out of 102. Combined with the association with smoking history, these analyses further emphasized that we were unable to detect an impact of initial HIV infection on this epigenetic clock among our participants. However, our specific substudy (and the MACS overall) is limited in the number of non-white participants, and therefore, lacks the statistical power to appropriately explore the role of race in epigenetic measures of aging, highlighting the need to investigate the possibility of differences related to race in the context of HIV infection within more diverse populations.

HIV infects CD4 T cells and monocytes/macrophages of the immune system, and its impact on the number of T cells of various subtypes is part of the hallmark of initial HIV infection and, ultimately, its accompanying immunodeficiency(Killian et al., 2004). Therefore, it is possible that HIV-induced changes in T cell numbers or frequencies may be inextricably linked to observed changes in epigenetic measures over the course of initial HIV infection. We examined this question by utilizing direct flow cytometric measures of T cell subsets and developing two additional sets of mixed models, taking into account five representative T cell subsets

that gave the best consensus fit across all five epigenetic measures, but also are known to be altered as a result of HIV pathogenesis (total CD4 and CD8, naïve CD4, activated and senescent CD8) (Killian et al., 2004). The numbers and percentages of total and naive CD4 T cells, and senescent CD8 T cells, were significantly associated directly with most of the epigenetic measures except GEAA (Table 4, Table S10), indicating that for all but GEAA, immune system cell changes were playing an important role. However, the analyses of the interaction of study visit and HIV serostatus group, even after taking into account the five different T cell subset numbers or percentages, still showed a significant association with the same three epigenetic measures, EEAA, PEAA, and aaDNAmTL. This is consistent with at least one other study looking at chronic HIV infection using the Hannum Clock (Gross et al., 2016), which found that being infected with HIV had an effect beyond cell composition. Therefore, even though the changes in critical T cell numbers and percentages are strong contributors to the epigenetic changes observed, initial HIV infection is still making an additional contribution to accelerated aging as characterized by these particular epigenetic measures.

It is important to emphasize that this study of early effects of untreated HIV on these epigenetic measures was not designed to, and therefore, cannot directly answer whether such changes will ultimately be sustained and/or can predict longer term clinical and functional outcomes associated with aging such as co-morbidities and frailty, especially after initiation of highly active antiretroviral therapy (HAART). It has been reported that senescent T cell phenotypes(Hunt et al., 2014; Lee et al., 2014; Tenorio et al., 2014) and direct measures of TL(Erlandson et al., 2013) have failed to reveal a link with aging outcomes in persons living with HIV. However, this does not rule out the possibility that, early in HIV infection, some epigenetic measures (which capture different aspects of biological aging than T cell phenotypes alone) may have predictive value. Rather, our fundamental epigenetic observations at the time of infection highlight the need for additional studies (which are currently in progress) to determine whether epigenetic measures of aging continue to be associated with and predict subsequent development of morbidities, mortality, and frailty in persons living with and treated for HIV.

Before the availability of and/or use of HAART, it was shown that newly HIV-infected individuals typically experienced very high plasma HIV VL levels during acute infection, which resolved within the first year to a lower and relatively stable level, known as the HIV viral set-point(Mellors et al., 1996; De Wolf et al., 1997; Lefrère et al., 1998). By design, for the current study, the post-HIV infection time point in the SC was selected to be after the acute infection period, once the set-point had been established, but still within a relatively short time during which epigenetic aging effects would not be expected to be seen in the matched SN. In addition, the post-HIV infection time point was required to be before the initiation of HAART. This enabled us to demonstrate significant positive correlations between HIV VL and the EEAA and PEAA clocks (i.e., older epigenetic age), and negative correlations with the estimated aaDNAmTL (i.e., estimated shortening of telomeres) at the post-HIV infection visit (Figure S1). This is consistent with the mixed models demonstrating a role for initial HIV infection even after controlling for T cell changes, and supports the concept that the amount of HIV present as a result of the viral set-point may contribute to the magnitude of the early acceleration of biological aging according to these three epigenetic measures. It is important to acknowledge, however, that the viral set-point is the cumulative result of the interplay of virologic, immunologic, and genetic factors over the course of the initial period of HIV infection, and not the virus itself acting in isolation. Nonetheless, the possibility of HIV VL early after infection contributing to accelerated biological aging, with predicted risks of earlier mortality and immune system senescence by EEAA and PEAA, and dramatic estimates of shortened telomeres, adds yet another reason to strive to achieve clinical suppression of HIV in as many persons with HIV as possible, as soon as possible after infection.

In addition to the five calculated epigenetic measures reported here, which are based on carefully validated CpGs, this case/control longitudinal study has generated a unique DNAm dataset from 850,00 + CpG sites, and provides an exciting opportunity to explore the epigenetic imprint of initial HIV infection. Our methylome-wide analyses have provided illumination of the many gene networks and pathways associated with HIV seroconversion. Similar to our previous report in persons living with HIV(Rickabaugh et al., 2015), enrichment analyses identified many genes and pathways associated with embryogenesis and morphogenesis. This is biologically consistent with the accelerated aging indicated by many of the epigenetic clocks and our previous published results demonstrating significant overlap of aberrantly methylated genes and gene pathways influenced by both HIV and aging, particularly in the polycomb group target

protein pathway (Rickabaugh et al., 2015). In addition, and not too surprisingly, many genes and pathways involved in immune responses were also altered by initial HIV infection. The ability of HAART to normalize these gene pathways and the epigenetic clocks is a critically-important question, but this report focuses on the rare opportunity to examine the question of epigenetic changes from before, to very soon after, documented initial HIV infection, when PBMC sample availability is extremely limited and very precious. A recent report by our group of a preliminary study of 15 pairs of HIV-infected and uninfected MACS participants demonstrated that initiation of HAART may slightly improve epigenetic measures of accelerated aging, but does not return any of them to levels comparable to HIV-uninfected persons of the same chronologic age(Sehl et al., 2020). Similarly, that report utilized WCGNA to identify a cluster of CpG sites impacted by treatment of HIV, paving the way for additional analyses in a larger case-control dataset (manuscript in preparation, Sehl et al.).

Three of the greatest strengths of the MACS/MWCCS are the length of its longitudinal follow-up (from the early 1980s to the present), the depth of its repository of biologic samples (typically collected every 6 months), and its inclusion of both HIV-infected and uninfected participants from the same at-risk population. Coupled with an extensive demographic and clinical database, we are able to utilize the MACS to not only explore critical longitudinal questions related to HIV infection itself, but to address longer term questions related to living and aging with HIV. The extraordinary opportunity to evaluate biologic aging in more than one hundred individuals over the course of initial HIV infection, and in parallel in matched individuals who were documented to remain HIV-uninfected, was only possible in a prospective study like the MACS/MWCCS. Additional longitudinal analyses have very recently demonstrated that, over the course of years living with HIV before beginning HAART, the rate at which epigenetic age increases and estimated TL shortens is two to three times faster in HIV-infected men (Sehl et al., 2022). This emphasizes the importance of recognizing how quickly the process of initial HIV infection begins accelerating epigenetic measures of aging, and lays a foundation for further exploration of characterizing these epigenetic measures as predictors of future clinical outcomes and impacts on healthspan.

LIMITATIONS OF THE STUDY

The MACS includes only men who have sex with men, limiting the generalizability of our results to women living with HIV. The MACS enrolled small numbers of non-white participants, especially in the early years of the cohort when many of the documented new HIV infections and seroconversions occurred. Although this epigenetic substudy could not be designed with sufficient statistical power to examine both initial HIV infection and race, later enrollments for the MACS, and the merged MWCCS (which includes both men and women at risk or living with HIV) are intended to provide a more diverse cohort for future studies including those focused on aging with HIV(D'souza et al., 2019). Because of the scarcity of viably-preserved pre-HIV seroconversion PBMC samples, our sample size was limited to approximately 100 seroconverters, not all of whom also had post-treatment samples available. Based on our preliminary study(Sehl et al., 2020), a sample size of 200 HIV-infected individuals and matched controls is needed to properly evaluate the impact of initiation of HAART on these epigenetic measures, so our current sample has insufficient power to address this and other important issues such as prediction of clinical outcomes. Flow cytometry was designed to assess T cell subsets known to be important to HIV pathology and immunosenescence, which limited our ability to account for contribution of changes in non-T cell populations to changes in epigenetic measures.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2022.104488.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

Peter Langfelder is a paid consultant for The Bioinformatics CRO, Inc and Quantigic Genomics, LLC. Steve Horvath is a founder of the non-profit Epigenetic Clock Development Foundation which plans to license several patents from his employer UC Regents. These patents list SH as inventor.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
CD3-PerCP	BD Biosciences	SK7 (RUO (GMP)), Cat#347344; RRID: AB_400286
CD4-V450	BD Biosciences	RPA-T4 (RUO), Cat#561838; RRID: AB_10924599
CD8-APC-Cy7	BD Biosciences	SK1 (RUO (GMP)), Cat#348793; RRID: AB_400383
CD45RA-PE-Cy7	BD Biosciences	L48 (RUO (GMP)), Cat#337167; RRID: AB_647424
CCR7-AF647	BD Biosciences	150,503 (RUO), Cat#560816; RRID: AB_2033948
HLA DR-BV605	BD Biosciences	G46-6 (RUO), Cat#562845; RRID: AB_2744478
CD38-PE	BD Biosciences	HB7 (RUO (GMP)), Cat#347687; RRID: AB_400341
CD28-PE	BD Biosciences	L293 (RUO (GMP)), Cat#348047; RRID: AB_400368
CD57-BV605	Biolegend	QA17A04 (RUO), Cat#393304; RRID: AB_2728426
CD4-BV510	Biolegend	OKT4 (RUO), Cat#317444; RRID: AB_2561866
IgG2a-AF647	BD Biosciences	G155-178 (RUO), Cat#557715; RRID: AB_396824
IgG2a-BV605	BD Biosciences	G155-178 (RUO), Cat#562778; RRID: AB_2869434
IgG1-PE	BD Biosciences	×40 (RUO (GMP)), Cat#349043; RRID: AB_400398
IgG1-PE-Cy7	BD Biosciences	MOPC-21 (RUO), Cat#557872; RRID: AB_396914
Biological samples		
Viably-frozen peripheral blood mononuclear cells	MACS/WIHS Combined Cohort Study (MWCCS)	MWCCS concept sheet number C15039
Chemicals, peptides, and recombinant proteins		
Zombie Aqua Fixable Viability Kit	Biolegend	(RUO), Cat#423102
Critical commercial assays		
DNeasy Blood & Tissue Kit	QIAGEN	Cat#69506
Quant-it PicoGreen dsDNA Assay Kit	Invitrogen	Cat#P7589
EZ-96 DNA Methylation Kit	Zymo Research	Cat#D5004
Infinium MethylationEPIC BeadChip	Illumina	Cat#WG-317-1003
Deposited data		
Raw methylation data	This paper	MACS/WIHS Combined Cohort Study (MWCCS) when study aims are completed per MWCCS policy, via the concept sheet approval process (https://statepi.jhsph.edu/mwccs/work-with-us/); MWCCS concept sheet number C15039
Calculated age-regressed epigenetic clock and estimated telomere length data, as well as necessary de-identified demographic or descriptive data	This paper	MWCCS upon reasonable request via the concept sheet approval process (https://statepi.jhsph.edu/mwccs/work-with-us/); MWCCS concept sheet number C15039
Software and algorithms		
Epigenetic clock software Cell proportion imputation software	http://dnamage.genetics.ucla.edu	Horvath (2013); Hannum et al., 2013; Chen et al., 2016; Levine et al., 2018; Lu, Quach, et al., 2019a; Lu, Seeboth, et al., 2019b; Horvath and Levine (2015); Horvath et al., 2016
Weighted Gene Correlation Network Analysis, WGCNA R package	This paper	Langfelder and Horvath (2008)
EnrichR gene list enhancement tool	This paper	Kuleshov et al. (2016)
Attune NxT Software	ThermoFisher	Cat#A25556

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Dr. Beth Jamieson (bjamieso@ucla.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The raw Infinium MethylationEPIC BeadChip methylation data that support the findings reported in this study cannot be deposited in a public repository at this time because of the policies of the MACS/WIHS Combined Cohort Study (MWCCS) from which they were generated. Per MWCCS policies, these raw data will be released via a concept sheet approval process (https://statepi.jhsph.edu/mwccs/work-with-us/) once the original aims of our approved study are complete. All analytic data utilized in this paper (calculated age-regressed epigenetic clock and estimated telomere length data, T cell counts and percentages, as well as necessary de-identified demographic or descriptive data), have been deposited with the MWCCS, and are available upon reasonable request via the MWCCS concept sheet approval process (https://statepi.jhsph.edu/mwccs/work-with-us/). The MWCCS concept sheet number for all data related to this paper is listed in the Key Resources Table.
- All original code is available in this paper's Quantification and statistical analyses section below
- Any additional information required to reanalyze the data reported in this paper, if not restricted to the MWCCS concept sheet process, is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Human subjects

Participants for the study reported here were selected from among participants of the Multicenter AIDS Cohort Study (MACS), now part of the MACS/WIHS Combined Cohort Study (MWCCS). The MACS is an ongoing prospective study of the natural and treated history of Human Immunodeficiency Virus (HIV) infection in men who have sex with men (Kaslow et al., 1987). Participants for the current substudy of initial HIV infection were selected whenever possible from among MACS participants from a large biomarker study, which has been described elsewhere (Wada et al., 2015). The MWCCS complies with all relevant ethical regulations, including obtaining informed consent for research from all study participants. This MACS/MWCCS substudy was given exempt status by the University of California, Los Angeles Medical Institutional Review Board IRB#15001179.

102 men were selected who had undergone documented initial HIV infection and HIV antibody seroconversion (SC) after entry into the MACS, and 102 matched persistently HIV seronegative (SN) men. Selection criteria are described below in the Method Details section. Clinical and demographic information on all subjects can be found in Table 1.

The original predetermined sample size calculation was as follows: a sample size of 234 (117 seroconverters and 117 seronegative men) achieves over 80% power to detect an R-squared of 0.05 attributed to the 2 independent variables using an F-Test with a significance level (alpha) of 0.05 and adjusted for an additional 3 confounding variables. Upon querying the MACS/MWCCS repository for archived viably-frozen peripheral blood mononuclear cell (PBMC) sample availability within our specified study design criteria (see study design details below), it was only possible to obtain pre/post HIV infection PBMC samples from 102 seroconverters and from equivalent visits in 102 matched seronegative men. No additional pre/post HIV PBMC samples, which are rare even in large cohort studies, were available to us without compromising the study design, so we proceeded with our original study design with the 102 pairs of participants (204 compared to 234, or 87% of the original calculated sample size).

METHOD DETAILS

Participant selection and samples

Viably-frozen peripheral blood mononuclear cells (PBMC) were obtained from the national repository of the MACS/MWCCS. MACS study visits typically occur at 6 months intervals, clinical and questionnaire data are collected, and peripheral blood samples are processed and frozen.

SC participants were selected who had PBMC samples available in the repository from two time periods: (1) up to 1.5 years prior to the first HIV-seropositive study visit (pre-HIV infection, Visit A), and (2) up to 2.5 years after the first seropositive visit (post-HIV infection, Visit B). The pre-HIV PBMC sample was required to be from a visit that was both HIV antibody seronegative and with undetectable plasma HIV RNA. All post-HIV infection PBMC samples were required to be before initiation of HAART; if multiple PBMC samples were available post-HIV infection, the visit closest to 3 years after the pre-HIV visit was selected. 102 SC with 204 PBMC samples were available for inclusion in the current substudy.

Matched persistently HIV seronegative (SN) controls were then selected among MACS participants for each SC. SN were selected matched by age ($\pm$2 years) and Hepatitis C Virus (HCV) status (HCV RNA positive/negative) at both visits, as well as by availability of PBMC at two visits (Visits A and B) with comparable time interval between visits ($\pm$0.75 years). 102 matched SN controls were identified, but a PBMC sample matched on age and HCV status within a comparable time interval was not available from one control at Visit A (equivalent to pre-HIV infection in the matched SC), yielding 203 SN PBMC samples.

Participant demographics and characteristics

HIV serostatus, plasma HIV viral load (VL), absolute CD4 T cell numbers, Hepatitis B Virus (HBV) and cytomegalovirus (CMV) status, and other demographic and clinical data were available from the MWCCS database, and are summarized in Table 1. Where data are missing from the 102 SC or 102 SN, the exact n is shown in Table 1. An estimated date of HIV infection for each SC was calculated utilizing HIV serostatus (HIV antibody and Western Blot) and HIV VL data from all MACS study visits. Date of HIV infection was estimated as the midpoint between the last MACS study visit at which the participant was HIV seronegative and HIV VL undetectable (if VL data were available) and the first MACS study visit with either HIV-positive serostatus or detectable HIV VL, whichever came first. For 10 SC for whom VL data were missing at Visit B, the VL from the MACS visit immediately prior was used (0.3–0.5 years prior, approximately 3–6 months). For post-HIV infection visits with undetectable VL, a value equal to the lower limit of detection of the VL assay was assigned; four SC had VL < 400 copies/mL (Roche Amplicor 2nd generation assay, Roche Molecular Systems, Branchburg, NJ, USA), and 1 had <50 copies/mL (ultra-sensitive Roche Amplicor assay). HBV status at each visit was categorized as positive (HBV surface antigen [HBsAg] positive) or negative (HBsAg negative), and smoking history was evaluated by cumulative pack years reported. CMV status at Visit A (pre-HIV infection visit in SC group, equivalent visit in SN group) was categorized when available as seropositive (detectable anti-CMV antibody titer before or at Visit A) or seronegative (undetectable anti-CMV antibody titer at or after Visit A), based on data in the MWCCS database from testing of selected MACS visits between 1984 and 1989.

Thawing and viability of frozen samples

Frozen PBMC vials were removed from liquid nitrogen storage tanks and placed into a 37 °C water bath. Once samples were thawed and removed from the water bath, the vials were wiped down with 70% isopropyl alcohol and the cell suspensions transferred using plastic transfer pipettes (Fisher Brand) to a 15 mL round bottom tube (Corning). Roswell Park Memorial Institute Medium (RPMI [Gibco]) with 10% Fetal Calf Serum (FCS [Omega]), 1% L-glutamine (Gibco), 100 U/mL Penicillin-Streptomycin (Gibco), 12.5 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES [Gibco]) buffer was added dropwise to each round bottom tube to gradually dilute the cell suspension. Between dropwise additions of culture medium, the cell suspensions were agitated to ensure homogeneity. Cells were centrifuged at 300g for 10 min at room temperature, then resuspended in 1 mL of 10% FCS-RPMI. Cell suspensions were counted using a Z2 Particle Counter (Beckman Coulter) and viabilities were assessed using 1:4 dilution of cell suspension to 0.2% Trypan Blue under a hemocytometer chamber; mean viability of PBMC was 89.6%. Thawed PBMC were divided for DNA extraction and flow cytometry.

Genomic DNA isolation and quantification

1.0 × 10^6 viable PBMC were diluted with 1 mL of Phosphate Buffer Solution (PBS [Gibco]) then spun at 2200g in a 5415C centrifuge (Eppendorf) for 3 min in a 2mL conical screw top tube (Stardstedt). Supernatants were aspirated, leaving a dry PBMC pellet which was stored in a −80°C freezer until genomic DNA isolation.

DNeasy Blood and Tissue kits (Qiagen) were used according to kit protocol to extract DNA from frozen dry PBMC pellets. 200 microliters of PBS, then 20 microliters of proteinase K and finally 20 microliters of Buffer AL was added to the dry pellet tubes. Mixtures were vortexed after each addition, then incubated in a 56°C water bath for 5 min. DNA mixtures were vortexed again and placed back into the water bath for an additional 5 min. 200 microliters of 200 proof ethanol was added to the mixture, vortexed, and then added to the DNeasy Mini spin columns. Columns were spun for 1 min at 6000g at room temperature. Flow through and collection tubes were removed and discarded. Spin columns were then placed into a new collection tube, 500 microliters of Buffer AW1 added to each column, and spun at 6000g for 1 min at room temperature. Again, flow through was discarded and columns were put into another collection tube, 500 microliters of Buffer AW2 added and spun at 14000g room temperature for 3 min. Flow through was once again discarded and columns placed into a new collection tube. 200 microliters of Buffer AE was added to the columns, incubated at room temperature for 1 min then centrifuged at 6000g for 1 min. This step was repeated 2 more times to increase DNA yield. 600 microliters DNA suspensions were added to Microcon DNA Fast Flow Centrifgual Filters (Millipore) and 2 mL collection tubes (Fisher Brand). Suspension, filter, and tube units were spun at 400g for 10 min. Centrifugal filters were then inverted into a new collection tube and spun at 1500g for 3 min. DNA concentration was determined using a NanoDrop One (ThermoFisher) using the dsDNA setting and automatic measurements generated from 220–340 nm wavelengths. Because the genomic DNA samples were finally resuspended in Buffer AE from Qiagen kits, the same Buffer AE was used to blank the NanoDrop One to ensure the background was accounted for appropriately. Genomic DNA samples were then stored in −80 °C freezers until plated for methylation analysis.

DNA methylation arrays

Methylation status at more than 850,000 potential methylation sites (CpGs) were measured using the Infinium MethylationEPIC BeadChip (Illumina, San Diego, CA), by the UCLA Neuroscience Genomics Core (https://www.semel.ucla.edu/ungc). Blinded matched sets of genomic DNA samples were created by the investigators, with each set containing samples from matched SN and SC participants at all visits; sets were then placed on an 8-well BeadChip by the Genomics Core. DNA concentrations were determined using a Quant-it PicoGreen dsDNA Assay Kit (Invitrogen/Molecular Probes, Inc., Eugene, OR). 500 ng of genomic DNA was bisulfate converted using the EZ-96 DNA Methylation Kit (Zymo Research, Orange, CA), prepared for use in the Illumina Infinium assay, followed by microarray hybridization and scanning (iScan, Illumina), according to the manufacturer's protocols. The methylation assays routinely included internal laboratory replicates to document satisfactory technical performance. All assays passed the Genomics Core technical requirements. DNA methylation levels (beta values) were determined by calculating the intensity of the methylated (M corresponding to signal A) and un-methylated (U corresponding to signal B) sites, as the ratio of fluorescent signals:

$$\frac{Max(M,0)}{[Max(M,0)+Max(U,0)+100]}$$

Therefore, beta values range from 0 (completely un-methylated) to 1 (completely methylated). A Euclidean metric (impute.knn function in R) (Troyanskaya et al., 2001) was utilized to find k-nearest neighbors and impute missing beta values by averaging non-missing elements of its neighbors. Quantile normalization was applied to the raw data, to detect and remove outliers, and to make data comparable to the training data of the epigenetic clocks and consistent with previous analyses(Sehl et al., 2020).

Flow cytometry for T Cell subsets

Percentages of naive ($CD45RA^+CCR7^+$), activated ($HLA\text{-}DR^+CD38^+$), and senescent ($CD28^-CD57^+$) T cells within the total CD4 ($CD3^+CD4^+$) and CD8 ($CD3^+CD8^+$) T cells of each PBMC sample were determined by multicolor flow cytometry (Mahnke et al., 2013; Brenchley et al., 2003). Depending on recovery and viability after thawing, 0.5 × 10^6 to 1.0 × 10^6 viable PBMC per tube were stained on the same day as they were thawed for flow cytometry, with a total of 3 staining tubes per sample. PMBCs were surface-stained as shown in Table S13, for 30 min in the dark at room temperature. Specific antibody conjugates were added

to each tube (which contained up to 1.0 × 10^6 cells) in a volume equivalent to one test, as defined by the manufacturer. Isotype antibody volumes added per tube were calculated to match the corresponding markers' antibody concentrations. The dead cell discriminator, Zombie Aqua, was reconstituted according to manufacturer recommendations: 100 microliters DMSO (Biolegend) was added to each lyophilized reagent, then diluted 1:100 with Phosphate Buffer Solution (PBS, Life Technologies). 100 microliters of the diluted Zombie Aqua was added to each tube to discriminate dead cells. All antibody conjugates were obtained from BD Biosciences with the exception of Zombie Aqua, CD57 Brilliant Violet 605 (BV605), and its corresponding isotype IgG2a (BV605), which were purchased from Biolegend. Conjugates were chosen based on availability and to maximize wavelength absorbance distances between detectors. After the staining incubation period, 1 mL of PBS with 2% newborn calf serum (Life Technologies) and 0.1% sodium azide (Sigma Aldrich) were added to each tube and centrifuged at 300g for 10 min. Supernatants were aspirated, and stained PBMC were then resuspended in 200 microliters PBS-sodium azide buffer and transferred into a 96 well round bottom plate (Falcon). Plated PBMCs were acquired and analyzed on an Attune NxT Flow Cytometer (ThermoFisher A29004 [blue/red/violet6/yellow]) with an Attune NxT Flow Cytometer Autosampler (ThermoFisher 4473928), using the Attune NxT Software (ThermoFisher). For each stained sample, 180 microliters of the 200 microliter total sample volume was acquired, yielding up to approximately 800,000 cell events for analysis. To ensure acquisition reliability and reduce cross contamination between samples, run settings of the autosampler were set to 100 microliters/minute with 2 mixes and 4 rinses between samples and a 1 s delay of recording after the start of each sample acquisition. Single color antibody and Fluorescence Minus One (FMO) techniques were utilized to establish photomultiplier tube (PMT) settings for acquisition and cursor settings for subset data analysis. Isotype antibodies were implemented to detect any non-specific binding to proteins or binding to Fc receptors. UltraComp eBeads Plus Compensation Beads (ThermoFisher) were used in conjunction with 1 test of each corresponding antibody. CD4 BV510 (Biolegend) was implemented to compensate the Violet 2 channel as recommended by the manufacturer since CD4 BV510 has similar emissions to Zombie Aqua. Due to the weight of the beads, the compensation panel was acquired using individual tubes instead of the plate reader. Attune Performance Tracking Beads (ThermoFisher) and chicken red blood cells (Biosure) tracked the Attune's performance over time and ensured accuracy and sensitivity of the instrument.

QUANTIFICATION AND STATISTICAL ANALYSES

Epigenetic age acceleration measures

Five measures of epigenetic age acceleration were estimated for each of the 407 PBMC samples in total, representing samples from all participants at both visits, using the online epigenetic clock software (http://dnamage.genetics.ucla.edu). Each of these DNA methylation-based estimates was calculated using methylation beta values obtained from the Infinium MethylationEPIC BeadChip, on all samples at the same time without linkage to HIV serostatus group. There were no adjustments for multiple comparisons, as each epigenetic measure was developed taking this into account. Features of each clock examined are provided in Table S1. Briefly, Age Acceleration Residual (AAR) is based on the DNAm age estimated from 353 CpGs of Horvath's original epigenetic clock(Horvath, 2013), which is then regressed on chronologic age. AAR captures epigenetic age acceleration (i.e., older epigenetic or biological age than chronological age), is valid for a wide range of tissue types, and is known to be accelerated in disease states. Extrinsic epigenetic age acceleration (EEAA) is based on 71 CpGs of Hannum(Hannum et al., 2013), and was constructed to be positively correlated with senescent T lymphocytes and negatively correlated with naive T lymphocytes(Chen et al., 2016; Hannum et al., 2013).This measure captures both intrinsic methylation changes and extrinsic blood cell composition changes. Second generation clocks, including Phenotypic Age and Grim Age, were examined as they are much stronger predictors of mortality. Phenotypic Epigenetic Age Acceleration (PEAA), based on 513 CpGs, was developed by regressing a phenotypic measure of mortality risk on CpGs(Levine et al., 2018). Grim Epigenetic Age Acceleration (GEAA), based on 1030 CpGs, was developed by regressing time-to-death on DNAm-based surrogate biomarkers of smoking pack-years and a selection of plasma proteins previously associated with mortality or morbidity (Lu et al., 2019a). Finally, a DNA methylation-based estimator of Telomere Length adjusted for chronologic age (aDNAmTL) was examined in our analyses to evaluate whether HIV infection causes accelerated shortening of telomeres with increased age and/or rate of cellular replication (Lu et al., 2019b).

In this study, there is one time point occurring post-seroconversion to examine the difference between HIV-infected and uninfected, so it is not possible to determine exactly when and over what period of time the observed elevation in epigenetic age occurs. However, "epigenetic age acceleration" measures are

compared, defined as the residual that results from regression of epigenetic age on chronologic age, at both visits for the SC and SN groups. Because these measures are age-adjusted, they are technically termed "accelerations" in the epigenetic clock literature, rather than elevations or advancements, even though the time course and rate of acceleration is unknown.

Absolute counts of T Cell subsets

Percentages of naive, activated, and senescent T cells among CD4 T cells, or among CD8 T cells, were directly determined in each aliquot of thawed viable PBMC (see Table S13 for staining protocol); out of 407 thawed aliquots of PBMC utilized in DNAm analyses in SC and SN groups at visits A and B, 404 had sufficient viable PBMC to stain for flow cytometry. Absolute total CD4 and total CD8 T cell counts (cells/mm^3) for almost all samples were available from the MACS/MWCCS database, which had been determined by standardized protocols on the day each blood sample was originally obtained(Giorgi et al., 1990; Hultin et al., 2007). Flow cytometry percentages on thawed PBMC were utilized in combination with absolute total CD4 and CD8 T cell counts to calculate absolute cell counts for naive, activated, and senescent CD4 and CD8 T cells for each sample. Naive and senescent CD4 and CD8 T cells were stained and analyzed in one tube, and activated CD4 and CD8 T cells were stained and analyzed in a separate tube. Due to technical issues during flow cytometry acquisition, the activated cell tube, or both tubes was/were unable to be acquired on a small number of PBMC samples at one or both visits, and/or the absolute CD4 and CD8 T cell counts were missing from the MWCCS database, resulting in some variability in the number of PBMC samples for which absolute cells counts could be calculated, as shown in Table 3.

Frequencies of T Cell subsets within the live lymphocyte population

Percentages of total CD3 T cells, CD4 T cells, and CD8 T cells, and naive, activated, and senescent CD4 and CD8 T cells among the total live lymphocytes in each aliquot of thawed viable PBMC were calculated by utilizing the live lymphocyte gate established by forward vs. side scatter for lymphocytes combined with Zombie Aqua viability dye (lymphocytes negative for Zombie Aqua staining). As noted above, naive and senescent CD4 and CD8 T cells, and activated CD4 and CD8 T cells, were stained and analyzed in separate tubes. Therefore, staining for total CD3 T cells, and for CD4 and CD8 T cell subsets, were performed in duplicate for each PBMC sample. When available, duplicate determinations were utilized to calculate mean percentages of live lymphocytes for CD3, CD4, and CD8 cells. However, mean values with a coefficient of variation (CV) > 10% between the two tubes from the same PBMC sample were excluded. Of 404 PBMC samples with sufficient viable cells to stain for flow cytometry, 27 samples were excluded due to CVs >10% on mean % CD3, and 1 each was excluded due to CVs >10% on mean % CD4 and % CD8. Due to additional technical issues during acquisition as described above, there is some variability in the number of PBMC samples for which percentages were available, as shown in Table S9.

Statistical analyses of epigenetic measures

No raw methylation data, nor calculated epigenetic clock or estimated DNAmTL data were excluded from the analyses. HIV serostatus groups (SC and SN) were compared to each other (t-test, 2-sided) on each age-adjusted epigenetic measure at Visit A (all participants HIV-uninfected), and again at Visit B (post-HIV infection in SC, time interval-matched visit in uninfected SN). Median values, and 25^{th}-75^{th} percentile and 5^{th}-95^{th} percentile ranges, are shown in Figure 1. Within-person changes in age-adjusted epigenetic measures from Visit A to Visit B were calculated for each participant (Visit B value – Visit A value), and SC and SN groups were each evaluated by paired t-tests (2-sided) for differences from zero. Median values and 25^{th}-75^{th} percentile ranges are shown in Figure 2. Similar analyses were performed on the absolute counts of T cell subsets (Table 3) and percentages of T cell subsets within live lymphocytes (Table S9), comparing SC vs SN at Visit A and again at Visit B (t-test, 2-sided), as well as for the absolute T cell counts (Table S4), evaluating within-person changes from Visit A to Visit B in SC and SN (t-tests, 2-sided, for differences from zero).

Pairwise correlation analyses were performed for each of the epigenetic measures, for all participants at Visit A (all HIV-uninfected), and for SC at Visit B (recently HIV-infected) and SN at Visit B (persistently uninfected). Pearson correlation coefficients (rho) and p values are shown in Table S3. Pairwise correlation analyses were also performed for each of the absolute T cell subsets counts as well as all of the epigenetic measures, for all participants at Visit A, for SC at Visit B, and for SN at Visit B. Pearson correlation coefficients (rho) and p values are shown in Tables S5–S7.

Potential contributions of co-variates (study visit, HIV serostatus group, interaction between study visit*HIV serostatus group, race [non-white vs. white], current HBsAg status [negative vs. positive], Body Mass Index [BMI], and smoking cumulative pack years) to the changes in each age-adjusted epigenetic measure between the two visits were analyzed in linear mixed effects models using random intercept and slope, with all participants in the same model. Due to missing data for some demographic co-variates, n = 387 samples for these mixed models. The F values and p values from the mixed effect models for all five epigenetic measures are shown in Table 2; individual parameter estimates and p values from fixed effects analyses are reported in Table S2. We assumed compound symmetry covariance structure as more complicated models did not offer a better fit. The code for these mixed models was as follows:

```
PROC MIXED data = THREE;

CLASS macsidnumber casecontrol visit;

MODEL aar = visit casecontrol casecontrol*visit white

hepb

CUM_PKYEAR

BMI/SOLUTION outpred = PREDAAR;

RANDOM INTERCEPT/SUB = macsidnumber TYPE = CS G GCORR;

REPEATED visit;

LSMEANS casecontrol/DIFF = all;

ESTIMATE "Control Mean" intercept 1 casecontrol 1 0;

ESTIMATE "Case Mean" intercept 1 casecontrol 0 1;

LSMEANS casecontrol/DIFF = ALL AT (visit)=(1);

LSMEANS casecontrol/DIFF = ALL AT (visit)=(2);

ESTIMATE "Age Slope for Control" visit 1 casecontrol*visit 1 0;

ESTIMATE "Age Slope for Case" visit 1 casecontrol*visit 1 0;

store out = MixedModelAAR;

run;

quit;
```

For each additional DNAm measure, substitute the name ***eeaa***, ***peaa***, ***geaa***, or ***dnamtladjage*** where ***aar*** currently appears.

Potential contributions of absolute counts of T cell subsets (total CD4, total CD8, naive CD4, naive CD8, activated CD4, activated CD8, senescent CD4, senescent CD8) to the changes in each age-adjusted epigenetic measure between the two visits were analyzed in linear mixed effects models using random intercept and slope, with all participants in the same model. All absolute T cell counts were natural log-transformed (ln cells/mm^3) before inclusion into mixed models. Due to missing data for some flow cytometry variables, n = 374 samples for these mixed models. Five potential models were evaluated for all five epigenetic measures. Each model was constructed with a different combination of 3–5 T cell subsets, based on expected HIV pathogenesis and/or to minimize highly-correlated subsets (Tables S5–S7) to reduce co-linearity. We selected the model with the consensus

best fit across all five epigenetic measures using the Akaike Information Criterion (AIC); this model included: total CD4, total CD8, naive CD4, activated CD8, senescent CD8. The F values and p values from the mixed effect models for all five epigenetic measures are shown in Table 4; individual parameter estimates and p values from fixed effects analyses are reported in Table S8. The code for these mixed models was as follows:

PROC MIXED data = THREE;

CLASS macsidnumber casecontrol visit;

MODEL ***aar*** = visit casecontrol casecontrol*visit lnabs_cd42

lnabs_cd82

lnAbsNaiveCD4

lnAbsSenCD8

lnAbsActCD8/SOLUTION outpred = PREDAAR;

RANDOM INTERCEPT/SUB = macsidnumber TYPE = CS G GCORR;

REPEATED visit;

LSMEANS casecontrol/DIFF = all;

ESTIMATE "Control Mean" intercept 1 casecontrol 1 0;

ESTIMATE "Case Mean" intercept 1 casecontrol 0 1;

LSMEANS casecontrol/DIFF = ALL AT (visit)=(1); * group intercept diffs;

LSMEANS casecontrol/DIFF = ALL AT (visit)=(2); * group intercept diffs;

ESTIMATE "Age Slope for Control" visit 1 casecontrol*visit 1 0;

ESTIMATE "Age Slope for Case" visit 1 casecontrol*visit 1 0;

store out = MixedModel***AAR***;

run;

quit;

For each additional DNAm measure, substitute the name ***eeaa***, ***peaa***, ***geaa***, or ***dnamtladjage*** where ***aar*** currently appears.

The consensus best fit model was repeated for each of the DNAm measures to account for natural log-transformed T cell subset percentages instead of absolute T cell counts, using the same code, substituting:

lncd4 for lnabs_cd42

lncd8 for lnabs_cd82

lnNaiveCD4 for lnAbsNaiveCD4

lnSenCD8 for lnAbsSenCD8

lnActCD8 for lnAbsActCD8.

Due to missing data for some flow cytometry variables, n = 382 samples for these mixed models. The F values and p values from these mixed effect models for all five epigenetic measures are shown in Table S10.

At the post HIV-infection visit (Visit B) in the SC group only, regression analyses were performed for each of the epigenetic measures and HIV VL, as well as for HIV VL and absolute CD4 T cell counts together in a single analysis. In all analyses where HIV VL was included, viral load (copies/mL) was log10 transformed. For the analyses with HIV VL, Pearson correlation coefficients (rho) and p values are shown in Figures S1A–S1E.

Weighted Gene Correlation Network Analysis (WGCNA) of genomic methylation data

Weighted Gene Correlation Network Analysis (WGCNA) (Langfelder and Horvath, 2008) was utilized to identify clusters of CpGs that are correlated with each other across the genomic DNA (co-methylation modules) of the samples analyzed (all samples from all participants at both visits, n = 407 samples), using methylation levels measured at over 850,000 individual CpG methylation sites on the Infinium MethylationEPIC BeadChip. Missing values were imputed using k-nearest neighbor imputation implemented in function impute.knn in R package impute (Troyanskaya et al., 2001). CpGs were then sorted by decreasing variance and the top 400,000 CpGs were retained for WGCNA. Because network analysis on 400,000 CpGs in a single block is impractical, pre-clustering implemented in WGCNA R package was used to split the CpGs into blocks of no more than 40,000 variables. Network construction and module identification was then carried out in each block separately. Average linkage hierarchical clustering was performed using the topological overlap-based dissimilarity measure, and modules, defined as branches of the resulting clustering tree, were identified using the Dynamic Hybrid branch cutting approach implemented in the R package dynamicTreeCut. A total of 67 co-methylation modules were identified by WGCNA. A representative methylation profile for each module, referred to as the module eigenvector, was defined as the first principal component of the module methylation matrix, and for each CpG within each module, the intramodular connectivity measure kME was calculated as

$$kME_i^I = cor(x_i, E^I)$$

where x_i is the methylation profile of CpG labeled i and E^I is the representative of module I. kME can be considered a continuous measure of module membership for each CpG(Horvath and Dong, 2008). When a CpG has a high kME for a given module (e.g., above a threshold value $\geq$ 0.85), it is considered a hub site.

Mean and standard deviation (SD) eigenvector methylation values for each Module at each Visit were calculated separately on 102 HIV seroconverters (SC group), and on 101 persistently HIV-uninfected controls (SN group), who had observations at both Visits A and B. Non-parametric group comparison tests (Kruskal-Wallis) were performed in each group, comparing mean Module eigenvector methylation from Visit A to Visit B. The level of significance for changes in mean Module eigenvector methylation values adjusting for multiple comparisons was $p < 0.05/67$ or $<7.5 \times 10^{-4}$. In the SC group, out of the 67 Modules, there were 18 Modules with a p value $< 7.5 \times 10^{-4}$, indicating a significant association between changes in methylation values among CpGs in each of these Modules and initial HIV infection (i.e., a change from HIV-uninfected at visit A to HIV-infected at visit B). These 18 Modules are summarized in Table 5. None of the 67 Modules showed significant differences between visits A and B in the SN group, and were not analyzed further.

All of the CpGs from each of the 18 HIV infection-associated Modules are listed in Table S11, which is a supplemental Excel file. The file lists, on a separate tab for each Module, the CpG Illumina ID number for the unique site on the EPIC Bead Chip, name(s) of the gene(s) that contain(s) the unique CpG site, and the kME value for each CpG. The gene names are derived from the Illumina array UCSC_RefGene_Name, which is the target gene name from the UCSCdatabase. If a CpG site falls within multiple genes, all gene names are shown separated by semi-colon. Multiple listings of the same gene name indicate splice variants.

Pathways enrichment analyses of genomic methylation data

Enrichment analyses were performed using the EnrichR gene list enhancement tool(Kuleshov et al., 2016) to identify overrepresented biological pathways for those CpG sites with high connectivity (kME $\geq$0.85 from WGCNA) within each of the 18 HIV infection-associated Modules. Table S12 (a supplemental Excel file) lists, on a separate tab for each Module, enrichment terms (names of biological processes or pathways)

identified in the EnrichR analysis, along with the overlap (number of genes identified in our analysis over the total number of genes in the literature for a given pathway), p value (computed using Fisher exact test, assuming a binomial distribution and independence for probability of any gene belonging to any set), adjusted p value (correction for all known genes in the set), Odds Ratio for each enrichment term [given by (a/b)/(c/d), where a = number of genes in the Module that fall in the enrichment term, b = number of genes in the Module that do not fall in the enrichment term, c = number of genes in the enrichment term that are not in the Module, and d = 20,000-(a+b + c); 20,000 is the total number of genes in the human genome], and combined score (the product of the log of the p value from the Fisher exact test with the *Z* score deviation from the expected rank for each term in each gene-set library) for each enrichment term identified for each Module. Enrichment terms within each Module are ordered based on p value, from most to least significant.

ADDITIONAL RESOURCES

N/A

Longitudinal changes in epigenetic age in youth with perinatally-acquired HIV (YPHIV) and youth who are perinatally HIV-exposed uninfected (YPHEU)

PEB0312

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BACKGROUND

- The onset of age-related conditions (e.g. osteoporosis, dementia) often occurs earlier in life among those living with HIV than those without HIV, suggesting accelerated aging is occurring in people with HIV.
- Recently, research has begun to characterize molecular profiles, such as patterns of DNA methylation, that reflect this accelerated aging, which can be inferred when the estimated biological age exceeds chronological age.[1]
- Accelerated epigenetic age (i.e. patterns of DNA methylation that correspond to an estimated biological age that exceeds chronological age) has been linked to aging-related outcomes, including all-cause mortality, frailty, and cognitive decline in the elderly.
- Cross-sectional studies have reported epigenetic age acceleration in adults living with HIV on ART,[2-4] but few studies have examined this question amongst youth with perinatally-acquired HIV (YPHIV), and findings have not been consistent.[5,6]

OBJECTIVE

- We quantified the rate of change in epigenetic age compared to chronological age over time in YPHIV and youth who are perinatally HIV-exposed uninfected (YPHEU), and among YPHIV, examined associations with time-averaged area under the curve (AUC) HIV RNA viral load (VL) and CD4$^+$ T-cell count.

METHODS

Study Population

- 32 YPHIV and 8 YPHEU with active follow up were selected from the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS) network, which enrolled YPHIV and YPHEU from March 2007 through November 2009 at clinical sites in the United States and Puerto Rico.
- Inclusion criteria included youth with peripheral blood mononuclear cell (PBMC) samples collected at two time points ≥3 years apart, and all YPHIV who had HIV RNA VL measured within 1 year of birth and within 1 year of each of the sample time points.
- Participants were selected to have an equal distribution of male and female participants in each group with the largest time difference between the first and last sample.
- One YPHEU was excluded from the analyses due to a mislabeling of one of the specimens.

Measurements

- Demographic, clinical, and laboratory data were collected through self-report and medical chart abstraction, including information on history of ART, HIV RNA VL, and CD4$^+$ T-cell lymphocyte measurements.
- Time-averaged area under the curve (AUC) CD4 T-cell count and HIV RNA VL were calculated using the trapezoidal rule from the first VL measurement to each of the sample time points.[7]
- DNA was isolated from PBMCs and profiled for genome-wide DNA methylation using the Illumina MethylationEPIC (850K) BeadArray (Illumina Inc., San Diego, CA).
- Data were processed via a standardized pipeline implemented by the *minfi* Bioconductor package using R statistical software, version 3.4.4. We excluded 3070 CpG probes that had poor detection *p*-values. The final analytic sample included 39 samples and 482,694 probes.
- DNA methylation-estimated cell type proportions (B-cells, CD4 T-cells, CD8 T-cells, natural killer cells, granulocytes, monocytes) were calculated using the Houseman method.[8]
- Epigenetic age was calculated using the Horvath method (353 CpGs) via the online calculator.[1]

METHODS

Statistical Analysis

- Descriptive statistics were used to summarize demographic and clinical characteristics of the subset of YPHIV and YPHEU selected for this analysis at the two time points. Given the modest sample size with repeated measures, we evaluated the 32 YPHIV and 7 YPHEU separately, rather than attempting to statistically compare these two groups.
- At each of the two timepoints, an epigenetic age acceleration residual was calculated as the difference between epigenetic age and chronological age.
- Box and whisker plots were used to graphically depict the epigenetic age acceleration residual at timepoint 1 and timepoint 2 separately for YPHIV and YPHEU.
- Scatter plots were used to graphically depict epigenetic age by chronological age for YPHIV and YPHEU.
- To examine longitudinal changes in epigenetic age compared to chronological age, linear mixed effects models were fit to estimate the average change in epigenetic age for a one year change in chronological age separately for YPHIV and YPHEU.
- Given the small sample size, a limited number of additional covariates (HIV status, sex, geographic region, race, and cell type proportions) were investigated as additional predictors of epigenetic age in separate linear mixed effects models including chronological age.
- Among YPHIV only, ART regimen, time-averaged AUC CD4 T-cell count and HIV RNA VL were evaluated as additional predictors of epigenetic age in separate linear mixed effects models and together in a single model including chronological age.
- Statistical analyses were all performed using R statistical software, version 3.4.4 (Vienna, Austria) and SAS, version 9.4 (Cary, North Carolina, USA). Statistical significance was defined using two-sided P-value less than 0.05.

RESULTS

- **Table 1:** Median age was 10.9 (range 7.0 – 16.9) and 16.8 (range 14.9 – 20.8) years at timepoints 1 and 2, respectively. At timepoint 1, median age was higher in the YPHIV group than the YPHEU group (11.4 vs. 8.1 years). Median duration of time between timepoint 1 and timepoint 2 was 6.0 years (interquartile range [IQR]: 4.0-7.7). Groups were balanced by sex (51% male) and race (67% Black).
- **Table 2:** Median time-averaged AUC CD4 T-cell count was 1,228 and 1,140 cells/mm^3 and time-averaged AUC HIV RNA VL was 2.5 and 2.3 log10 copies/ml at timepoints 1 and 2, respectively. At timepoint 1 the majority of YPHIV (78%) were on a protease inhibitor (PI)- containing ART regimen and 2 children (6.3%) were not on ART. At timepoint 2, 12.5% were not on ART.
- **Figure 1:** The median epigenetic age acceleration residual was -0.1 year (IQR: -1.8, 1.9) at timepoint 1 and 0.1 year (IQR: -3.7, 4.1) at timepoint 2 for YPHIV. The median epigenetic age acceleration residual was -0.6 year (IQR: -3.7, 0.7) at timepoint 1 and -0.9 year (IQR: -7.5, -0.7) at timepoint 2 for YPHEU.
- **Figure 2:** Epigenetic age increased for all YPHIV and YPHEU from time point 1 to time point 2.
- **Table 3 Models 1-4:** In linear mixed effects models, epigenetic age increased by 1.22 years (95% confidence interval [CI]: 1.03, 1.42) for YPHIV and 0.95 years (95% CI: 0.74, 1.17) for YPHEU per year increase in chronological age. HIV status, sex, race, and geographic region, were not associated with epigenetic age in separate models including chronological age.

RESULTS

Table 1: Characteristics of 32 YPHIV and 7 YPHEU by group

Characteristic	YPHIV (N=32)	YPHEU (N=7)	Total (N=39)
Chronological age at Timepoint 1 (years), Median (Q1, Q3)	11.4 (9.9, 12.8)	8.1 (7.4, 9.0)	10.9 (8.7, 12.4)
Chronological age at Timepoint 2 (years), Median (Q1, Q3)	17.0 (16.2, 17.6)	16.0 (15.1, 17.0)	16.8 (16.0, 17.5)
Time between Timepoint 1 and 2 (years), Median (Q1, Q3)	5.2 (3.9, 7.1)	8.0 (7.6, 8.1)	6.0 (4.0, 7.7)
Sex, N (%)			
Male	16 (50.0%)	4 (57.1%)	20 (51.3%)
Female	16 (50.0%)	3 (42.9%)	19 (48.7%)
Race, N (%)			
White	10 (31.3%)	2 (28.6%)	12 (30.8%)
Black	21 (65.6%)	5 (71.4%)	26 (66.7%)
Other	1 (3.1%)	0 (0.0%)	1 (2.6%)
Site Region, N (%)			
Northeast	9 (28.1%)	0 (0.0%)	9 (23.1%)
South	3 (9.4%)	0 (0.0%)	3 (7.7%)
West	6 (18.8%)	3 (42.9%)	9 (23.1%)
Midwest	14 (43.8%)	4 (57.1%)	18 (46.2%)
Age at First ARV (years), Median (Q1, Q3)	0.2 (0.2, 0.5)		
Age at First HAART (years), Median (Q1, Q3)	0.3 (0.2, 1.2)		

Table 3: Predictors of epigenetic age in 32 youth with YPHIV and 7 YPHEU in linear mixed effects models including chronological age

Model	Covariate	Level	Estimate	(95% CI)	P-value
Model 1	Chronological age (years)		1.15	(0.99, 1.31)	0.067
	HIV status	YPHIV	2.47	(-0.60, 5.55)	0.11
		YPHEU	Ref.		
Model 2	Chronological age (years)	-	1.17	(1.01, 1.33)	0.038
	Sex	Female	-1.54	(-3.92, 0.84)	0.20
		Male	Ref.		
Model 3	Chronological age (years)	-	1.15	(0.99, 1.31)	0.068
	Site Region	Midwest	2.38	(-0.60, 5.36)	0.11
		Northeast	3.76	(0.32, 7.20)	0.033
		South	2.98	(-1.87, 7.83)	0.22
		West	Ref.		
Model 4	Chronological age (years)	-	1.16	(1.00, 1.32)	0.051
	Race/Ethnicity	Black	-0.16	(-2.82, 2.49)	0.90
		Other	-3.42	(-11.35, 4.51)	0.39
		White	Ref.		
Model 5	Chronological age (years)	-	0.91	(0.71, 1.10)	0.32
	Percentage of B Cells[1]	-	-0.15	(-0.32, 0.02)	0.084
	Percentage of CD4 T cells[1]	-	-0.13	(-0.24, -0.03)	0.014
	Percentage of CD8 T cells[1]	-	-0.0002	(-0.0003, -0.00004)	0.013
	Percentage of Natural Killer cells[1]	-	-0.09	(-0.24, 0.06)	0.23
	Percentage of Granulocytes[1]	-	-0.005	(-0.04, 0.03)	0.76
	Percentage of Monocytes[1]	-	-0.03	(-0.17, 0.12)	0.72

- **Table 4 Model 6:** Among YPHIV, the chronological age-adjusted difference in epigenetic age comparing youth not on ART to those on PI-containing ART was 3.32 years (95% CI: -0.11, 6.75).
- **Table 4 Models 7:** Higher time-averaged AUC HIV-RNA VL was associated with an increase in epigenetic age over time [2.72 years per log10 copies/mL, (95% CI: 1.09, 4.34)]
- **Table 4 Model 8:** Higher time-averaged AUC CD4 T-cell count was associated with a decrease in epigenetic age over time [-0.44 years per 100 cells/mm^3, (95% CI: -0.73, -0.14)].
- **Table 4 Model 9**: In a multivariable model, higher AUC HIV-RNA VL was associated with an increase in epigenetic age over time [2.19 years per log10 copies/mL, (95% CI: 0.65, 3.74)], whereas a higher time-averaged AUC CD4 T-cell count was associated with a decrease in epigenetic age over time [-0.34 years per 100 cells/mm^3, (95% CI: -0.63, -0.06)] in YPHIV.

Table 2: HIV-Related Characteristics at Two Timepoints for YPHIV

Characteristic	Timepoint 1	Timepoint 2
Time-averaged AUC CD4 T-cell count (cells/mm^3), Median (Q1, Q3)	1,228 (1,000, 1,530)	1,140 (879, 1,359)
Time-averaged AUC HIV RNA viral load (log10 copies/ml), Median (Q1, Q3)	2.5 (2.1, 3.2)	2.3 (2.0, 2.9)
ART Regimen, N (%)		
INSTI-based ART	1 (3.1%)	8 (25.0%)
PI-based ART	25 (78.1%)	7 (21.9%)
NNRTI-based ART	3 (9.4%)	10 (31.3%)
Other ARV	1 (3.1%)	3 (9.4%)
No ARV	2 (6.3%)	4 (12.5%)

Figure 1: Epigenetic age acceleration residual at timepoint 1 and timepoint 2 by HIV status

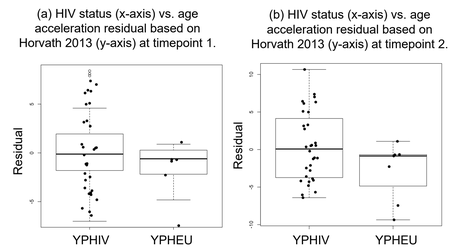

Figure 2: Epigenetic age by chronological age for YPHIV and YPHEU

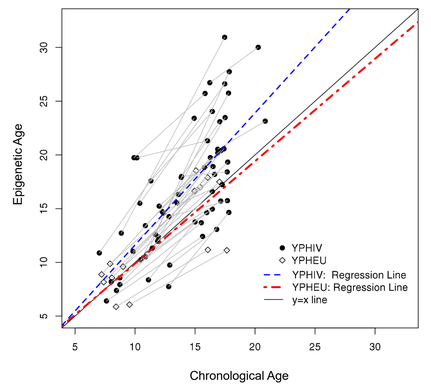

Table 4: Predictors of epigenetic age in 32 youth with perinatally-acquired HIV (YPHIV) in linear mixed effects models including chronological age

Model	Covariate	Level	Estimate	(95% CI)	P-value
Model 6	Chronological age (years)	-	1.15	(0.85, 1.44)	0.31
	ART Regimen	INSTI-based ART	0.18	(-2.69, 3.05)	0.90
		PI-based ART	Ref.		
		NNRTI-based ART	0.66	(-1.96, 3.28)	0.61
		Other ARV	1.29	(-2.38, 4.95)	0.48
		No ARV	3.32	(-0.11, 6.75)	0.058
Model 7	Chronological age (years)	-	1.27	(1.08, 1.45)	0.007
	Time-averaged AUC HIV RNA viral load (copies/ml)	-	2.72	(1.09, 4.34)	0.002
Model 8	Chronological age (years)	-	1.09	(0.87, 1.31)	0.39
	Time-averaged AUC CD4 T-cell count (100/cells/mm^3)	-	-0.44	(-0.73, -0.14)	0.005
Model 9	Chronological age (years)	-	1.15	(0.94, 1.36)	0.17
	Time-averaged AUC CD4 T-cell count (100/cells/mm^3)	-	-0.34	(-0.63, -0.06)	0.021
	Time-averaged AUC HIV RNA viral load (copies/ml)	-	2.19	(0.65, 3.74)	0.007

SUMMARY

- To our knowledge, this is the first study to examine longitudinal changes in epigenetic age compared to chronological age over time in YPHIV, making use of repeated samples over time.
- We observed accelerated epigenetic aging over time in YPHIV, but not in YPHEU.
- This longitudinal observation is consistent with findings from cross-sectional studies of individuals with HIV, which have reported a higher increase in the gap between epigenetic age and chronological age among ART-treated individuals with HIV and HIV-uninfected controls.[2-5]
- We found that a lower cumulative CD4 T-cell count and a higher cumulative HIV RNA VL were associated with accelerated epigenetic aging. We also observed that those not on ART had a higher epigenetic age compared to those on ART and those with a higher percentage of time not on ART tended to have higher epigenetic ages.
- Our small sample size limited our ability to explore whether epigenetic age acceleration in YPHIV may be associated with early markers of other age-related comorbidities, such as dyslipidemia, impaired renal function, or low bone mineral density, but future larger longitudinal studies to explore these associations, including studies utilizing banked specimens from the PHACS, are warranted.

CONCLUSIONS

- In conclusion, we observed descriptive differences in the rate of epigenetic aging in YPHIV and YPHEU.
- Our findings add to the existing research suggesting accelerated biological aging in individuals living with HIV. Older epigenetic aging relative to chronological age has been found to be associated with a wide spectrum of aging outcomes. Our finding of an increased rate of epigenetic age over time in YPHIV provides preliminary evidence of accelerated aging at a young age and may have future consequences.
- A major strength of this study was its longitudinal design with repeated measures of epigenetic age. These analyses will directly inform effect sizes and potential confounders to consider in a larger study.
- Further, these findings emphasize the importance of early and sustained suppressive treatment for YPHIV, who will age on lifelong ART.
- In addition, future work should examine the dynamic nature of epigenetic age, through examinations of differences in viral load over time, or how interventions leading to improved adherence impact epigenetic age.

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Ryan White Part A Directive for Aging Persons with HIV (PWH)
(Approved by the HIV Planning Council on October 28, 2021)

Directive for Aging PWH

Rationale for Creating this Directive

Research Evidence: 1) PWH over 50 represent a majority of the total PWH population (59% of PWH in New York City (NYC) in 2019)[i] and yet their unique intersectional needs are often underrecognized and unaddressed by HIV service organizations; 2) PWH over 50 have achieved the highest proportions of sustained viral suppression of any age group [ii] and yet care for their comorbid health conditions remains suboptimal; and 3) PWH still have shorter life expectancies[iii] than those not living with HIV with two thirds of deaths among PWH due to non-HIV-related causes.[iv] PWH have 16 fewer healthy years than uninfected adults, with diagnoses of common comorbidities beginning at age 34, and no improvement over time or with early ART initiation.[v] Perinatally infected PWH also have unique challenges in regard to HIV and aging.[vi] Greater attention to comorbidity prevention for PWH is warranted. Multimorbidity is expected to grow over the next 10 years, researchers are calling for new HIV Care Models that address prevention and treatment of comorbidities of Aging PWH.[vii,viii] Local focus group results underscore the need for improved resources for Aging PWH, including the need to develop services that address social isolation, increase coordination between programs, increase the benefits of navigation, increase the availability of services offered in Spanish, and address medical conditions of women with HIV over 50.[ix] Given the finding from these focus groups the intent of this directive is to ensure the provision of services in additional languages of clients served.

Lived Experience Evidence: This directive was initiated at the request of and developed by the Consumers Committee, PWH with lived experience of the issues to be addressed. They identified the following barriers:

1) **Aging PWH Have More Engagement in System and Higher Data Burden**

Rationale: A need exists to reduce the amount and duplication of data burden. There is an overwhelming amount of required documentation and supplemental paperwork put upon Aging PWH who seek services. It has become more challenging to manage and for them to respond, and relief is needed.

2) **Income/Entitlements for Aging PWH Fluctuate Causing Interrupted Access to Care**

Rationale: A need to promptly update patient records. Communications between agencies, billing departments, and insurance carriers need to be prompt to ensure uninterrupted access to and coverage of healthcare. Delays updating records cause clients to be ineligible for and denied services, and/or increase wait time. Specific attention should be paid to the needs of Tri County Residents in this regard.

3) **Need for Mental Health Practitioners Who Are Culturally the Same as Clients**

Rationale: It is critical to address the needs of those disproportionately infected and affected by HIV. It is important that PWH seeking counseling have more choice of seeing and having dialogue with providers who are culturally the same. With greater inequities in certain populations, having providers that reflect the communities served is a critical factor in Ending the Epidemic.

4) **Oral Health Care is Suboptimal and Lacks Crucial Coverage**

Rationale: Oral health has an essential role in maintaining good health, diet and nutrition, and structurally functional teeth. Unfortunately, HIV has a declining effect on PWH's oral health. In general, dental services are

suboptimal and costly, and often result in preventable tooth removal and dentures instead of implants that would complement and keep permanent teeth.

5) **Implementation Practices May not Adapt nor be Flexible**

Rationale: Adopt various integration and assessment methods. Increased engagement goals should not rely on existing implementation practices. Service delivery protocols should be regularly reassessed, updated, and developed to have more agile responses to population needs. Providers should be able to address quickly and easily to what is happening with specific clients and their individual issues.

6) **Increased Relationship Building with PWH Needed for Providers**

Rationale: Providers should prioritize their relationship with clients and develop partnerships that build on open and honest communication. They need to invest more time and care toward listening to their concerns, and willingly explain details of test results, trends, and disclose the full range of options when available.

7) **PWH Should Have the Option to Select the Gender of Their Providers**

Rationale: Patients may not feel comfortable discussing concerns affecting their anatomy and sexual activity with differently gendered providers. PWH are usually excluded during provider selection and accommodate those designated to avoid being stereotyped as temperamental or difficult.

8) **Resilience of Aging PWH and Overlooked Need for Independence and Decision Making**

Rationale: Providers often do not include their clients in making decisions about their care. Protocols are dictated and medications prescribed without consideration for their ability to be adherent. They feel unheard, vulnerable, and fear divulging habits and behaviors, and engage in self-diagnosis and alternative treatments.

9) **Maintain Consistency with Scheduled Appointments**

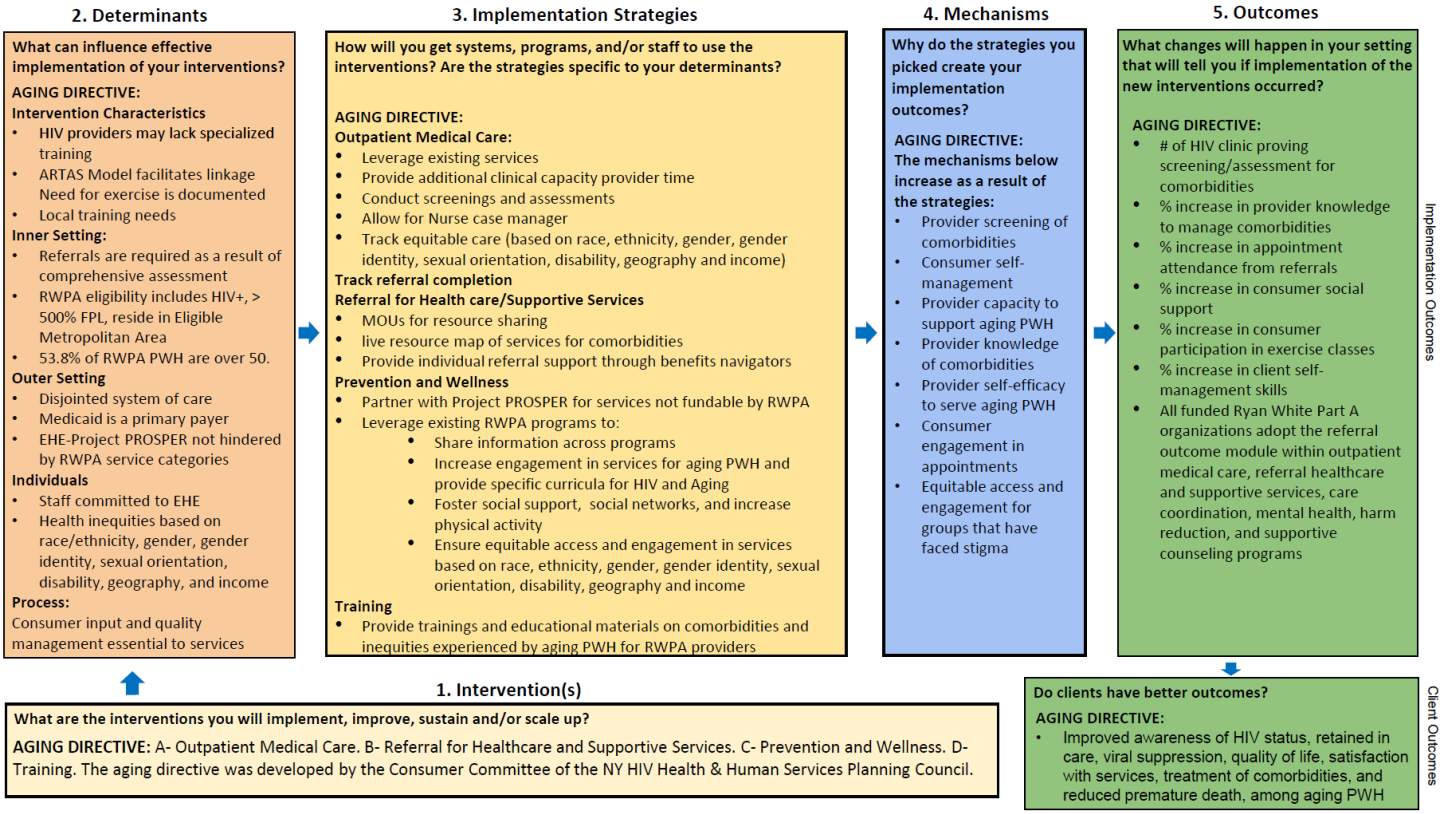
Rationale: Canceling and rescheduling appointments often has adverse effects. It can appear inconsiderate, uncaring, and disrespectful to not keep appointments. It is often done close to an upcoming appointment date and causes more delays, sometimes weeks or months, before being able to see the provider.

Terminology: Throughout this directive, we use the term “aging” to recognize that the spectrum of disease and onset of health issues can occur at different ages, and to be inclusive of long-term survivors who were perinatally infected. “PWH over 50” is used when it mirrors the data cited.

Format: The directive mirrors the format of the Implementation Research Logic Model (IRLM), a logic model designed to improve the uptake of research evidence into routine healthcare and public health practice. See this website, for more information on the IRLM.

Ryan White Part A Directive for Aging Persons with HIV (PWH)
(Approved by the HIV Planning Council on October 28, 2021)

Snapshot view of directive:



Full directive:

1. INVERVENTIONS

This directive seeks to increase screening to support early detection and treatment for comorbidities (CVD, osteoporosis, social support, mental health, etc.) among aging PWH through 4 intervention activities:

A. **Outpatient Medical Care:** Increase capacity of Outpatient Medical Care to treat the complex needs of Aging PWH. Intervention to mirror aspects of Golden Compass model[x] through use of clinical staff (MD, RN, Pharmacist, Medical Assistant) to provide health education, Geriatric, Psychiatric, and Cardiology consultation, and referral to ongoing specialty care in line with HHS Guidance.[xi] Funded services should be supported to improve health education and self-advocacy/self-management so that Aging PWH can talk to their medical providers about broader health concerns.
B. **Referral for Healthcare and Supportive Services:** Increase the knowledge of resources available to support Aging PWH among RWPA funded providers. Utilize referral tracking to ensure Aging PWH are engaged in needed services. Utilize an adaptation of effective referral practices from the Anti-retroviral treatment and access to services (ARTAS) model, [xii] including development of referral partnerships (resource sharing agreements, linkage agreements), verification of insurance coverage, communication/outreach/education and training on availability of referral service, provide navigation and transportation if needed, provide program supervision to navigation staff.
C. **Prevention and Wellness** There is a need to "Strengthen and expand PLHIV networks and increase funding for community-based organizations that provide social support services for older people living

with HIV."[xiii] Services will provide social support for exercise by setting up a buddy system, making contracts with others to complete specified levels of physical activity, or setting up walking groups or other groups to provide friendship and support.[xiv] [xv] Program will provide peer support using navigation, structured health education (including wellness information and exercise, diet/nutrition, communication with a provider, and common comorbidities) and practical and emotional peer support services (support groups and/or buddy programs) to increase engagement in care and promote self-care.[xvi] Identify ways to leverage technology for social support and connection and to overcome barriers that older people living with HIV face in using technology. [xvii]

D. **Training** Increase training of RWPA providers to ensure they are able to effectively support Aging PWH through increased ability to identify comorbidities, link Aging PWH to needed resources, and increase ability to effectively serve Aging PWH given the intersectional identities experienced by this population. [xviii]

2. DETERMINANTS

What factors can influence effective implementation? What contextual factors could influence implementation at the structural, interpersonal, and individual levels?

Intervention Characteristics -

A. Outpatient Medical Care
- Hospitals, clinics, community-based organizations, correctional health, and some public health programs can serve as service sites, but they need resources to address the needs of Aging PWH.[xix]
- RWPA sites can adapt best practices from the Project PROSPER-funded Be InTo Health, Older People Living with HIV program[xx] adapted from the Golden Compass model.

B. Referral for Healthcare and Support Services
- The ARTAS model is an evidence-based intervention supported by the CDC since 2005 that can be utilized by NYC RWPA.

C. Prevention and Wellness
- Exercise and social support are well documented needs among Aging PWH, but exercise has not been commonly offered in Ryan White Programs.[xxi] Social support services are commonly provided in such RWPA services as Harm Reduction, Mental Health, Supportive Counseling, and Health Education/Risk Reduction.

D. Training
- New trainings are being developed to reflect the available science on Aging PWH. We can leverage non-RWPA resources (AETC, city, and Project PROSPER funded training). Trainings need to include assessing readiness and identifying barriers to coordinating integrated service delivery for Aging PWH.

Inner Setting: The characteristics of the HIV Care and Treatment Program (CTP)/NYC Department of Health & Mental Hygiene (DOHMH) & RWPA-funded organizations:
- The RWPA Program requires referrals for services through a comprehensive assessment completed at intake and every 6 months thereafter and as needed and identified by clients.

- RWPA fills in the gaps in Medicaid services by providing support & coordination, i.e. navigation and services not paid by Medicaid or another payer
- The RWPA Program eligibility – Aging PWH with incomes up to 500% of the federal poverty level (FPL) who reside in the eligible metropolitan area (EMA).
- In the NY EMA RWPA program, over 53.8% of actively served PWH are over 50.[xxii]
- CTP provides quality management and technical assistance to funded programs to improve client services and support fidelity to models of care.
- RWPA-funded and HRSA-defined service categories address gaps in the service system to stabilize clients and support anti-retroviral treatment (ART) adherence. Service categories are limited by legislative definitions. The Planning Council has allocated funding to the NY EMA portfolio of services which currently consists of a wide array of medical and non-medical case management support: housing, food/nutrition, mental health, harm reduction, health education/risk reduction, emergency financial assistance, oral health, legal, supportive counseling, and medical transportation (in Tri County only). Not all HRSA defined service categories are funded in the NY EMA.
- NYC DOHMH is funded for the HRSA 078 EHE-Project PROSPER which supports PWH over 50. The current Project PROSPER-funded Be InTo Health, Older People Living with HIV program is adapted from the Golden Compass model from San Francisco.[xxiii] Services are currently limited to three programs, two in Brooklyn and one in upper Manhattan.
- The disjointed and multiple funded system of care creates a challenge in coordinating care and support for Aging PWH. Care must be integrated. [xxiv] [xxv]

Outer Setting:

- Income inequality is a defining characteristic of the prevalence and disproportionate impact of HIV in the EMA.
- Medicaid is the primary payer for medical services. RWPA fills in the gaps in Medicaid services by providing support & coordination, e.g., navigation and services not paid by Medicaid or another payer.
- Medicaid is the primary payer for HIV services; data sharing between payers and between service sites has multiple barriers (e.g., data accessibility, timeliness of data), which impedes population health.
- Data sharing impedes coordination of care.
- The NYC DOHMH Training and Technical Assistance Program (T-TAP), HIV Clinical Operations and Technical Assistance Program (COTA) supports programs with up to date, interactive trainings.

Characteristics of Implementers:

<u>DOHMH and contracted RWPA program staff</u>:

- DOHMH and RWPA program staff are committed to the new federal Ending the HIV Epidemic (EHE) Plan and the NYS Ending the Epidemic (EtE) Plan.
- Geriatric expertise is uncommon among providers in HIV organizations.[xxvi] [xxvii]
- Need additional skills in anti-stigma, intersectionality, and trauma-informed approaches.[xxviii]

<u>Aging PWH have the following identified needs</u>:

- Persistent health inequities exist related to race/ethnicity, gender, gender identity, sexual orientation, disability, geography, and income.[xxix]
- Higher rates of social isolation.[xxx]
- Food and nutrition services.[xxxi]
- Increased rates of osteoporosis, chronic liver disease, and in particular cardiovascular disease.[xxxii]
- Increased risk of cardiovascular disease, mental health, lack of social support, substance use, smoking, HCV, HPV, osteoporosis, and chronic inflammation.[xxxiii]
- Health disparities also widen with aging as more disabilities and chronic illnesses accumulate.[xxxiv]
- In addition to multiple comorbidities (multimorbidity), Aging PWH are at risk for geriatric (henceforth termed aging-related) syndromes, such as frailty, falls, and cognitive and functional impairment.[xxxv]
- Aging-related syndromes can be seen before Aging PWH are chronologically elderly.[xxxvi]
- Clinical management requires preparing patients to be educated and supported in regard to healthy aging (as a way of trying to forestall or prevent these syndromes) as well as assessment and care of those who have aging-related syndromes.[xxxvii]
- COVID-19 has diverted many resources/staff and exacerbates existing inequities.
- Lack of housing access and the presence of housing discrimination is pervasive.

Process:

- Community planning processes: Planning Council, HIV Planning Group (HPG), consumer advisory boards (CABs), ad-hoc listening sessions, town halls, focus groups (consumers and planning body members not employed by HIV service agencies are not paid for planning work).
- Annual dissemination of HIV data for planning: HIV surveillance, Ryan White programmatic data, population-based surveys (Medical Monitoring Project (MMP), National HIV Behavioral Study (NHBS), Sexual Health Study (SHS), Community Health Advisory and Information Network (CHAIN)).
- Quality management supported by the HIV Care and Treatment Program (CTP) and at RWPA-funded organizations supports program implementation and continuous quality improvement.
- Informal and formal mechanisms for client input within HIV organizations (e.g., patient satisfaction surveys, support groups, etc.).
- All Ryan White Programs must ensure each client is aware of the agencies' grievance process and must include contacting the Recipient if the grievance does not reach a resolution. This can serve as an important tool for reporting stigma and human rights abuses.

3. IMPLEMENTATION STRATEGIES

How will you get systems, programs, staff, and/or clients to use the interventions?

Required Activities: <u>All services must be equitably provided, as per the Council's Framing Directive, to all Aging PWH. This shall be monitored and will be an ongoing subject of technical assistance.</u>

A. **<u>Planning and Quality Management Strategies for Clinical Services, Outpatient Medical Care[xxxviii]:</u>**

- Obtain formal commitments to coordinate care that leverage existing resources (current RWPA programs, Ryan White Part B, C, and D programs, Medicaid funded services and other resources at program sites).
- Provide additional capacity and clinical time to pay for extended visits to conduct comprehensive screenings/assessments to identify needed geriatric and healthcare-based services and support, [xxxix] [xl] outlined by the NYS HIV Clinical Guidelines.[xli]
- Conduct screenings and assessments for HCV, HPV, osteoporosis, mental health, cognition, social support, exercise, nutrition, oral health, sexual health, transgender health, medical issues specific to women (mammograms, etc.), cancer screening, substance use, smoking, cardiovascular disease (CVD) and any other issues included in HHS guidance for Aging PWH.
- Allow for a Nurse Case Manager or other qualified provider to coordinate the medical and behavioral health needs of those with multiple comorbidities, with referrals to case management for benefits and entitlement programs and programs that may be of assistance to partners and families of PWH.
- Provide education and support for advance directives.
- Track referral completion. Utilize Continuous Quality Improvement (CQI) tools to ensure equitable access and engagement in services based on race/ethnicity, gender identity, sexual orientation, disability, geography, and income.
- Deliver capacity building and technical expertise that promotes increased capacity and equitable access, regarding race/ethnicity, gender identity, sexual orientation, disability, geography and income, to geriatric and healthcare services for funded providers.

B. **Planning and Quality Management Strategies for Referral for Health Care/Supportive Services[xlii]:**

- Develop Memoranda of Understandings (MOUs) to establish resource sharing agreements, with language in regard to expedited access to appointments, as appropriate, among specialty medical and support service providers addressing comorbidities for Aging PWH (e.g., HCV, HPV, osteoporosis, mental health[xliii], assessment for suicidal ideation, cognition, social support, sexual health, transgender health, medical issues specific to women (mammograms, etc.), cancer screening, substance use, smoking, CVD) to leverage existing resources and increase engagement in services.
- Develop or support RWPA provider access to a live resource map to identify resources to lower risk and provide support for the management of CVD, chronic inflammation, osteoporosis, mental health, social support, exercise, nutrition, smoking cessation, and substance use when not available through primary care, resource map should include services provided outside of RWPA, such as NYC Department for the Aging (DFTA) resources, local Geriatricians, Health and Wellness Programs, Diet/Nutrition, Exercise, other resources that support client self-management, etc.) for Aging PWH. Resource map should be non-stigmatizing, easily accessible, provider developed and updated in real time.
- Provide individual referral support through trained certified benefits navigators, including education on insurance such as appropriate plans for Medicare, Medicaid, and other insurance to address a client's needs. Track referral completion and insurance

verification, including confirming the referral connection happened, and any follow-up needed. Use CQI to ensure equitable access and engagement in services.

C. **Prevention and Wellness**:

- Develop a system for referrals and linkages with DOHMH's Project PROSPER and Be InTo Health to conduct physical and social activities based on interests of clients at least monthly (e.g., yoga, fitness sessions, Zumba, art classes, movie showings).
- Leverage existing RWPA programs to increase engagement in services for Aging PWH.
- Modify and/or enhance RWPA supportive counseling, food and nutrition services, psychosocial support, health education and risk reduction programs to support prevention and wellness in their current service provision to Aging PWH.
    - Tailor social groups that foster community and social connections to address the needs of Aging PWH in RWPA supportive counseling/psychosocial support, harm reduction, and mental health programs. Allow for exercise groups (virtual or face to face, including yoga, neighborhood-based walking groups, or other exercise activities that may be popular with Aging PWH). Support faith-based organizations in the provision of social support services, including pastoral counseling as outlined in the Supportive Counseling directive.
    - Require the development of services that enhance social support networks among clients in Supportive Counseling, Psychosocial support, Food and Nutrition programs providing congregate meals, Mental Health, and Harm Reduction Programs through such tools as peer networks or use of technology for virtual communication/connection (including training for the use of such technology). Provide education and support to family members (as defined by the client) so that they too can be sensitive to the needs of Aging PWH.
    - Maximize the employment and support of peers[xliv] in supportive counseling, psychosocial support, food, and nutrition programs providing congregate meals, mental health, and harm reduction programs to support Aging PWH.
    - Develop specific curricula for Aging PWH in Health Education and Risk Reduction programs, the curricula should include such issues as physical exercise (including low cost/accessible physical exercise options), common comorbidities, wellness/prevention, sexual health, and any other common issues affecting Aging PWH including those in the HHS guidance for Aging PWH.
    - Define and develop the referral process for services that provide and/or increase access to disease prevention and wellness activities that address the needs of Aging PWH. Use CQI methods to ensure equitable access and engagement in services.
    - Include resources in health education/health promotion sessions in care coordination, harm reduction, mental health, and psychosocial support with such topics as; diet/nutrition, exercise, and fitness, sexual health, smoking cessation, harm reduction, social support and engagement, stress management, communicating with medical providers, technological support for virtual visits and services and any other issues included in the HHS guidance on HIV and Aging, as appropriate.
    - Ensure Food and Nutrition Providers maximize the potential of congregate meals as a means of reducing social isolation. Update provision of food so that it reflects the nutritional and dietary needs of Aging PWH.

- Utilize shared intakes or technology to allow information to be shared across programs as allowable by law.

D. **Training**:

- Identify/develop and deliver a dynamic, in-depth, comprehensive training on co-morbidities associated with aging, the disparate impact of co-morbidities on PWH, and how to moderate these impacts through prevention, wellness, and medical care.
- Develop effective educational materials to support providers and PWH's understanding of the impact of aging and the intersectional needs of Aging PWH from communities most impacted by the HIV epidemic.
- Educational materials shall be updated as needed based on the HHS guidance for HIV and Aging.

4. MECHANISMS

Why do the implementation strategies you picked work to affect your implementation outcomes? Mechanisms are how we expect the strategies in the previous column will lead to the outcomes in the next column; e.g., increases in provider knowledge and willingness to utilize interventions, improved shared decision-making processes between PWH and providers, reduction in staff burnout and turnover.

1. Increase provider screening of comorbidities associated with Aging PWH (including HCV, HPV, osteoporosis, mental health, oral health, cognition, social support, exercise, nutrition, sexual health, transgender health, medical issues specific to women (mammograms, etc.), cancer screening, substance use, smoking, CVD). (Intervention A)
2. Increase consumer self-management that support behavior changes (exercise, increased social support, engagement in specialty care, self-advocacy with medical providers) that prevent the onset of comorbidities among Aging PWH. (Interventions A, B, C, D)
3. Increase provider capacity to support Aging PWH in needed services through increase in provider knowledge of comorbidities of Aging PWH. (Interventions A, D)
4. Increase in self-efficacy rating regarding provider ability to serve Aging PWH. (Interventions A, C, D)
5. Improve consumer engagement in first-time appointments (and continued follow-up) for services that manage comorbidities for Aging PWH to reduce morbidity and mortality associated with these conditions.
6. Increase equitable access and engagement in services based on race/ethnicity, gender identity, sexual orientation, disability, geography, and income.

5. OUTCOMES

Implementation Outcomes

What changes happen as a result of the strategies you used? How would you know your implementation strategies were successful?

These outcomes will be reported to the Planning Council on an annual basis post implementation.

# of HIV clinics providing screening/assessment for comorbid conditions. (Intervention A)
% increase in provider knowledge of common comorbidities for Aging PWH as evaluated through pretest-posttest surveys administered to training participants. (Intervention A)
% increase in appointment attendance for Aging PWH with comorbidities over 12 months (attendance at one appointment resulting from referral). (Interventions A, B, C)
% increase in consumer social support (peer delivered services, support groups, health education groups) activities over 12 months. (Intervention C)
% increase in consumer participation in fitness and exercise classes over 12 months. (Intervention C)
% increase in client perception of self-management skills when surveyed. (Intervention C)
100% adoption of referral outcome module among RWPA Outpatient Medical Care, Referral healthcare and supportive services, Care Coordination, Mental Health, Harm Reduction, and Supportive Counseling providers. (Interventions A, B, C, D)

Clinical/Client Outcomes

How are clients affected?

- Increase in PWH over 50 aware of their status, retained in care, and virally suppressed. (Intervention A)
- Increase in PWH over 50 quality of life and satisfaction with HIV services. (Interventions A, B, C)
- Increase in treatment of comorbidities for PWH over 50. (Interventions A, B, C)
- Improve health outcomes for PWH over 50. (Interventions A, B, C)
- Reduction in premature death among those served. (Interventions A, B, C)

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[xli] https://www.hivguidelines.org/hiv-care/aging-guidance/#tab_0
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LOS ANGELES COUNTY
COMMISSION ON HIV

BE A PART OF THE MOVEMENT TO END HIV. THE TIME IS NOW.

COMMISSIONERS NEEDED

VACANCIES

- Unaffiliated consumer* for Service Planning Areas (SPAs)** 1, 2, 3, 4, and 7
- Unaffiliated consumer* for Supervisorial Districts** 1, 2, 3, 4, and 5
- 1 Unaffiliated consumer* at-large
- Part C Representative
- 1 Provider Representative
- 4 HIV Stakeholders
- 1 local health/hospital planning agency

Incentives for Unaffiliated Consumers:

- Monthly stipends (county-issued checks, gift cards)
- Reimbursement for local mileage, transportation, childcare and other eligible expenses incurred by Commission participation
- Letters of Reference for Volunteer Work
- Certificates of Appreciation and Participation
- Leadership Training
- Professional development training, including but not limited to: (1) Community Planning, 2) Data Understanding, 3) Community Engagement, 4) Advocacy, and 5) Public Speaking
- Build Professional Networks

APPLY HERE

hivcomm@lachiv.org | (213) 738-2816

For more information, please see our Commission on HIV fact sheet.

*Unaffiliated consumers are people living with HIV, and a current user of a Ryan White Part A service, and not employed by an agency receiving Part A funds from the County.
**To find your SPA and Supervisorial District, please click here.