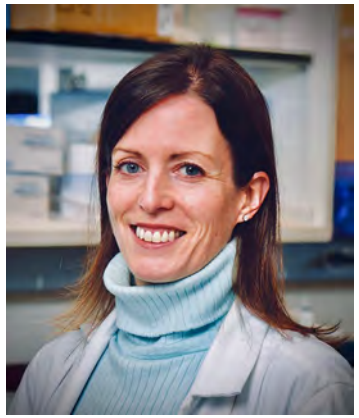
HIV Cure: Clinical Considerations Across the Life Course



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Disclosures

- Gilead scientific advisory board, site investigator under clinical research contract managed through JHU, investigator-initiated grant (Agwu)
- None (Scully, Graham)

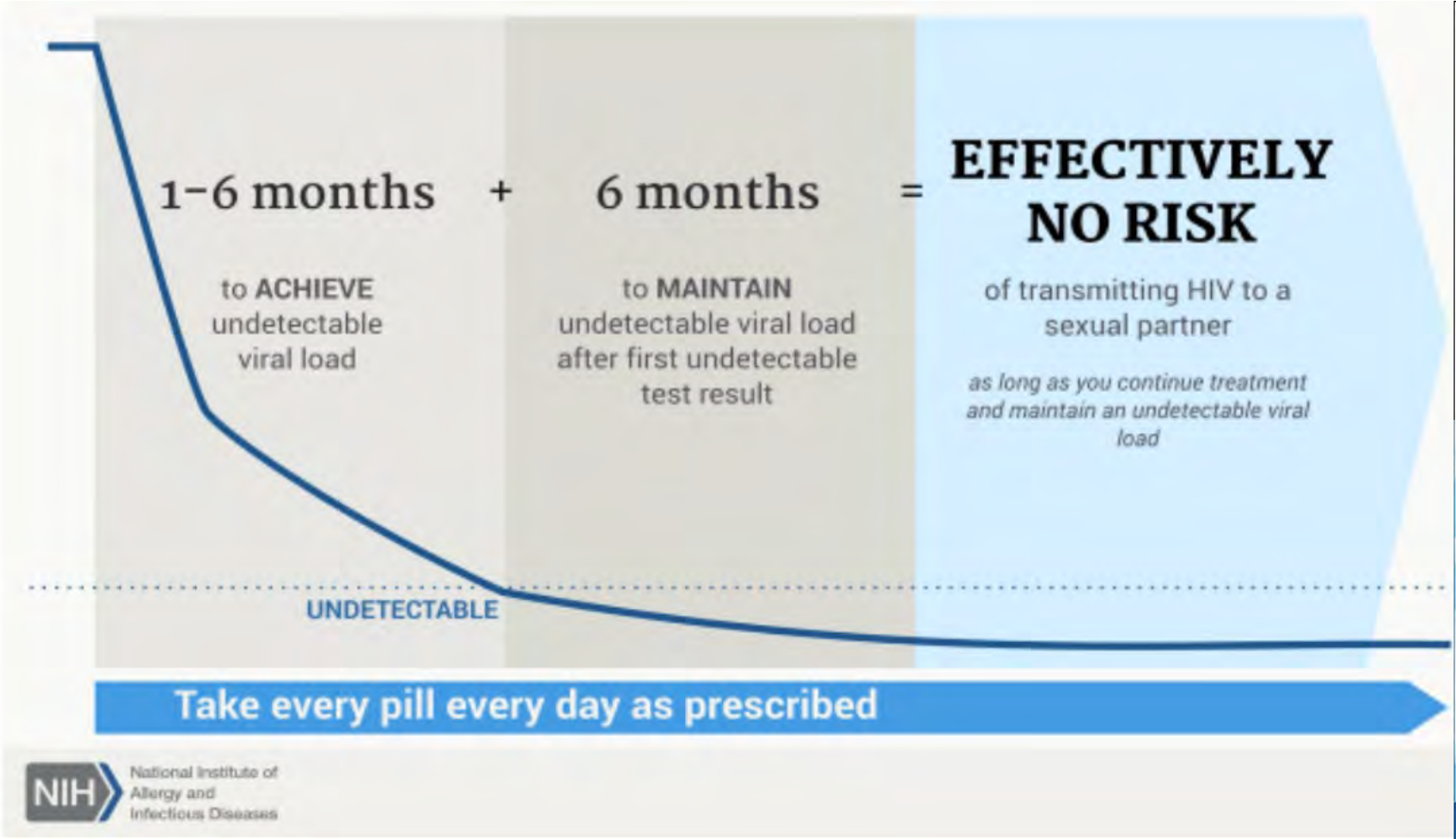
HIV Cure: Lived Experience Perspective

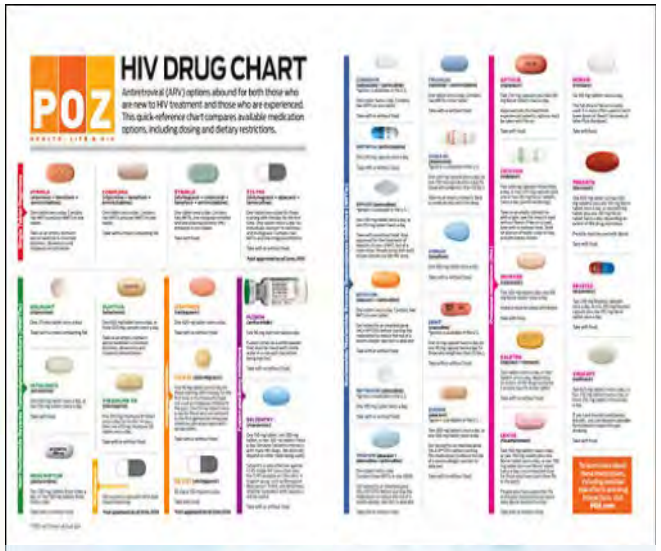
Gail Graham, HIV Advocate

Objectives

- GG real world perspective
- HIV Continuum of care
  - Outcomes and Comorbidities
- Current cure strategies and clinical considerations
  - Weighing risk-benefit
  - Scenarios
- GG mic drop

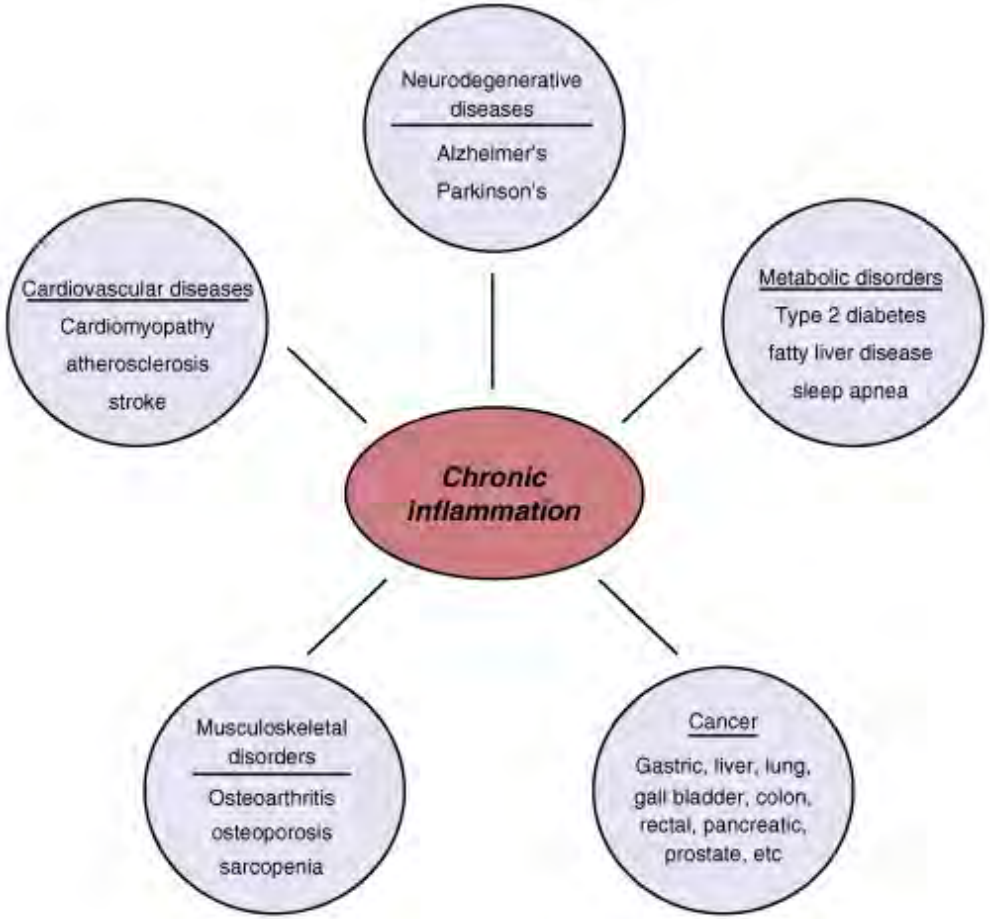
HIV Care Management and Goals of Therapy



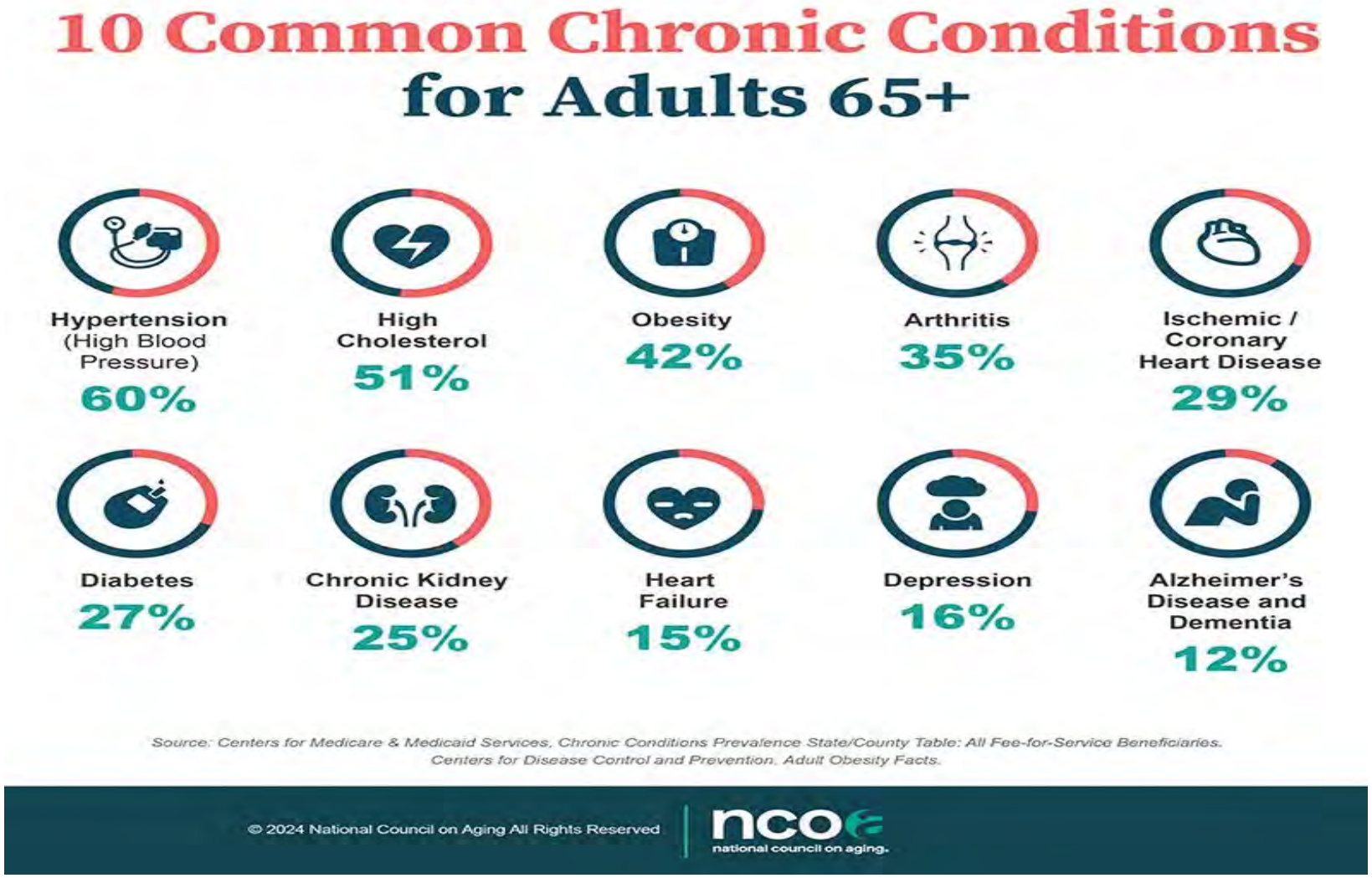


https://aidsresource.com/treatment-as-prevention-campaign/uisu/

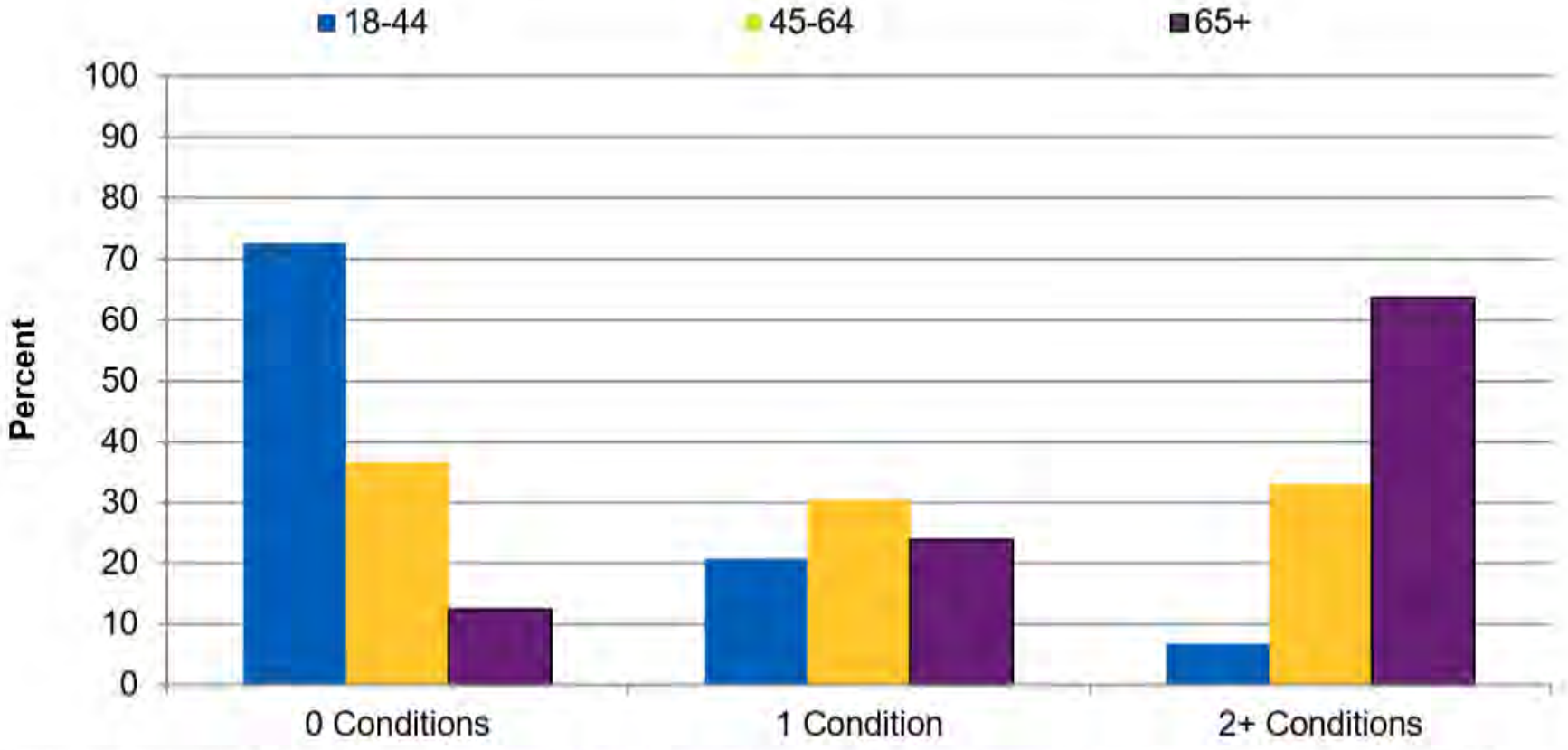
Disease and Chronic Inflammation



How Common are Chronic Conditions?



Prevalence of Multiple Chronic Conditions



Source: Boersma P, Black LI, Ward BW. Prevalence of multiple chronic conditions among U.S. adults, 2018. Prev Chronic Dis. 2020 Sep 17:17:E106. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7553211/.

Note: Chronic conditions measured were arthritis, cancer, chronic obstructive pulmonary disease, coronary heart disease, current asthma, diabetes, hepatitis, hypertension, stroke, and weak/failing kidneys.

JOHNS HOPKINS MEDICINE

Most Common Causes of Death by Age, 2021 (U.S.)

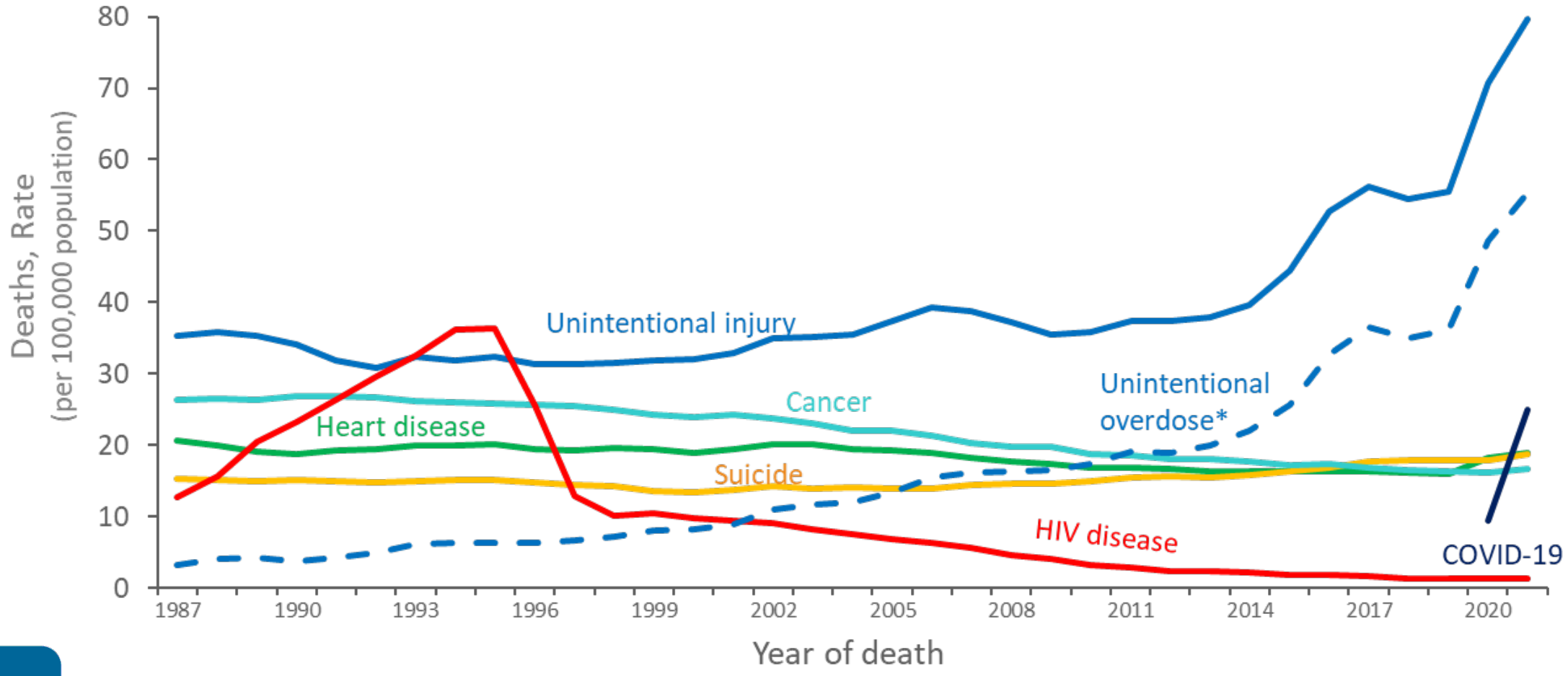
Rank	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
1	Accidents (1,174)	Accidents (11,338)	Accidents (23,486)	Accidents (23,293)	Cancer (24,948)	Cancer (80,085)	Cancer (131,013)	Heart disease (123,645)	Heart disease (180,040)
2	Cancer (576)	Homicide (4,849)	Suicide (6,340)	Heart disease (9,079)	Heart disease (24,946)	Heart disease (65,346)	Heart disease (102,564)	Cancer (119,913)	Cancer (74,819)
3	Suicide (451)	Suicide (4,547)	Homicide (5,344)	Cancer (8,097)	Accidents (20,864)	**COVID-19** (27,740)	**COVID-19** (46,945)	**COVID-19** (57,100)	**COVID-19** (59,620)
4	Homicide (340)	Cancer (956)	Heart disease (2,884)	Suicide (5,486)	**COVID-19** (11,100)	Accidents (21,686)	Chronic respiratory (27,018)	Chronic respiratory (33,264)	Alzheimer disease (55,602)
5	Congenital (241)	Heart disease (630)	Cancer (2,606)	**COVID-19** (4,635)	Liver disease (7,127)	Diabetes (13,761)	Stroke (20,855)	Stroke (32,664)	Stroke (49,120)
6	**COVID-19** (165)	**COVID-19** (553)	**COVID-19** (2,078)	Liver disease (3,704)	Suicide (5,437)	Chronic respiratory (12,550)	Diabetes (20,621)	Alzheimer disease (25,593)	Chronic respiratory (26,183)

Notes: For leading causes other than COVID-19, data are 9 month average in 2020 for accidents, suicides and homicides, and 2021 for other leading causes.

Source: KFF analysis of CDC data • Get the data • PNG

Peterson-KFF Health System Tracker

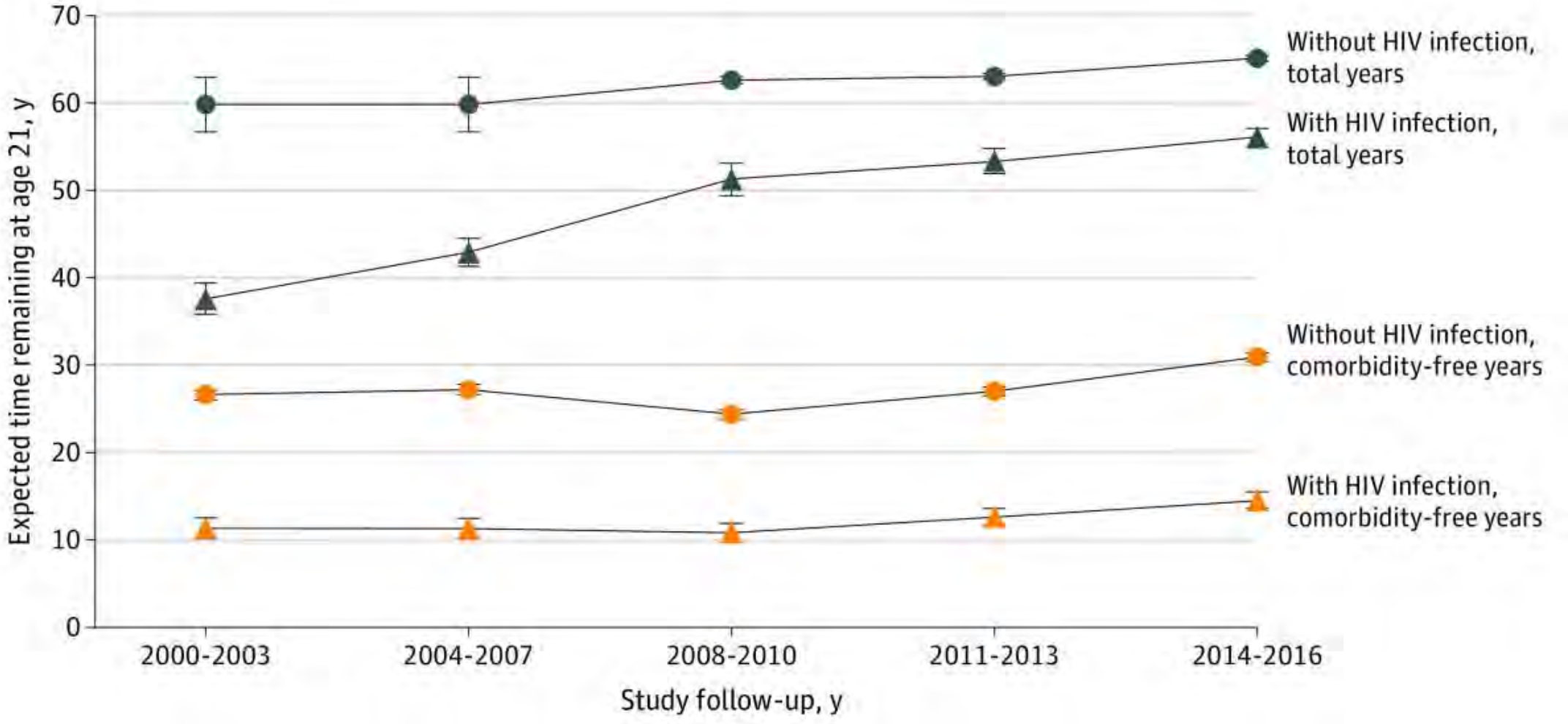
Trends in Annual Rates of Death in the General Population with HIV Disease as the Underlying Cause versus the 5 Leading Causes among Persons Aged 25–44 Years, 1987–2021—U.S.



Note. Data from CDC WONDER Online Database based on death certificate data compiled by the National Center for Health Statistics.

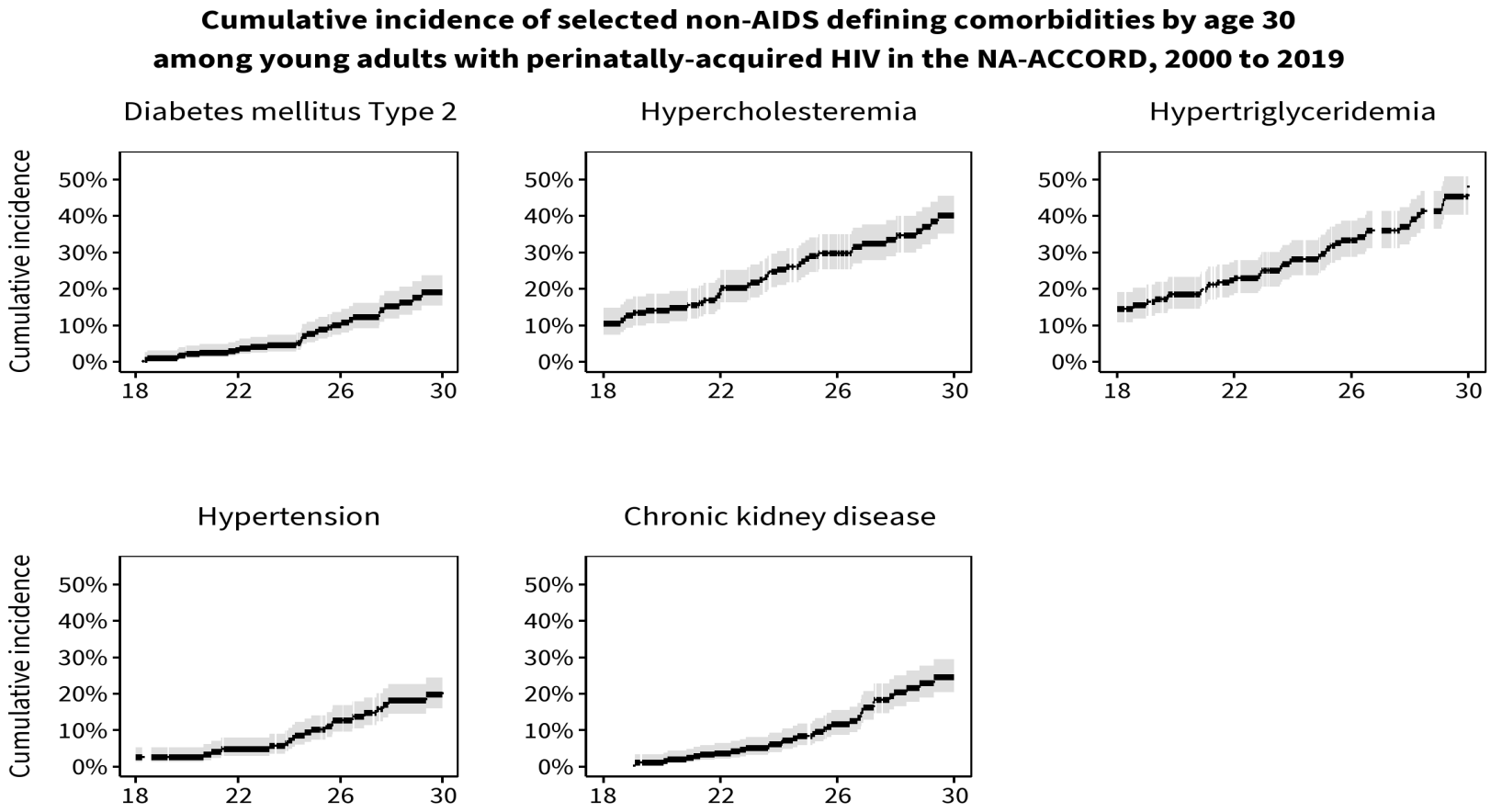
* Deaths with an underlying cause of unintentional overdose are a subset of deaths with an underlying cause of unintentional injury.

Overall & Comorbidity-Free Life Expectancy at Age 21 years for Individuals with & without HIV, 2000-2016



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

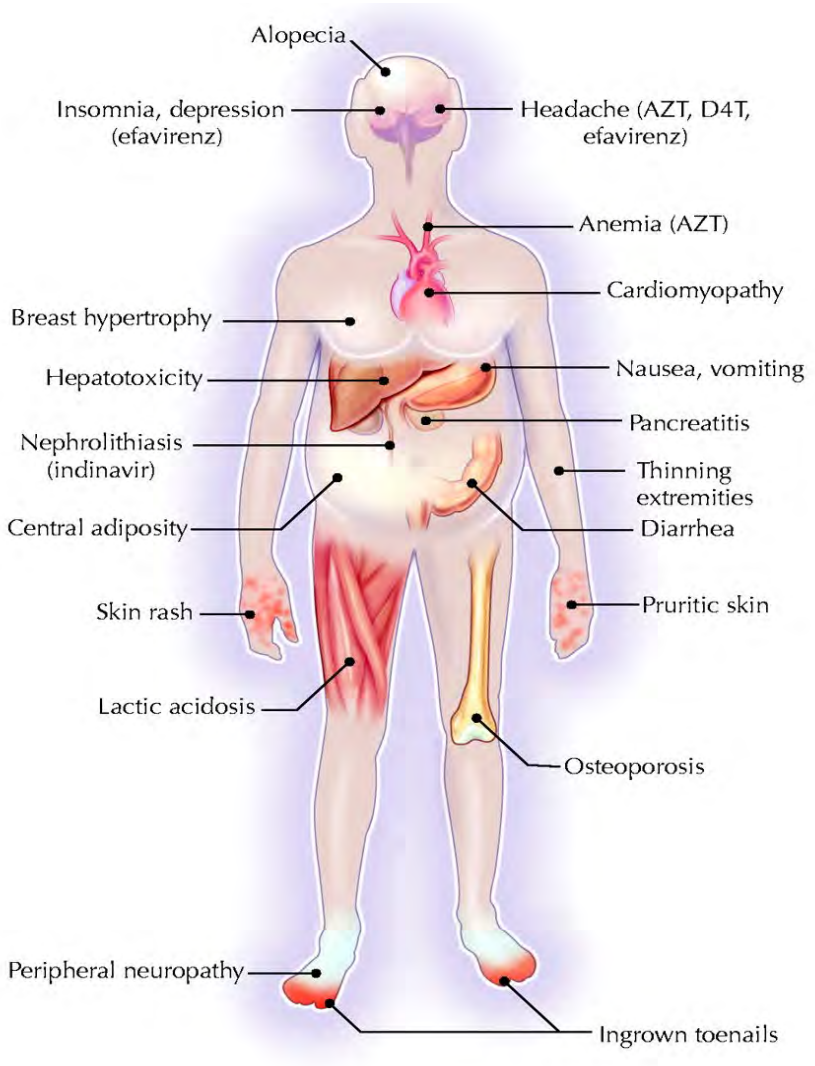
Lifetime Survivors: Comorbidities by Age 30

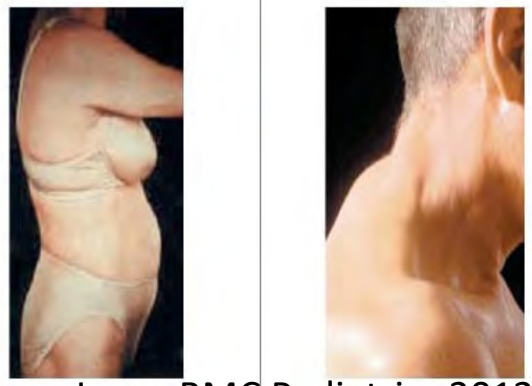


Total sample: 375 participants. Bands indicate 95% confidence interval.

Haw NJL et al. HIV & Aging Workshop 2023

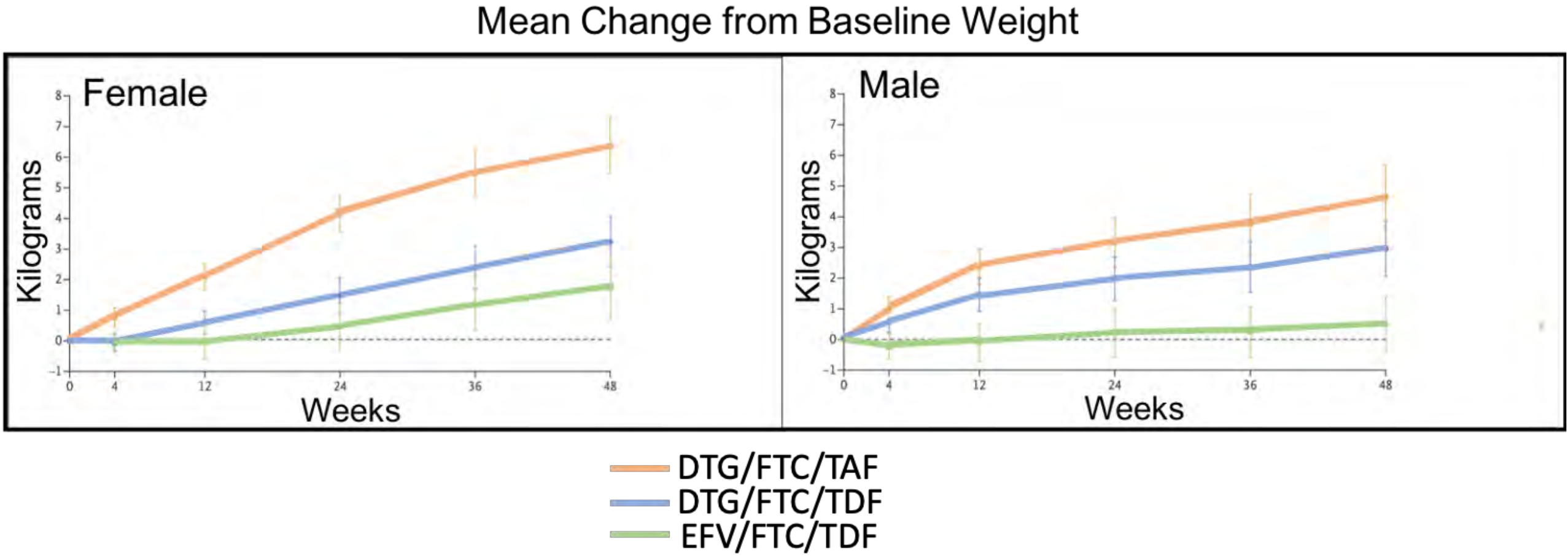
Adverse Effects of ART





Grinspoon NEJM 2005; HIV.VA.gov; Innes BMC Pediatrics 2012

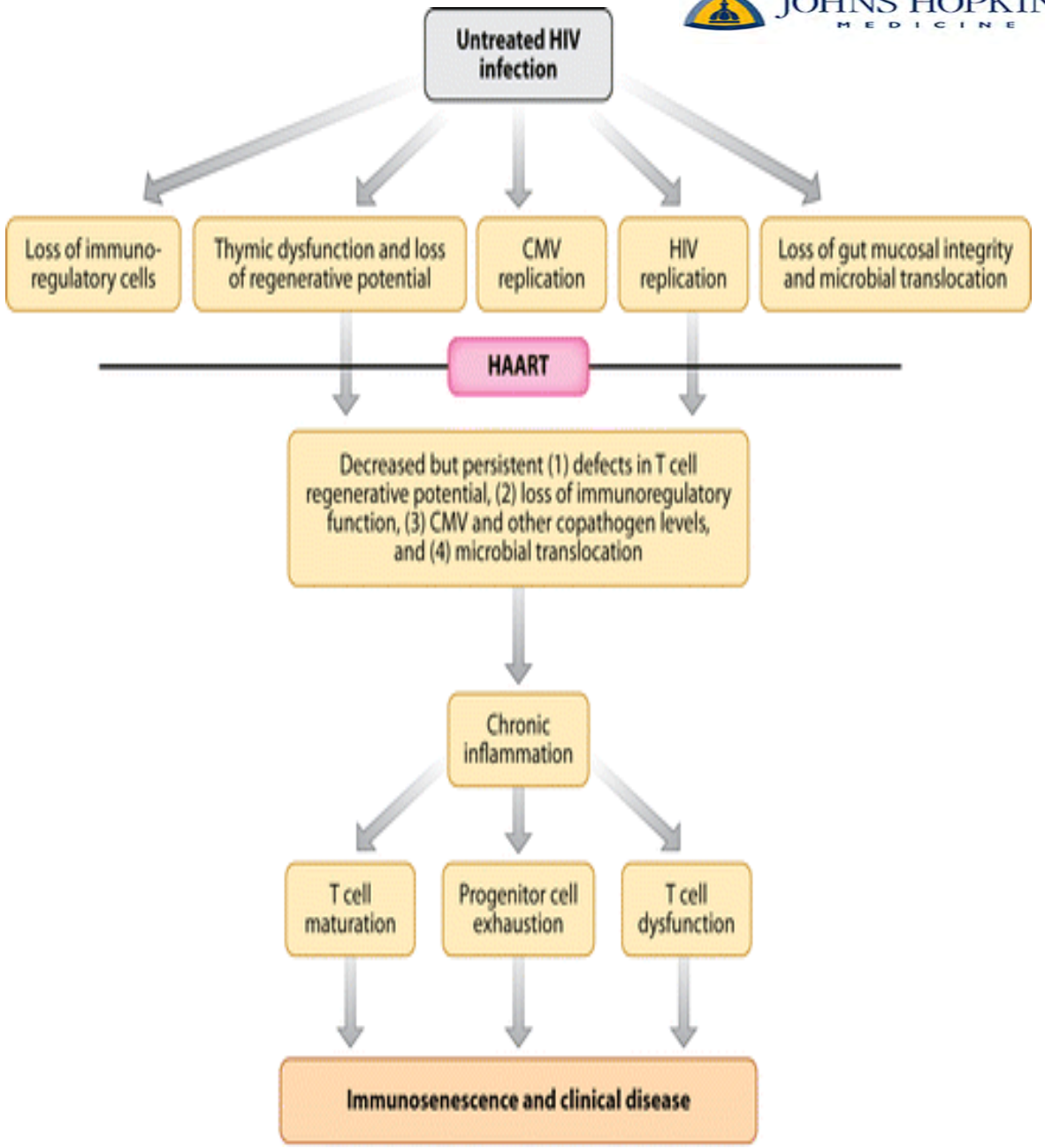
Adverse Effects of ART



Venter NEJM 2019

Inflammation & HIV

- HIV: independent risk factor for inflammation
- Long term treated/suppressed individuals with HIV have residual inflammation
- Immunologic abnormalities seen in chronically treated individuals with HIV are consistent with changes seen in elderly
  - Chronic inflammation likely causative mechanism→ "premature aging" in HIV



Deeks SG. Annu Rev Med 2011. 62:141-55
http://ars.els-cdn.com/content/image/1-s2.0-S1471491410000468-gr1.jpg

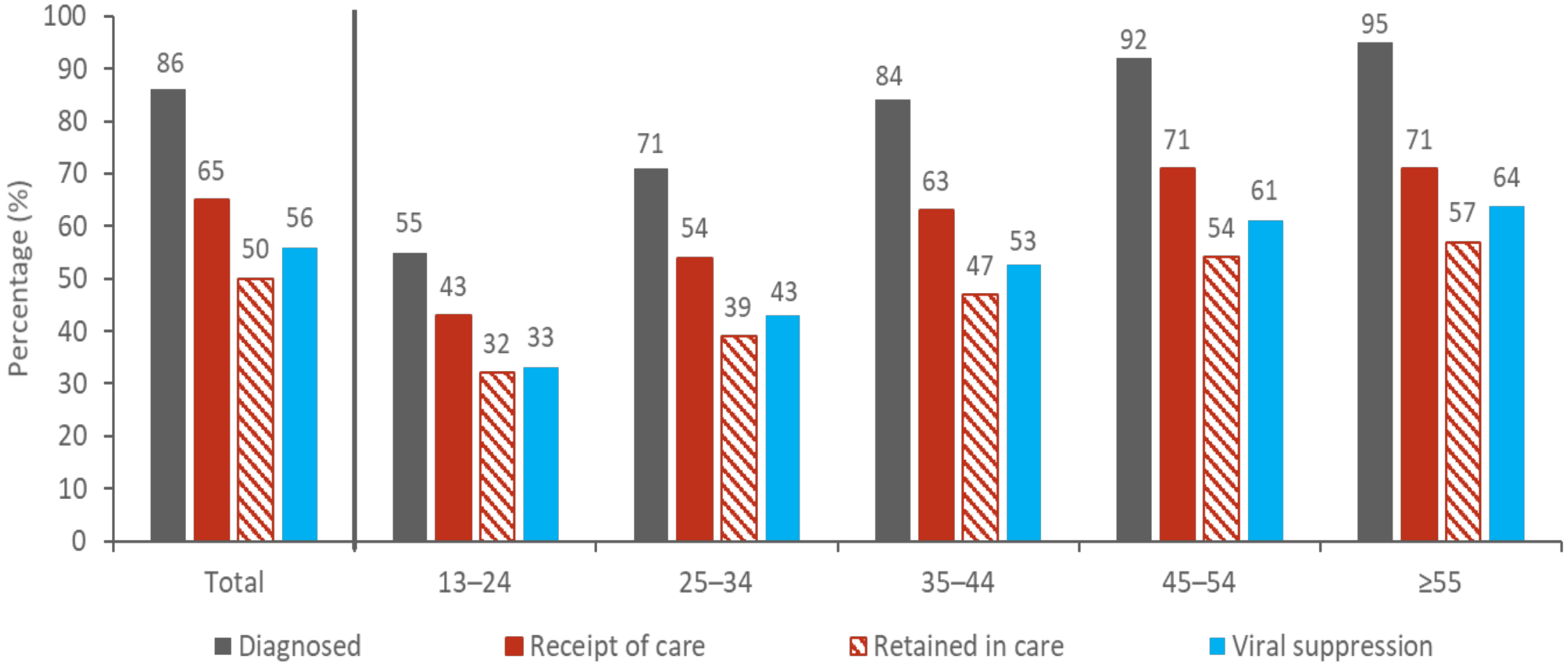
What does age have to do with it?

	Infants, Children, Adolescents			Adults		
	Suppression Duration					
	Short	Intermediate	Long	Short	Intermediate	Long
Reservoir Size						
Replication-competent HIV (infectious units/10^6 resting CD4+ T cells [IUPM])	0.32 [25]	<0.1-0.1 [7]	<0.1 [26]	<0.07-0.42 [27;28]	0.28 [29]	0.00064‡ [30]
Cell-associated HIV DNA (log_{10} HIV DNA copies/10^6 PBMC)	1.0-2.1 [13;26]	1.7 [15]	0.6-0.7 [14;26]	2.9-3.0† [27;31]	1.7 [29]	2.15 [32]
Cell-associated HIV DNA (log_{10} HIV DNA copies/10^6 CD4+ T cells)	nr	<0.4-2.1 [7;12]	<0.6-0.99 [26]	nr	2.3 [29]	nr
Cell-associated HV usRNA (log_{10} HIV RNA copies/10^6 PBMC)	0.94* [13]	0.7 [15] 1.11-1.94* [7]	nr	0.4 [31]	nr	nr
Reservoir Composition						
Replication-intact non-induced proviral genomes	<1% [33]	nr	nr	nr	11% [34]	nr
HIV-Specific Immune Responses						
HIV-specific antibodies	46-94% seronegative [35;36]	47% seronegative [12]	36-100% seronegative [7;14;26]	nr	nr	nr
HIV-specific T cell responses	0% undetectable [36]	50-100% undetectable [12;36]	100% undetectable [7;26]	nr	nr	nr

- Development/evolution of immune system
- Exposures over life course
  - Nutrition
  - Infections
  - Substances
  - Exercise
  - Vaccinations
  - Pregnancy
  - Menopause
  - Hormones
  - Stress
  - Comorbidities
- Microbiome
- Duration of HIV infection
- Virologic control

Simon Proc Biol Sci. 2015; 282(1821): 20143085; Rainwater-Lovett Curr Opin Pediatr 2016

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



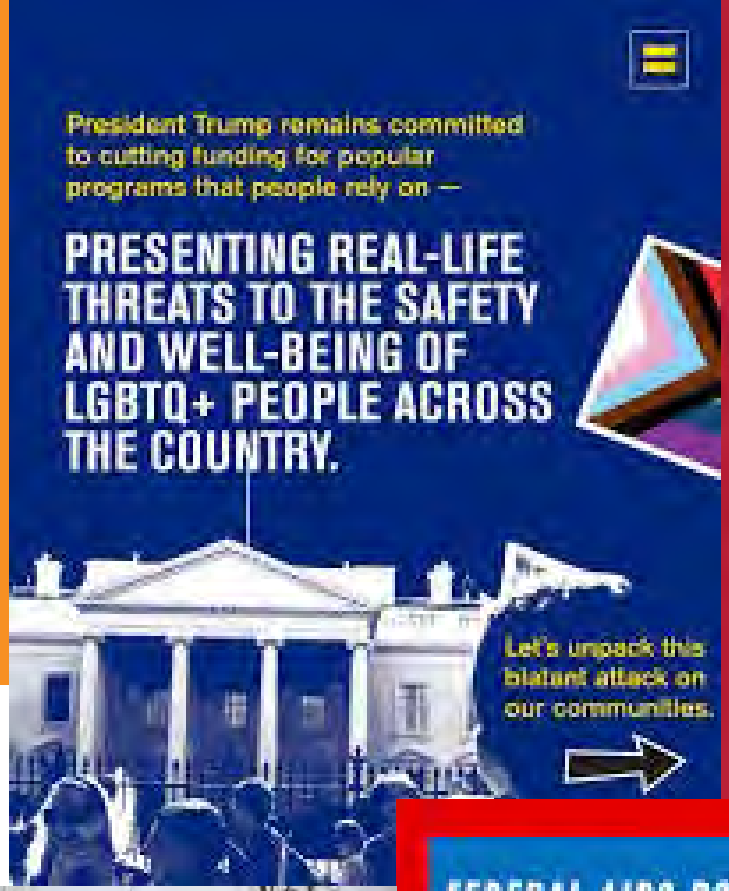
Note. Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2018. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2018. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2018.

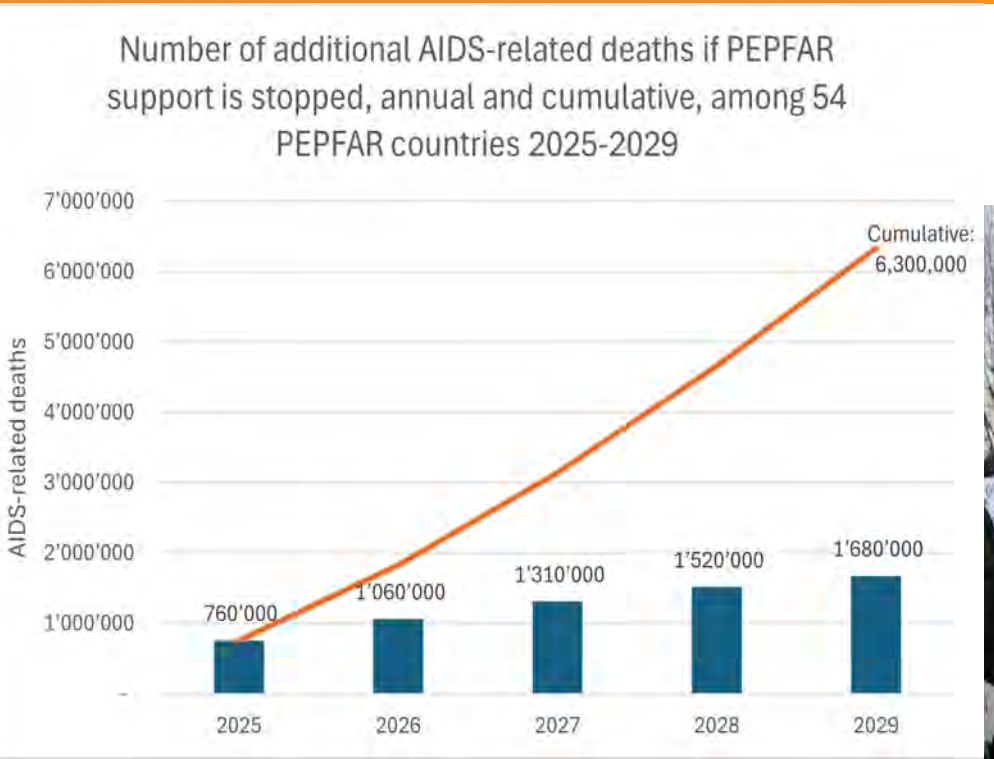
Eliminating HIV

Cutting Medicaid Threatens Plans to End the HIV Epidemic

A Fact Sheet by The AIDS Institute

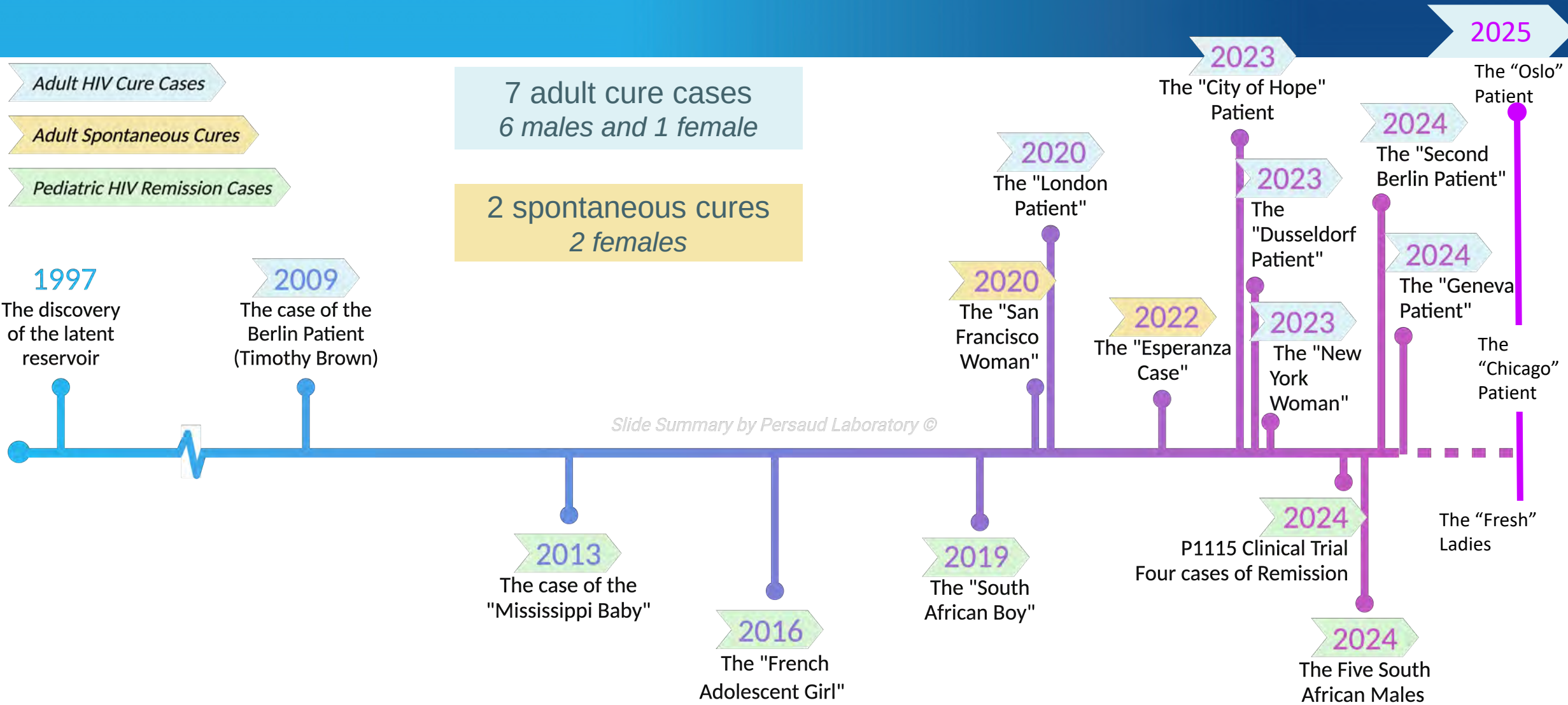
THE AIDS INSTITUTE





“Forever is a long time”
Beyond viral suppression as a destination….

HIV-1 Cure in Adults and Remission in Children



PAVE Pediatric Adolescent Virus Elimination
A Martin Delaney Collaboratory

Slide courtesy of D. Persaud

Aspirational HIV Therapeutic Goals

Remission	Marked reduction in reservoir size sufficiently to limit reactivation events and delay viremic rebound
Post-treatment control	Reduced reservoirs and control of viremic rebound through immune mediated mechanisms
Cure	Complete eradication of all replication-competent proviruses with a lifetime of no rebound

Reviewed in Deeks S et al; Nature Medicine 2021 and 2024 NIAID HIV Language guide

PAVE Pediatric Adolescent Virus Elimination
A Martin Delaney Collaboratory

Slide courtesy of D. Persaud

Cure goal 1: remove the burden of daily treatment.

Will HIV cure simplify treatment?

- Current HIV care options
  - Once daily single pill options for most people
  - Minimal physical side effects for most
  - Every one to two month options for some
  - Horizons of care: Every 6 month injections? Long-acting orals

Will HIV cure simplify treatment?

- Current HIV care options
  - Once daily single pill options for most people
  - Minimal physical side effects for most
  - Every one to two month options for some
  - Horizons of care: Every 6 month injections? Long-acting orals
- What treatment would be needed after a cure
  - PrEP?
  - Monitoring for rebound
  - Managing comorbidity risks
  - Additional interventions? Frequency?

Is the burden of daily treatment actually the pills?

- Sometimes yes

- Sometimes no

The Things They Carried

A WORK OF FICTION BY

Tim O'Brien

Is the burden of daily treatment actually the pills?

- For some, no amount of simplification can alleviate the weight of the diagnosis -> clear mandate for *cure*

The Things They Carried

A WORK OF FICTION BY

Tim O'Brien

When there is a mandate for cure what are the other clinical challenges

- Approach to "certifying" cure
  - Stratifying by probability of recurrence
  - Frequency of monitoring
  - Naming the state of being
  - Identity and insurance
- Secondary prevention
  - No vaccine yet
  - PrEP
  - Monitoring of comorbidity risks
  - Special considerations

Case 1

- 38 yo woman, presented with altered gait noted by her colleagues at work. Diagnosed with advanced HIV disease, encephalitis with significant disability. She was shocked by the diagnosis, had good family support but was deep stigma.

Case 1

- 38 yo woman, presented with altered gait noted by her colleagues at work. Diagnosed with advanced HIV disease, encephalitis with significant disability. She was shocked by the diagnosis, had good family support but was deep stigma.
- Excellent response to treatment, physical and cognitive recovery and returned to her daily life.

Case 1: Specific Challenges

- Long term partner HIV seronegative but has liver disease and is on the transplant list
- They want children
- She is somewhat avoidant of care, reporting that she is overwhelmed with shame.

Case 1: Specific Challenges

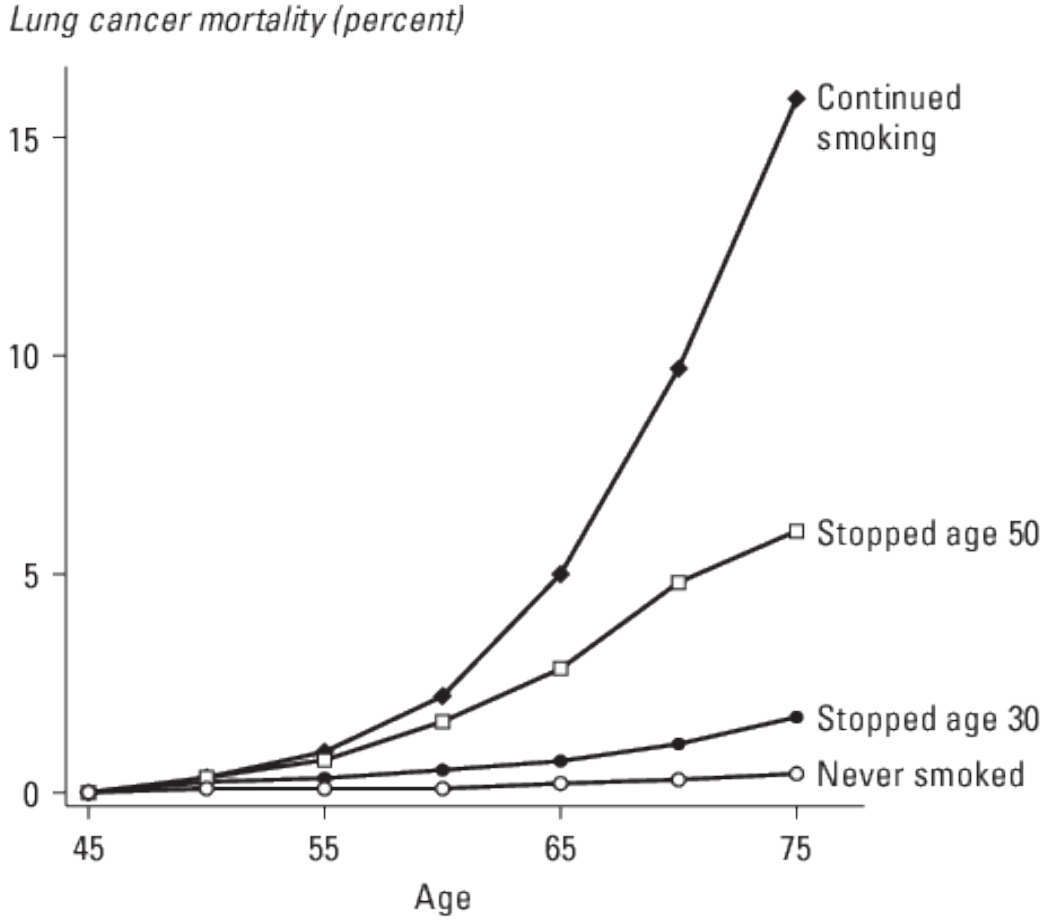
- Cure would be liberation!
- But – but when would we feel confident to say that she is no risk to her partner (he is very worried about his transplant status)?
- And – if she were cured and then pregnant, what would our monitoring look like?

$$U \overset{?}{=} U$$

Cure goal 2: reduce the risk of inflammation driven comorbidities.

Will HIV cure reverse inflammation associated risk or attenuate its progression?

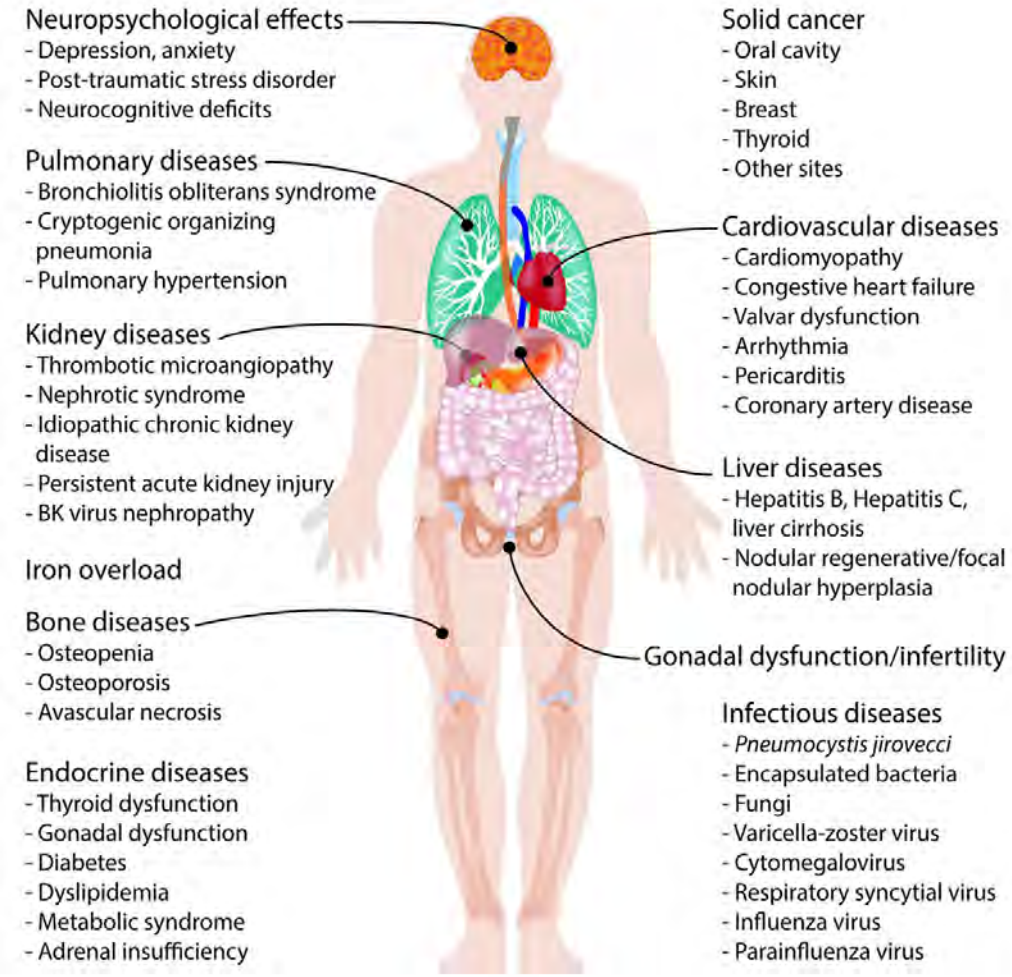
- Smoking?
  - Smoking cessation dramatically drops risk
  - Even after cancer diagnosis there is benefit to smoking cessation



Source: Peto and others 2000.

Will HIV cure reverse inflammation associated risk or attenuate its progression

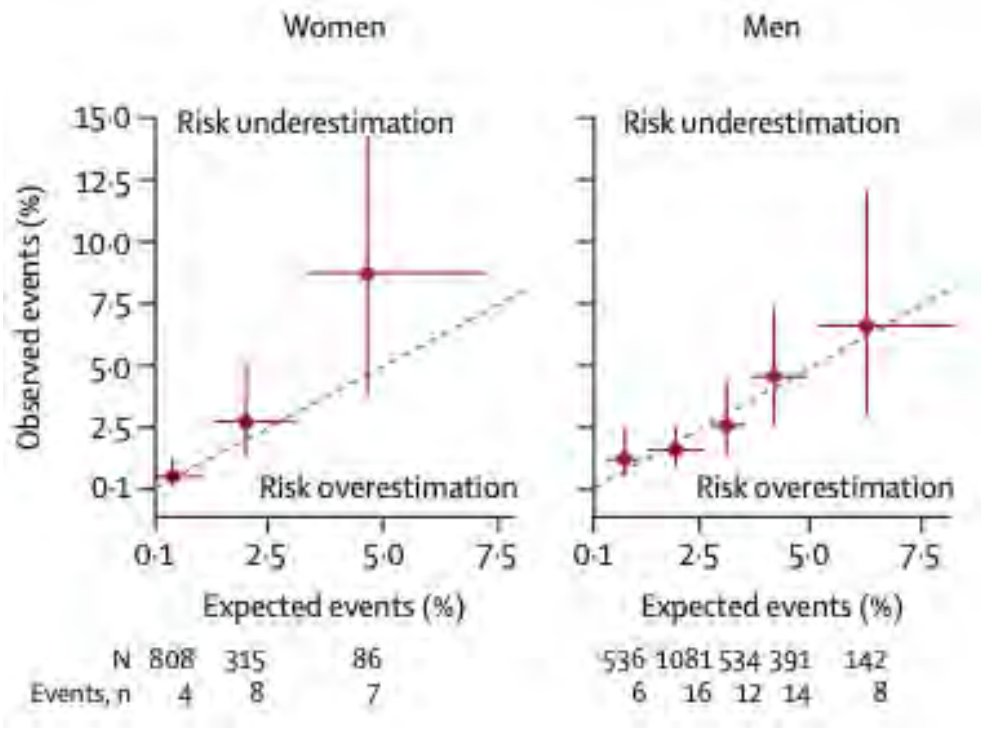
- Current generation of therapeutic approaches
  - Transplantation
  - Shock interventions -> generally activating
  - Block and lock interventions -> generally antiproliferative
  - Immune modulation -> risk of autoimmunity



https://haematologica.org/article/view/8027

Managing inflammation is urgent particularly in women

- Substantial elevation in cardiovascular disease risk
- Pooled cohort equation risk underestimates risk in:
  - Black women with HIV 2.8fold
  - All other women with HIV 2.6fold
  - Black men with HIV 1.25fold



Grinspoon, Zanni et al, Lancet HIV 2025

Case 2

- 47yo woman with a history of HIV, progressive kidney failure, cardiovascular disease. She has full viral suppression, maximal management of her cholesterol, is thin and is not diabetic. She is highly adherent to her medications, has deep stigma, but is coping. Perimenopausal with very frequent hot flashes.

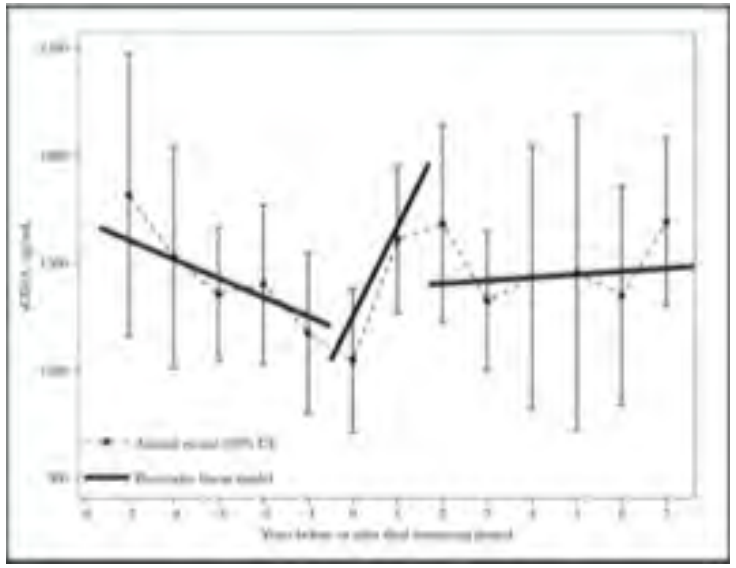
Case 2: Specific considerations

High risk for recurrent vascular event, a cure that reduced inflammation would be urgently welcomed.

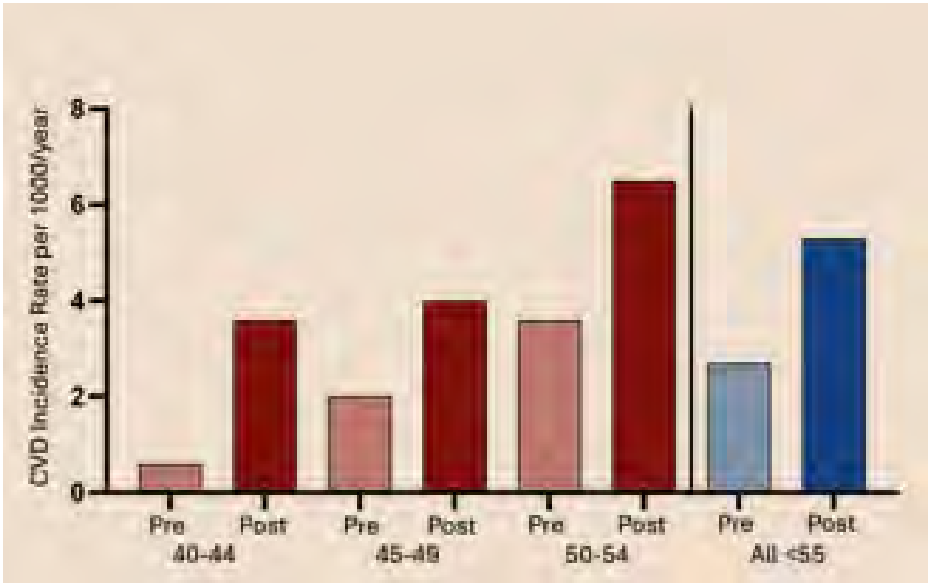
An unknown is whether cure will reduce her risk back to background population rates or if she will retain a higher risk even if improved.

Case 2: Specific considerations

- What kinds of risks would be associated with a curative intervention – transient increase in inflammation
- Does her perimenopausal state factor into decision making? Some evidence of increased inflammation during this time, but risk also known increase postmenopause



Peters et al., JID 2022



Kannel et al., Ann Int Med, 1976

Case 3

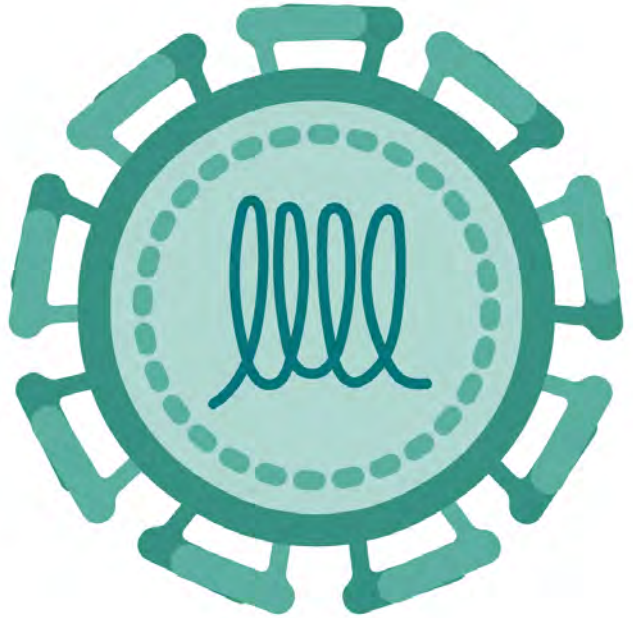
- 35 yo woman with HIV for approximately a decade, CD4<200. Only periods of viral suppression occurred during pregnancies. Recent episode of significant illness with PJP pneumonia. Continues to have challenges with adherence.

Case 3: Specific considerations

- Clear mandate for cure
- Cure strategies all focused on individuals with sustained viral suppression
  - Is a cure a motivation for adherence that is stronger than the others?
  - Is there any horizon for cure without prolonged suppression

Lessons from other conditions: Hepatitis C

Hepatitis C



- First generation: immunotherapy with interferon
  - Marked differences in therapy response -> 45% success
  - IL28B/IFNlambda polymorphisms
- First generation directly acting antivirals (DAAs)
  - Rashes, intolerance and incomplete efficacy
- Modern DAAs
  - Full and rapid treatment response in the vast majority of people with Hep C
- Implementation of the cure
  - Sustained virologic response (SVR) to cure
  - Insurance and access
  - Prevention of re-acquisition

An ideal HIV cure strategy looks like?

- Easy
- One time
- Durable
- Permanent
- Reverses impacts
- Definable status
- Limited toxicity
- Other?

HIV Cure Considerations

- Treatment burden & toxicity
- Monitoring burden
- Anxiety/fear
  - Treatment interruption
  - Relapse
  - Transmission
- Psychosocial:
  - Stigma
  - Disclosure
- Identity/isolation
- Employment
- Resources
- Others?

“I presumed that being cured of HIV I would be celebrated by the HIV community overall….I faced backlash, discrimination. You are not part of the club anymore so you cannot relate to me anymore… jealousy, bitterness. I am cured of HIV but I am always part of the community because that is who I am. I did not expect the rejection…..The focus is often on treatment but I want choices.”

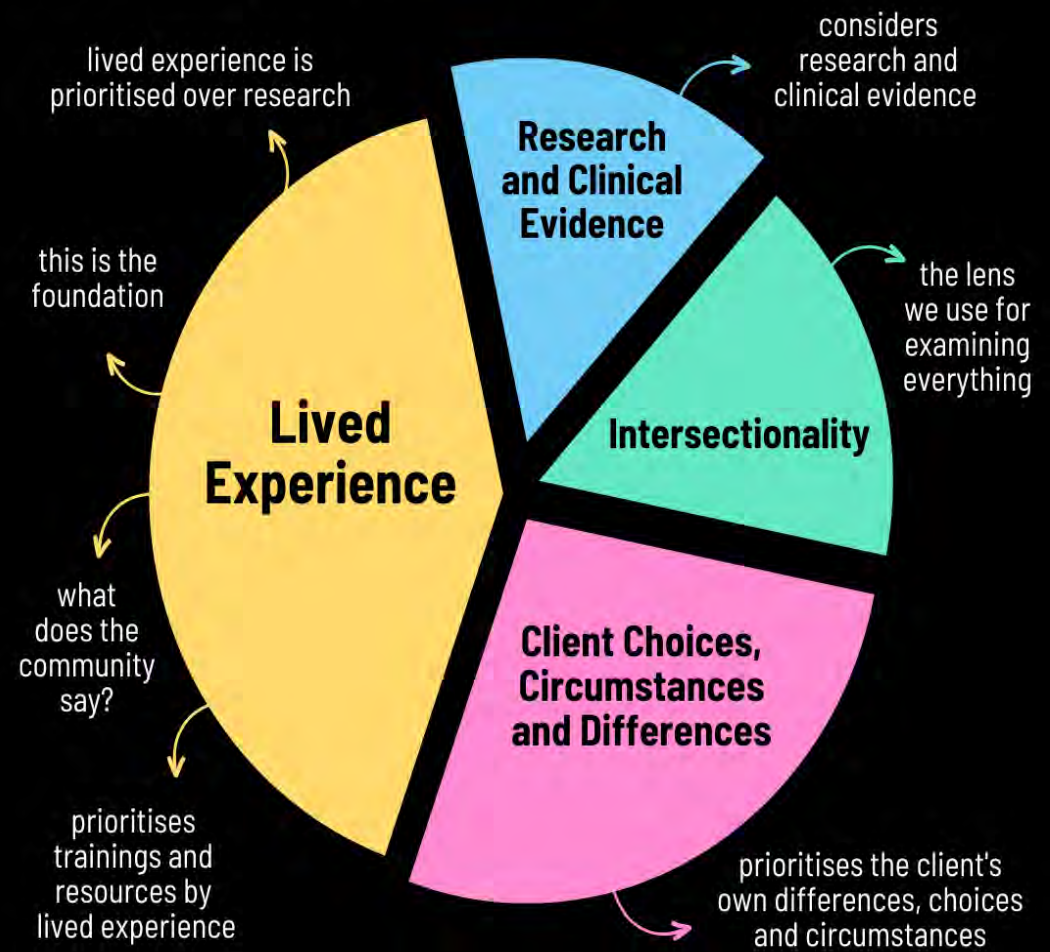
Adam Castillejo, The London Patient

Current Cure Messaging

HIV Cure: GG Mic Drop

Gail Graham, HIV Advocate

Lived Experience Informed Practice



developed by Sonny Jane Wise @livedexperienceeducator www.livedexperienceeducator.com

Questions & Discussion

HIV Cure: The Key Questions

What is the ideal cure strategy?
The ideal risk-benefit profile?
Is cure more of a priority for those who already have comorbidities? Those who do not have comorbidities?
Is cure more of a priority for those that are adherent to treatment? Those that are struggling with treatment?
Which populations should be prioritized? Younger? Older? Women?
Is cure more of a priority now with instability of access to HIV treatment?
How do you weigh the risk of ATI and potential rebound in different patient scenarios?
How can equity be assured?