NIH OAR Aging/HIV Virtual Meeting Report 2

Report 2

the NIH OAR Aging & HIV virtual meeting was held for 6 hours with a series of slide presentations & discussion
The 2nd meeting was a panel on sept 8. There were 500 registered people to participate.

A **virtual** research workshop, “HIV and Aging Research: Current Landscape and Opportunities,” scheduled for **Tuesday, September 5, 10 a.m.–4:30 p.m. ET**, will survey the current landscape of HIV and aging research and explore ways to identify future research directions to address the needs of people aging with HIV. View the agenda, and register here Click here to view a Quick Reference on HIV and aging efforts across NIH. Individuals with disabilities who need reasonable accommodations to participate in this event should contact OARevents@nih.gov by August 29.

A **hybrid** panel discussion, "Current Landscape and Opportunities for Federal HIV and Aging Effort” will take place virtually and in person at the U.S. Conference on HIV/AIDS (USCHA) on **Friday, September 8, 2 p.m.–4 p.m. ET**. The discussion will explore how federal agencies, the HIV community, researchers, and clinicians can work together to prioritize interdisciplinary research and training and implementation strategies to address the needs of people aging with HIV. In-person attendance is open only to individuals registered for USCHA. USCHA registrants who plan to attend in person do not need to register separately for this event. Virtual registration is open to any individual, regardless of their attendance at USCHA. View the agenda and click here to register for the virtual component by **August 25**. Individuals with disabilities who need reasonable accommodations to participate virtually should contact OARevents@nih.gov by August 25.

The Intersection of Frailty and Comorbidity in People Living With HIV

Todd T. Brown, MD, PhD, Johns Hopkins University, Baltimore, Maryland
NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

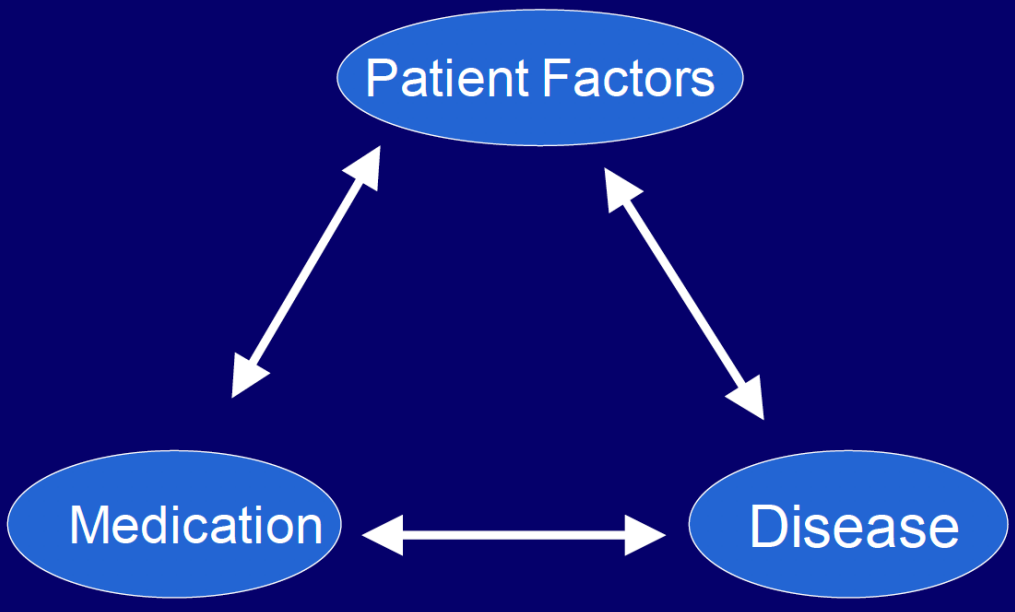
Abundant research links comorbidities like atherosclerosis, diabetes, and osteoporosis to impaired physical function and frailty in people with HIV, Johns Hopkins University’s Todd Brown reminded colleagues. But comorbid events can often be prevented or controlled through reliable screening tests, modified behavioral factors, and good treatment. Brown argued that preventing complications of comorbidities can alter the aging process.

Much research on physical function with HIV relies on the Fried frailty phenotype [1] to assess frailty in people with HIV. Presence of 3 or more of 5 criteria indicate frailty: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Brown placed those 5 criteria into a broader conceptual model that includes potential triggers and physiologic factors leading to frailty as well as frailty outcomes (**figure**).

Prevention of Comorbid Events is Essential and Achievable

- Good screening tests are available for comorbid conditions
- Many behavioral factors contribute to comorbid conditions and can be modified
- Early treatment is important
- Good treatments exist that can decrease the risk of events (cardiovascular disease, fracture)
- Preventing complications can alter the aging process

Causes of Comorbid Diseases in HIV



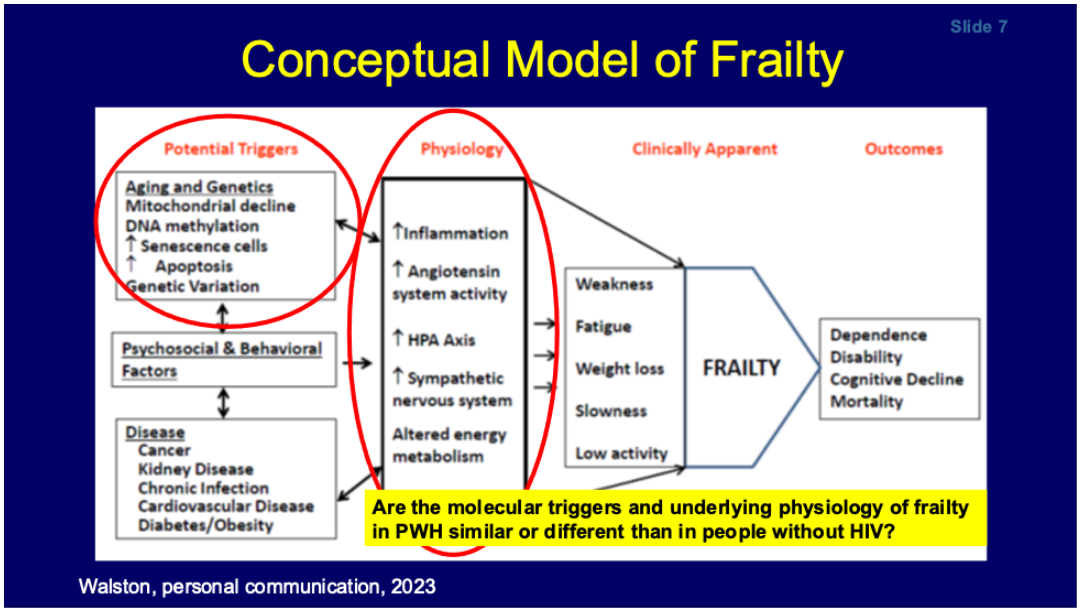
HIV Medications & Comorbidities

Current Effects

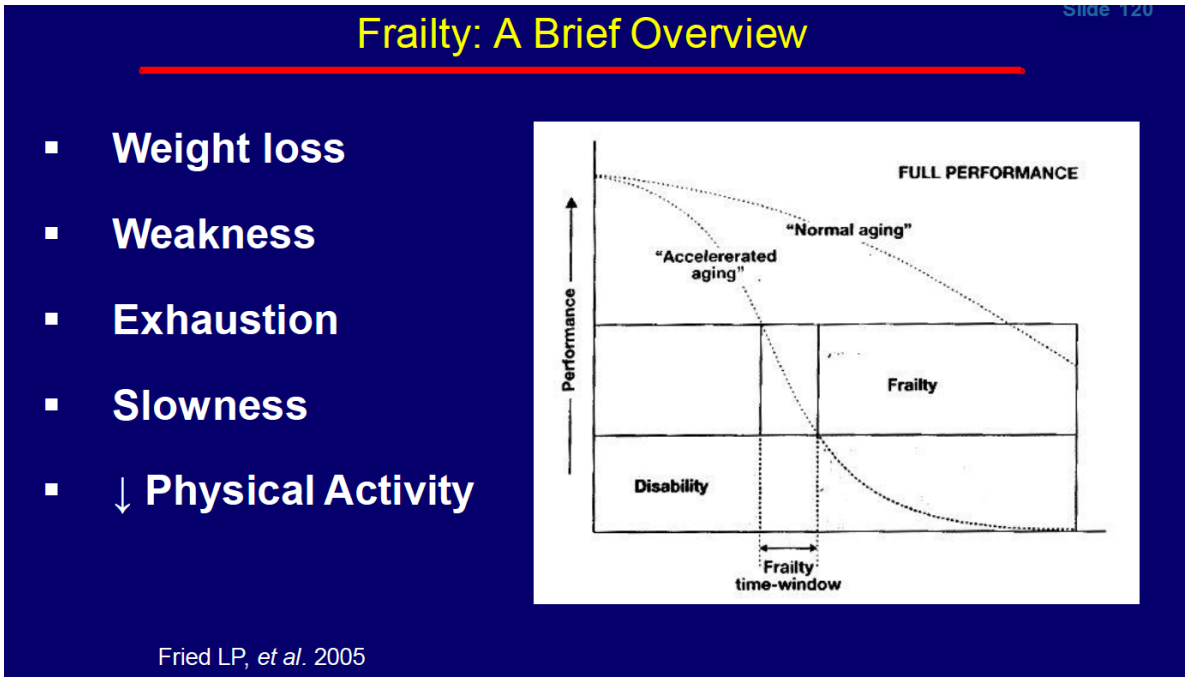
- Tenofovir DF → Bone and Kidney Disease
- Protease Inhibitors→ Cholesterol
- InSTI→ Weight Gain

Legacy Effects

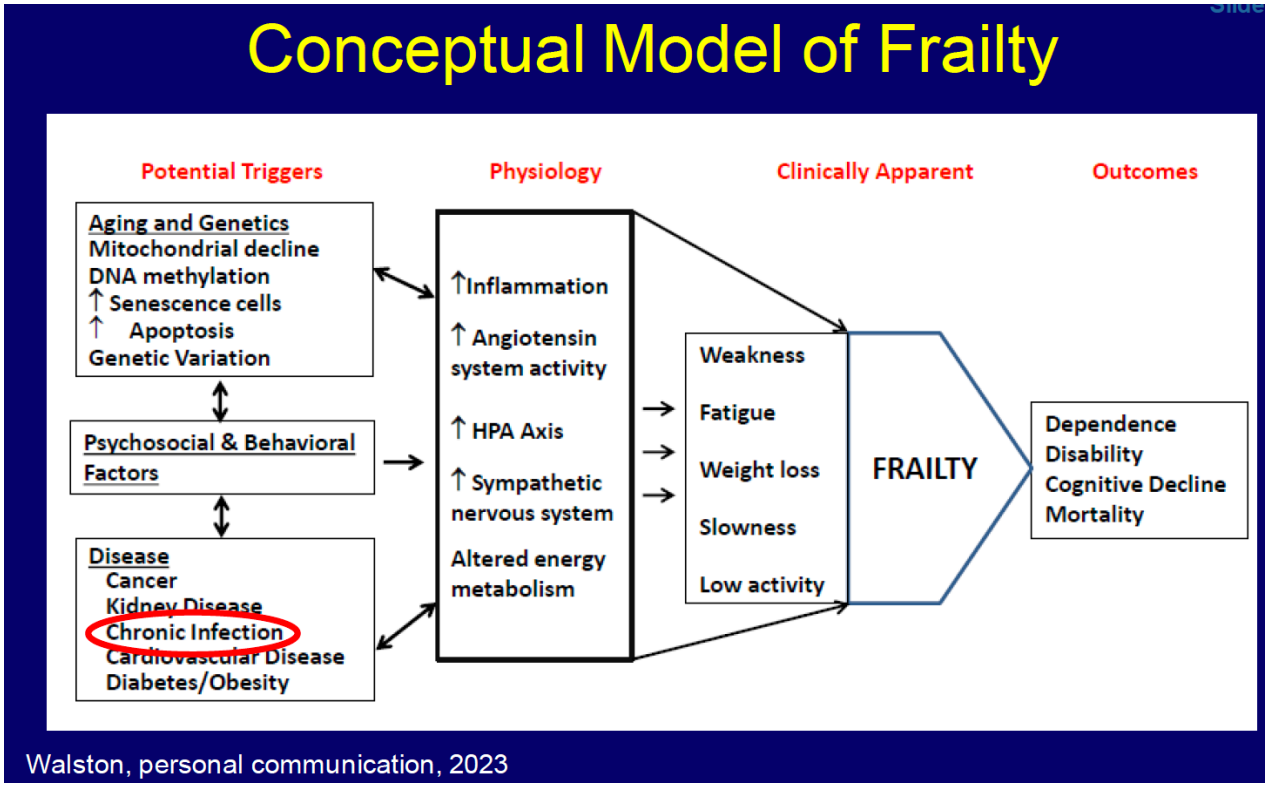
- Past use of stavudine can persist

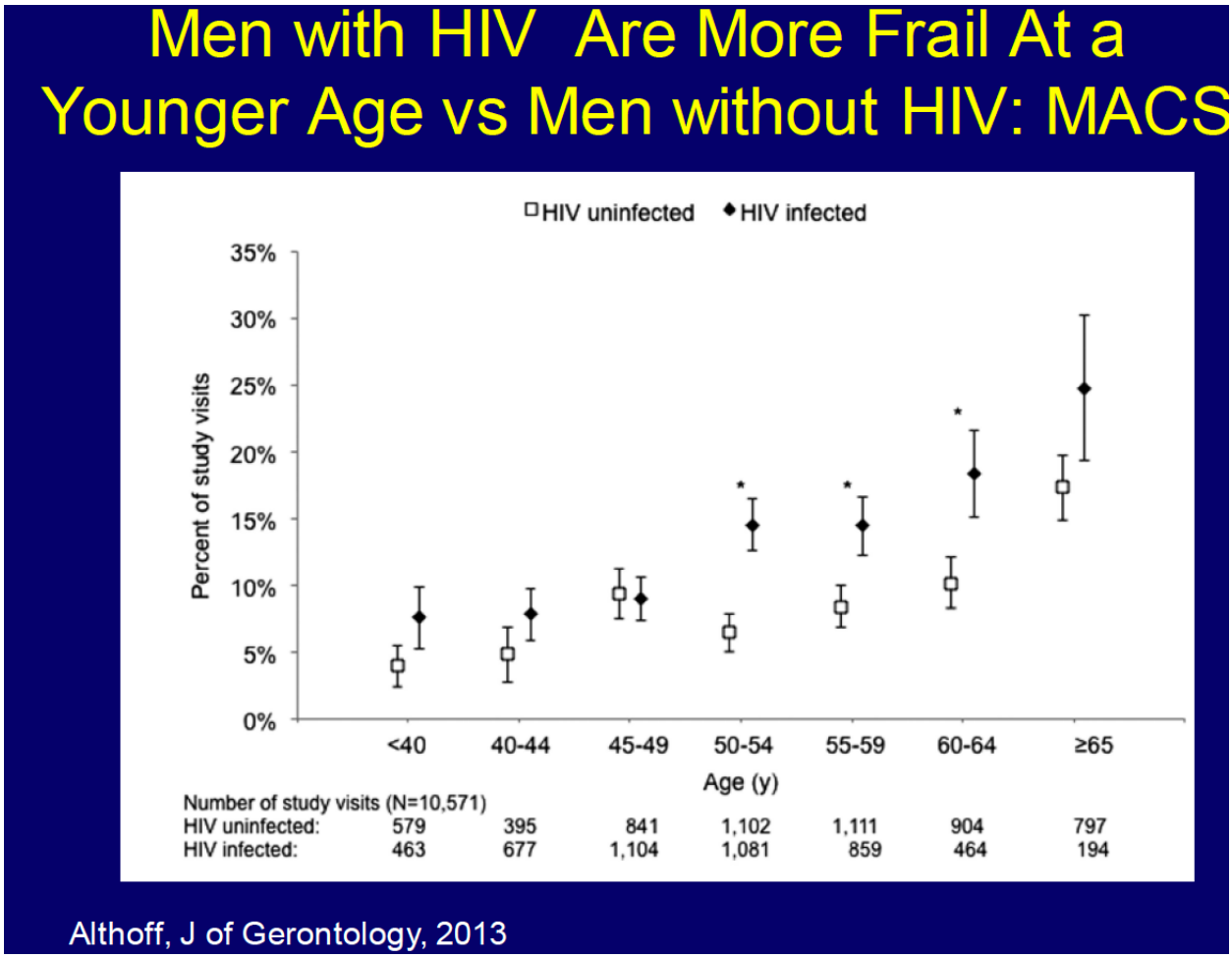


Todd Brown explored potential triggers and physiology that may lead to frailty and asked if those factors are similar or different in people with versus without HIV infection.



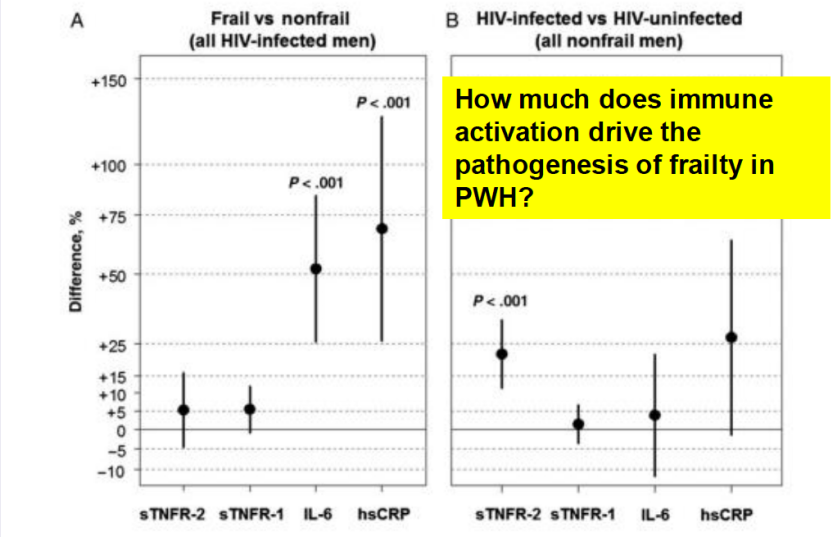
Brown cited evidence that men with HIV are more frail at a younger age than behaviorally similar men without HIV [2]. Other research showed that grip strength and walking speed—two components of the frailty phenotype—fall faster in men with than without HIV [3]. Those findings raise a still incompletely answered question: Does frailty in men with and without HIV share the same molecular triggers and pathophysiology? (*See figure above.*)





One attempt to address this question is a case-control study of men who have sex with men (MSM) with or without HIV infection [4]. Adjusted analysis linked frailty in men with HIV to higher levels of inflammation markers (interleukin 6 and high-sensitivity C-reactive protein) and lower hormone levels (testosterone and dehydroepiandrosterone), regardless of comorbid conditions. Multivariate analysis also determined that HIV infection—but not frailty—predicted significantly greater immune senescence and immune activation.

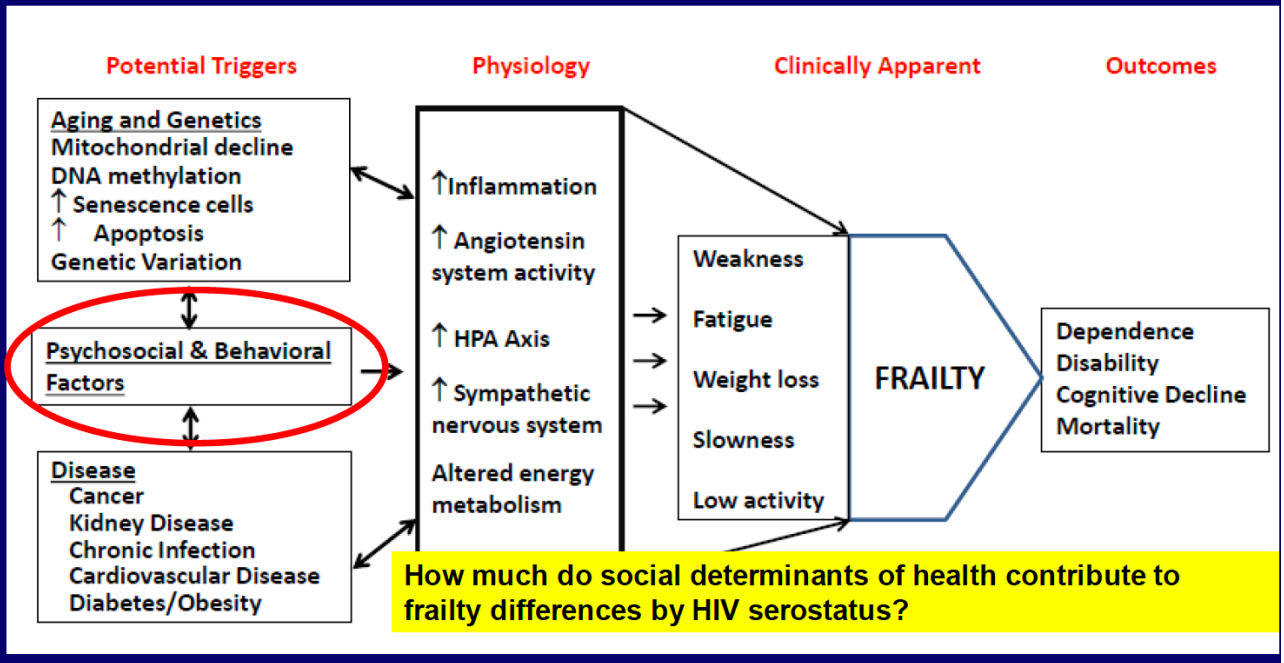
Markers of Inflammation Associated With Frailty-related Phenotype in MACS: Case-Control Study



How much does immune activation drive the pathogenesis of frailty in PWH?

Erlandson, JID, 2016

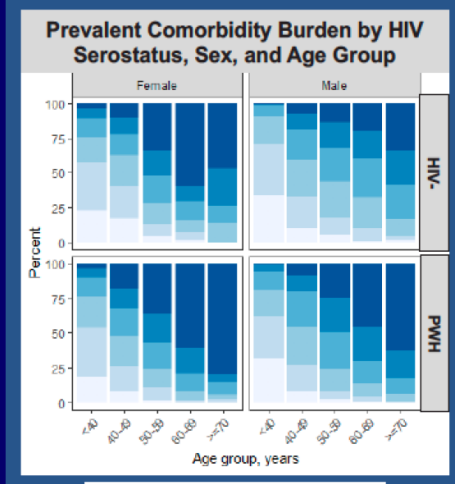
Conceptual Model of Frailty

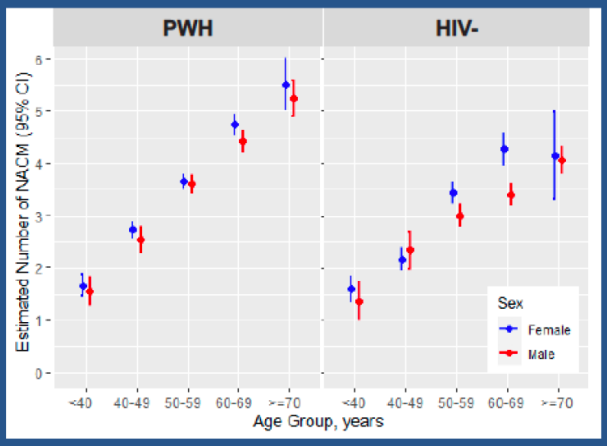


How much do social determinants of health contribute to frailty differences by HIV serostatus?

Walston, personal communication, 2023

Multimorbidity burden related to HIV status is greater in women than in men:MWCCS





In the adjusted model†, findings were attenuated but HIV and age still significantly modified the estimated mean NACM burden by sex (HIV*age*sex, *p*=0.038)

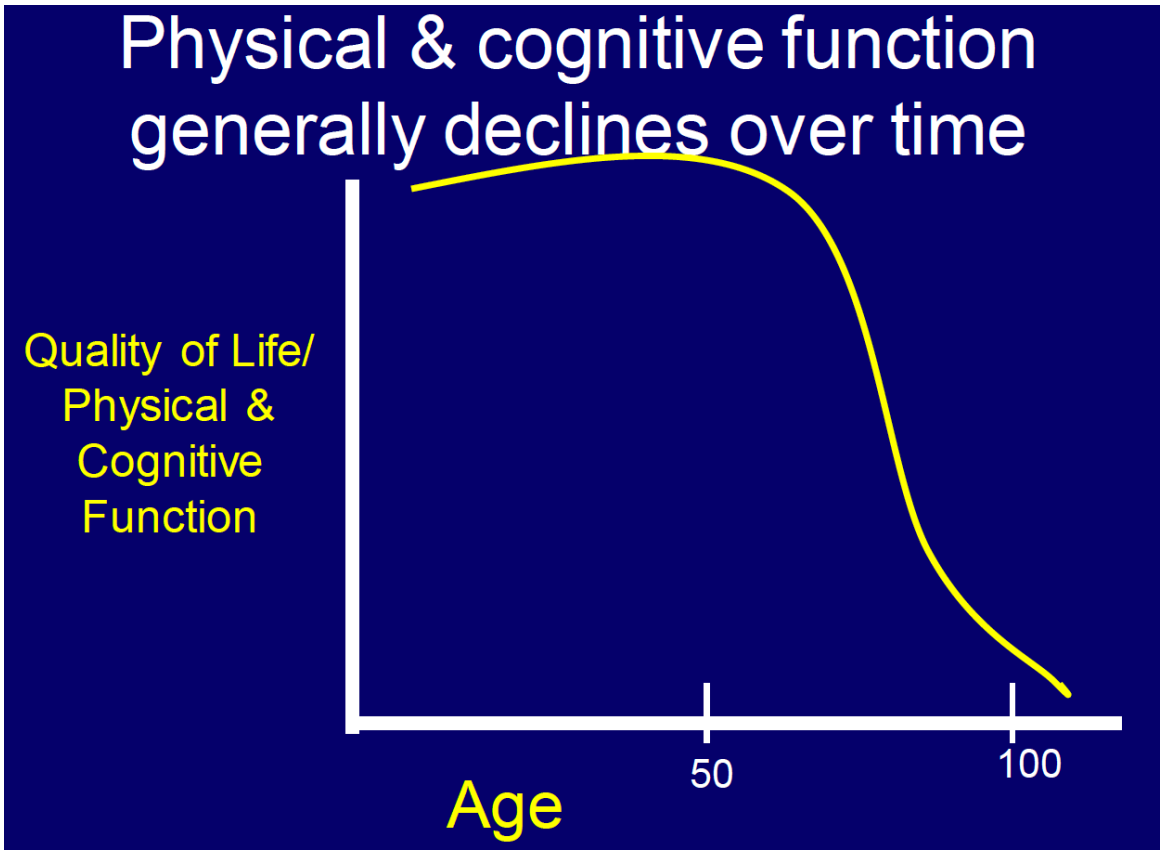
†Including covariates in the unadjusted linear regression model plus race, body mass index, smoking, drinking, cocaine, socioeconomic status

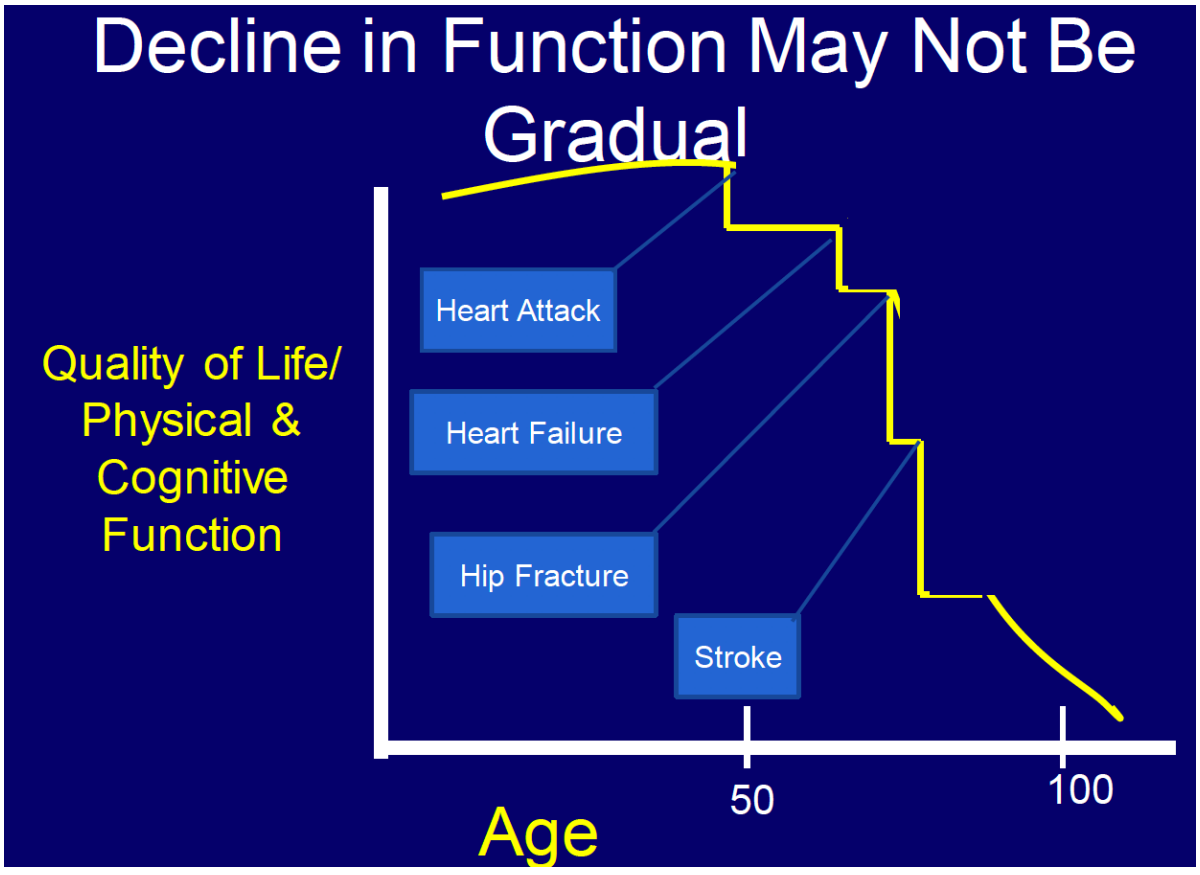
Collins, CROI 2021

Brown listed separate studies that tied an array of comorbidities to frailty and impaired physical function in people with HIV infection: abdominal adiposity, osteoporosis, coronary atherosclerosis, chronic obstructive pulmonary disease, hypertension, diabetes, and depression. He reminded colleagues that antiretroviral classes and individual antiretrovirals are linked to comorbidities: tenofovir DF (bone and kidney disease), protease inhibitors (abnormal cholesterol), and integrase inhibitors (weight gain). Also, the study of HIV-positive and negative men that addressed grip strength [3] found that greater cumulative viral load over time drove the drop in grip strength.

Comorbidities are associated with frailty & physical function impairment in PWH

- Abdominal adiposity (Hawkins, AIDS, 2018)
- Osteoporosis (Hawkins, AIDS, 2018)
- Coronary atherosclerosis (Korada, Atherosclerosis, 2017)
- COPD (Akgun, AIDS, 2016)
- Hypertension (Umbleja, JID, 2020)
- Diabetes (Masters, AIDS, 2022)
- Depression (Umbleja, JID, 2020)


Physical & cognitive function generally declines over time
Quality of Life/ Physical & Cognitive Function
50
100
Age


Decline in Function May Not Be Gradual
Quality of Life/ Physical & Cognitive Function
Heart Attack
Heart Failure
Hip Fracture
Stroke
50
100
Age

Brown called preventing comorbidities “essential and achievable.” He maintained that debilitating comorbidities can be prevented because most have good screening tests and many result from behaviors that can be modified. When a comorbidity does arise, Brown called for early treatment to prevent progression and a cascade of related conditions. Good available treatments can cut the risk of serious complications like cardiovascular events and fractures. He argued that “preventing complications can alter the aging process.”

References
1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-156. doi: 10.1093/gerona/56.3.m146. https://academic.oup.com/biomedgerontology/article/56/3/M146/545770
2. Althoff KN, Jacobson LP, Cranston RD, et al. Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. J Gerontol A Biol Sci Med Sci. 2014;69:189-98. doi: 10.1093/gerona/glt148. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4038242/
3. Schrack JA, Jacobson LP, Althoff KN, et al. Effect of HIV-infection and cumulative viral load on age-related decline in grip strength. *AIDS*. 2016;30:2645-2652. https://journals.lww.com/aidsonline/fulltext/2016/11130/effect_of_hiv_infection_and_cumulative_viral_load.10.aspx
4. Erlandson KM, Ng DK, Jacobson LP, et al. Inflammation, immune activation, immunosenescence, and hormonal biomarkers in the frailty-related phenotype of men with or at risk for HIV infection. J Infect Dis. 2017;215:228-237. doi: 10.1093/infdis/jiw523. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5897840/

Neurocognitive Decline in People With HIV Over 12 Years: Incidence and Predictors in CHARTER

Robert K. Heaton, PhD, University of California at San Diego
NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

Test-measured cognitive function dropped over 12 years in nearly one quarter of HIV-positive people taking effective antiretroviral therapy, reported Robert Heaton in a CHARTER study analysis. These declines in function occurred in similar proportions of people who were younger or older at the initial (baseline) visit. The analysis also found that comorbidities common in people with HIV predicted cognitive decline through 12 years better than HIV disease or treatment factors.

CHARTER enrolled HIV-positive antiretroviral-treated people at 6 sites across the United States. In this 12-year analysis the researchers hypothesized that people at least 60 years old at follow-up would have greater neurocognitive slippage over time than people under 60 at follow-up. They also hypothesized that the older group would have more neuromedical comorbidities at the baseline visit and would accumulate more comorbidities over time than the younger group.

Participants had comprehensive neuromedical and neurocognitive assessments at their initial visit and 12 years later, including a neuropsychological test battery assessing 7 cognitive domains. The CHARTER team rated cognitive changes by regression-based global change score compared with normative data from medically stable people with or without HIV. They defined neurocognitive decline as a drop worse than the 5th percentile (lowest 5%) of normative data. The investigators used multivariable regression to analyze demographic, disease, drug use, and therapy factors.

The 260 people in the younger group averaged 39.2 years of age at baseline and 51.8 years at the 12-year follow-up. For the 142 older people, baseline and 12-year follow-up ages were 51.5 and 64.4. The older group had somewhat more years of education than the younger group (13.5 vs 12.8), but the groups were similar in WRAT-III-determined IQ. The older and younger groups were similar in proportions of men (78% and 76%), blacks (47% and 45%), Hispanics (8% and 12%), and whites (44% and 40%). Baseline prevalence of neurocognitive impairment was also similar in older and younger participants (45.8% and 44.6%). Follow-up stood at a median of 12.4 years.

For the entire study group significantly higher proportions were taking antiretroviral therapy at the 12-year follow-up than at baseline (96% vs 74%), had a plasma viral load at or below 200 copies (92% vs 71%), and had a cerebrospinal fluid viral load at or below that mark (96% vs 91%).

Summary and Conclusions

- **Over a median of 12.4 years, nearly a quarter of PWH who were on suppressive ART experienced cognitive decline**
  - » **Younger and older PWH showed similar rates and degrees of cognitive worsening, arguing against premature or accelerated cognitive or brain aging within this cohort of PWH**
- **Younger and older participants had surprisingly comparable worsening of medical and psychiatric conditions**
  - » **Comorbidities, rather than HIV disease and treatment factors, best predicted cognitive decline over 12+ years in CHARTER**
- **HIV treatment and virologic control improved markedly over 12+ years, but comorbidities often were not being treated at follow-up.**
  - » **More and earlier medical attention to non-HIV risks may yield improved outcomes**

Demographic Characteristics of Younger and Older Cohorts

Demographic	Younger (n=260)	Older (n=142)	
Baseline age	39.2	51.5	
Follow-up age	51.8	64.4	
Education	12.8	13.5	O>Y
% Male	76%	78%	
% Black	45%	47%	
% Hispanic	12%	8%	
% White	40%	44%	
WRAT-III	**92.3**	**91.6**	
Baseline % NCI	44.6%	45.8%	

HIV Disease Characteristics of Total Cohort (N=402) at Baseline and 12-yrs

	Baseline	12-year Follow-up	Age Group Difference	Significant Changes
Duration of HIV (Years)[1]	9.8 (6.3)	22.6 (6.5)	O > Y	Not Tested
AIDS Diagnosis[2]	61%	74%	---	Higher
Nadir CD4+ T-cells[3]	172 [30-310]	114 [20-230]	---	Lower
CD4+ T-cells[3]	453 [279-642]	591 [365-818]	---	Higher
On ART[2]	74%	96%	---	Higher
Plasma HIV RNA ≤ 200[2*]	71%	92%	---	Higher
CSF HIV RNA ≤ 200[2*]	91%	96%	---	Higher

[1]Mean (SD), [2]Percent, [3]Median [IQR] *Among those on ART n for CSF: 229 at V1, 191 at V2

--- = Not Significantly Different

Baseline vs. 12-year Follow-up: Medical Comorbidities

	Baseline	12-year Follow-up	Age Group Difference	Significant Changes
HCV Co-infection	23.6%	36.5%	O > Y	Higher
Diabetes	6.5%	20.5%	---	Higher
Hypertension	18.7%	52.0%	---	Higher
Hyperlipidemia	9.7%	39.8%	O > Y	Higher
Chronic Pulmonary Disease	9.2%	20.5%	---	Higher
Peripheral Neuropathy	58.0%	71.4%	O > Y	Higher
Neuropathic Pain	29.7%	36.8%	O > Y	Higher
Elevated Serum AST	28.8%	10.4%	---	Lower
Low Serum Total Protein	22.1%	28.1%	---	Higher
Anemia	34.1%	28.9%	---	Lower
Frailty or Pre-Frailty	---	54.1%	---	Not Tested

--- = Not Significantly Different

Baseline vs. 12-year Follow-up: Psychiatric Comorbidities

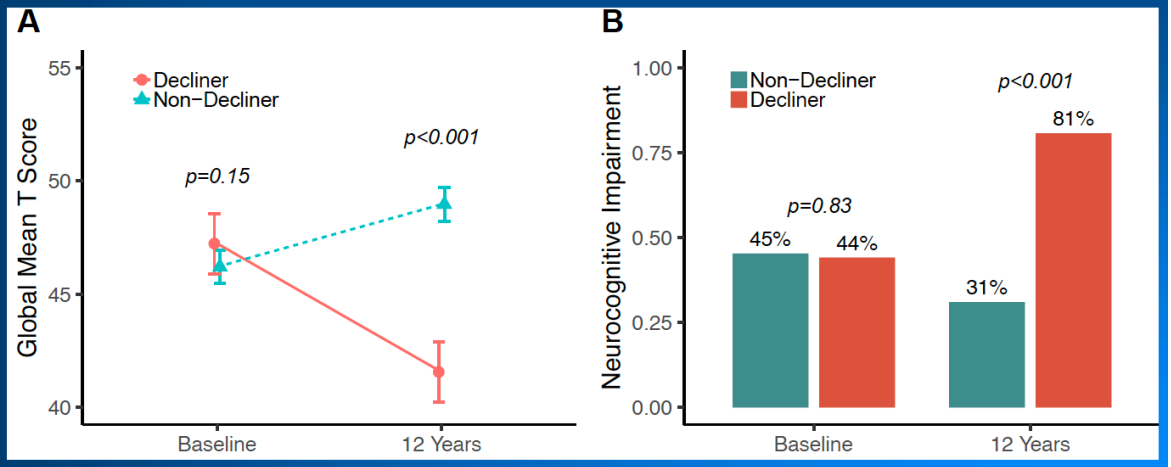
	Baseline	12-year Follow-up	Age Group Difference	Significant Changes
LT Major Depression	48.0%	62.5%	---	Higher
Beck Depression Inventory-II > 13	42.0%	28.4%	---	Lower
LT Alcohol Use Disorder	53.8%	57.9%	---	---
LT Cannabis Use Disorder	27.3%	32.0%	---	---
LT Methamphetamine Use Disorder	13.5%	15.6%	---	---
LT Any Substance Use Disorder	71.3%	76.3%	---	---

LT = Lifetime

--- = Not Significantly Different

Through 12 years of follow-up rates of several comorbidities and lab measures rose for the whole group: HCV coinfection (23.6% to 36.5%), diabetes (6.5% to 20.5%), hypertension (18.7% to 52.0%), hyperlipidemia (9.7% to 39.8%), chronic pulmonary disease (9.2% to 20.5%), peripheral neuropathy (58.0% to 71.4%), neuropathic pain (29.7% to 36.8%), and low serum total protein (22.1% to 28.1%). These gains were significantly greater in the older than younger group only for HCV coinfection, hyperlipidemia, peripheral neuropathy, and neuropathic pain. For the entire cohort rates of two conditions fell significantly through 12 years: elevated serum AST (28.8% to 10.4%) and anemia (34.1% to 28.9%).

Cognitive Functioning by Decliner Status: 24% Evidenced Abnormal Cognitive Decline



A) Global T-score by decliner status at baseline and 12 years (values are mean and 95% confidence interval), B) Global neurocognitive impairment by decliner status at baseline and 12 years

Significantly more participants had lifetime major depression at 12 years than at the initial visit (62.5% vs 48.0%), but significantly

fewer participants had a Beck Depression Inventory-II score greater than 13 (indicating worse depression symptoms) after 12 years (28.4% vs 42.0%). Older participants did not differ from younger participants in either of these measures or in lifetime use of alcohol, cannabis, methamphetamine, or any substance.

Almost one quarter of the entire study group, 24%, had declining cognitive function through 12 years, as determined by global mean T score ($P < 0.001$ compared with people with no cognitive decline). Multivariable regression picked out 6 independent baseline predictors of cognitive decline: hypertension, chronic pulmonary disease, Beck Depression Inventory-II greater than 13, lifetime cannabis use disorder, high serum AST, and low serum total protein. Independent 12-year predictors of cognitive decline were diabetes, chronic pulmonary disease, Beck Depression Inventory-II greater than 13, lifetime cannabis use disorder, anemia, and frailty or prefrailty (which was not determined at the baseline visit).

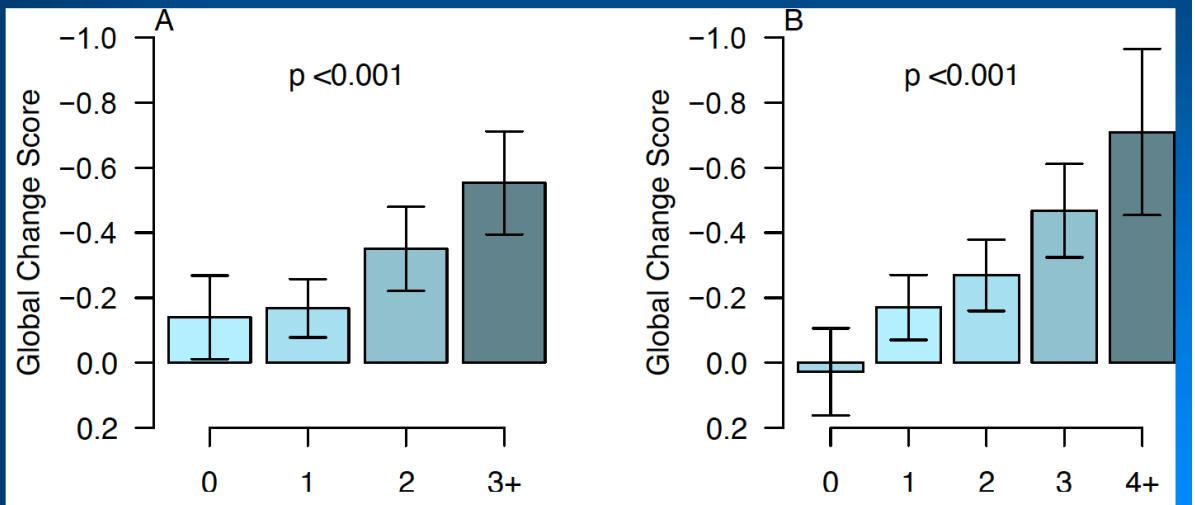
Higher numbers of comorbidities either at baseline or at 12 years were associated with greater global change score indicating worse cognitive function ($P < 0.001$ for both baseline and 12 years). More comorbidities at baseline were also linked to higher proportions of participants with cognitive decline ($P = 0.013$), and that association was stronger for more comorbidities at 12 years ($P < 0.001$).

Among 111 participants with a Beck Depression Inventory-II greater than 13, only 56 took an antidepressant. Among 82 with diabetes, 46 took an antidiabetic drug; among 208 with hypertension, 158 took an antihypertensive; and among 82 with chronic pulmonary disease, 39 took a bronchodilator. People with chronic pulmonary disease had a better global change score at year 12 if taking a bronchodilator ($P = 0.05$).

Multivariable Baseline and 12-Year Predictors of Neurocognitive Decline

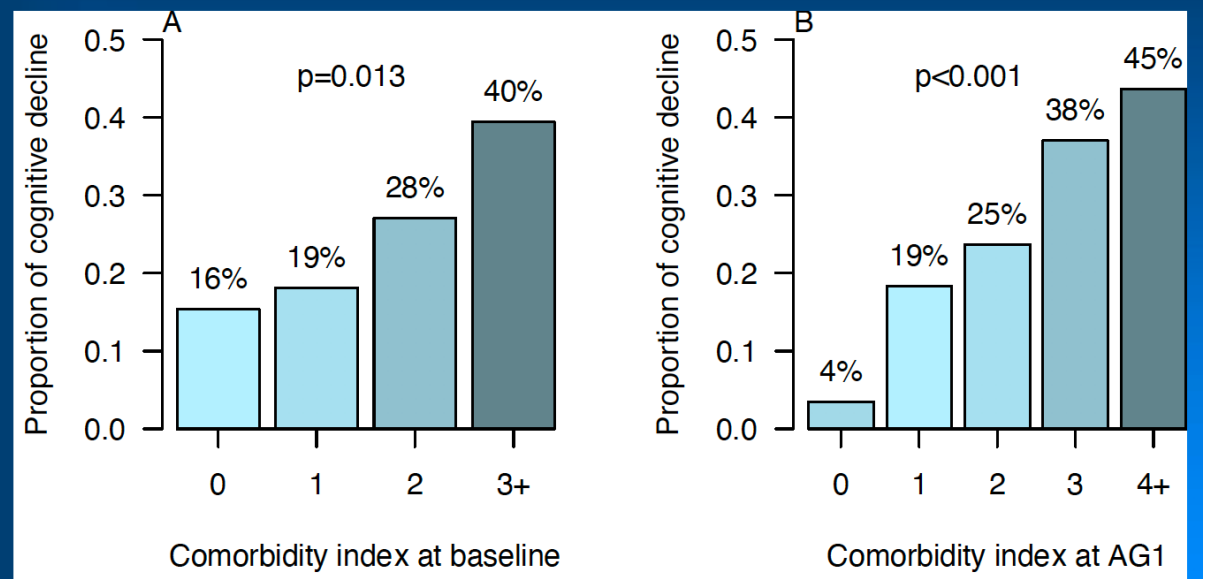
	Baseline	12 Years
Hypertension	X	
Diabetes Mellitus		X
Chronic Pulmonary Disease	X	X
Beck Depression Inventory-II > 13	X	X
Lifetime Cannabis Use Disorder	X	X
Frailty or Pre-Frailty	Not performed	X
Anemia		X
Elevated Serum AST	X	
Low Serum Total Protein	X	

Global Change Score by Comorbidity Indices at Baseline and at 12 Years



A) GCS by number of comorbidities at baseline, B) GCS by number of comorbidities at 12 years. Values are mean and 95% CI.

Decliner Status by Comorbidity Indices at Baseline and at 12 Years



A) Proportion of decliners by number of comorbidities at baseline, B) Proportion of decliners by number of comorbidities at 12 years. Values are observed proportions.

The researchers noted that their analysis is limited by lack of an HIV-negative comparison group in CHARTER and by possible

survivor bias, especially in the older group.

Heaton and his CHARTER colleagues stressed that rates and degrees of cognitive worsening proved similar in younger and older people in this cohort. Younger and older people also had "surprisingly comparable worsening of medical and psychiatric conditions." Noting the low comorbidity treatment rates, the CHARTER team suggested that "more and earlier medical attention to non-HIV risks may yield improved outcomes."

Understanding HIV Brain Health Inequities and How We Move Forward

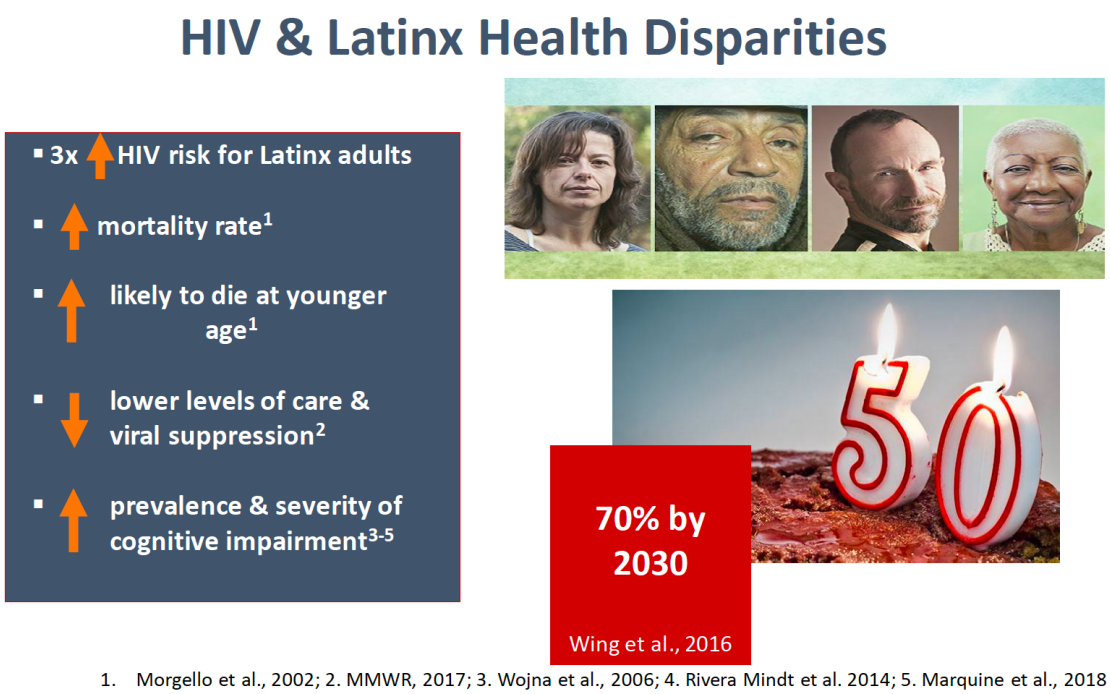
Monica Rivera Mindt, Fordham University and Icahn School of Medicine at Mount Sinai, New York, New York

NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

Inequities in HIV care and outcomes run deep in the United States, the Icahn School of Medicine's Monica Rivera Mindt reiterated at the NIH HIV and Aging Research Workshop. She offered one current breakdown of HIV prevalence in the United States that figures Blacks account for 44% of HIV infections (though making up 14% of the entire US population), Hispanics 25% (18% of the entire US population), Whites 26%, Asians, Native Hawaiians, other Pacific Islanders 2%, and American Indians/Alaska Natives (AI/AN)1%. Rivera Mindt added a few troubling footnotes: The years 2011 to 2015 saw a 35% jump in HIV among gay or bisexual Asian men, with drops in retention in care and viral suppression in this group. The same years saw a 54% vault in HIV among AI/AN people with Two-Spirit identity. (Some indigenous cultures in North America use the term Two-Spirit to encompass cultural, spiritual, sexual, and gender identities [1]).

Compared with non-Latinx adults, **Latinx adults run a 3 times higher risk of HIV infection**, Rivera Mindt reported. Latinx people with HIV have **higher mortality**, are **more likely to die at a younger age**, and **have lower levels of care and viral suppression** than comparison populations. Other research found **higher prevalence and greater severity of cognitive impairment in Latinx adults with HIV than in comparison groups** [2-4].



1. Morgello et al., 2002; 2. MMWR, 2017; 3. Wojna et al., 2006; 4. Rivera Mindt et al. 2014; 5. Marquine et al., 2018

To study neurocognitive disorders more closely in people with HIV, the CHARTER Study enrolled 1555 adults with HIV at 6 sites across the United States [5]. Cross-sectional analysis reported in 2010 found that 52% of these people—71% then taking antiretrovirals and 59% with an undetectable viral load in plasma—had HIV-associated neurocognitive disorder (HAND). Latinx participants were the only ethnocultural group with an increased risk of HAND.

CHARTER Study (N = 1,555)

Neurology. 2010 Dec 7; 75(23): 2087–2096.
doi: 10.1212/WNL.0b013e318200d727
PMCID: PMC2995535
PMID: 21135382

HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy

CHARTER Study

R.K. Heaton, PhD, D.B. Clifford, MD, D.R. Franklin, Jr., BS, S.P. Woods, PsyD, C. Ake, PhD, F. Vaida, PhD, R.J. Ellis, MD, PhD, S.L. Letendre, MD, T.D. Marcotte, PhD, J.H. Atkinson, MD, M. Rivera-Mindt, PhD, O.R. Vigil, MS, M.J. Taylor, PhD, A.C. Collier, MD, C.M. Marra, MD, B.B. Gelman, MD, PhD, J.C. McArthur, MBBS, S. Morgello, MD, D.M. Simpson, MD, J.A. McCutchan, MD, I. Abramson, PhD, A. Gamst, PhD, C. Fennema-Notestine, PhD, T.L. Jernigan, PhD, J. Wong, MD, I. Grant, MD, and For the CHARTER Group

- Cross-sectional findings
- 6 sites across US, including NYC (Mt. Sinai)
- **52.1% of the sample was globally NC impaired**
- **Latinx ethnicity was only ethnocultural group at increased risk for HAND**

Among CHARTER participants with declining neurocognitive function through an average 35 months of follow-up, **Hispanics had more than a 2-fold greater risk of declining function than non-Hispanic people in univariable analysis (RR 2.35**, *P* = 0.0018) [6].

CHARTER Longitudinal Findings

N = 436; Decliners *n* = 99; Stable *n* = 265; Improvers *n* = 72

Table 3. Univariable Predictors of Time to Neurocognitive Change (Decline or Improvement)

	Decline				Improvement			
Predictor	Risk	Reference	RR	*P* Value	Risk	Reference	RR	*P* Value*
Age	Younger	1 y[a]	1.02	.0937				
Sex	Female	Male	1.76	.0153				
Ethnicity	Hispanic	Non-Hispanic	2.35	.0018				
Education					Higher	1 y[b]	1.10	.0534
Premorbid IQ[c]					Higher	1 unit[b]	1.02	.0473
ART status[d]	Off ART	On ART	1.91	.0038				
CD4[d]	Lower	100 cells[a]	1.14	.0024				
Nadir CD4	Higher	100 cells[b]	1.09	.0833				
Plasma VL[d]	Higher	1 $\log_{10}$[b]	1.26	.0026	Lower	1 $\log_{10}$[a]	1.27	.0295
Det/Undet[d]					Undet	Det	1.53	.0876
CSF VL[d]	Higher	1 $\log_{10}$[b]	1.26	.0552	Lower	1 $\log_{10}$[a]	1.47	.0476
Det/Undet[d]	Det	Undet	1.50	.0790	Undet	Det	1.73	.0952
AST[d]					Lower	1 unit[a]	1.01	.0172
Protein total[d]					Lower	1 unit[a]	1.96	<.0001
Albumin[d]	Lower	1 unit[a]	2.36	<.0001				
HDL[d]	Lower	1 unit[a]	1.01	.0367				
HCT[d]	Lower	1 unit[a]	1.10	<.0001	Higher	1 unit[b]	1.06	.0244
Comorbidity[e]	Severe	Minimal	2.47	.0007				
Utox[d]	Positive	Negative	1.58	.0497				
LT cannabis Dx[d]					No	Yes	1.58	.0863
LT methamphetamine Dx[d]	Yes	No	1.81	.0148				
LT any substance Dx[d]					No	Yes	1.63	.0576
MDD (last 30 d)[d]	Yes	No	1.68	.0659				
LT MDD[d]	Yes	No	1.71	.0118	No	Yes	1.63	.0396
Beck (total)[d]	Higher	1 unit[b]	1.03	.0051				

Abbreviations: ART, antiretroviral therapy; AST, aspartate aminotransferase; Beck, Beck Depression Inventory II; CSF, cerebrospinal fluid; Det, detectable viral load; Dx, history of abuse or dependence diagnosis; HCT, hematocrit; HDL, high-density lipoprotein; IQ, intelligence quotient; LT, lifetime; MDD, major depressive disorder; RR, relative risk; SD, standard deviation; Undet, undetectable viral load; Utox, urine toxicology for drugs with central nervous system effects; VL, viral load.

[a] Higher/older.

[b] Lower.

[c] Measured using Wide Range Achievement Test, 3rd ed, Reading Standard Score (population mean = 100, SD = 15).

[d] Variable modeled in a time-dependent manner.

[e] Comorbidity rating [1, 2]: minimal/incidental, moderate/contributing, severe/confounded.

*$P < .10$ was considered significant.

Heaton et al., 2014

Comparing neurocognitive function in 84 Latinx adults and 42 non-Hispanic whites, Rivera Mindt found no significant differences between younger-than-50 members of those ethnic groups in global neurocognitive function or individual neurocognitive domains [4]. **But among 50-or-older study participants, Latinx people had significantly worse processing speed and learning, with trends toward worse global neurocognitive function and memory**. Effect sizes for these differences fell in the medium to large range.

Ethnocultural Groups & Cultural Heterogeneity

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Aging and HIV/AIDS: Neurocognitive Implications for Older HIV-Positive Latina/o Adults

Monica Rivera Mindt
Fordham University, Latino American Latino Studies Institute at Fordham University, Icahn School of Medicine at Mount Sinai
Caitlin Miranda, and Alyssa Arentoft
Fordham University
Desiree Byrd
Icahn School of Medicine at Mount Sinai
Jennifer Monzones,
Armando Fuentes, Francesca Arias, and Miguel Arce Rentería
Fordham University
Ana Rosario
Icahn School of Medicine at Mount Sinai
Susan Morgello
Icahn School of Medicine at Mount Sinai

Differential Cognitive Aging in Older Latinx People w/ HIV?

	Younger Group Mean (SD) n=82		Hypothesis 1		Older Group Mean (SD) n=44		Hypothesis 2	
	White n=20	Latina/o n=62	*F*	*d*	White n=22	Latina/o n=22	*F*	*d*
Global NC [a]	42.93 (7.66)	41.48 (7.20)	.09	.21	46.83 (5.92)	40.49 (6.47)	3.94+	1.02
Verbal Fluency [a]	46.13 (10.45)	42.94 (11.66)	.40	.28	50.23 (10.81)	41.70 (9.76)	.92	.83
Executive Function [a]	47.38 (13.29)	41.70 (10.02)	2.60	.52	47.91 (9.40)	42.07 (9.55)	1.32	.62
Processing Speed	48.15 (10.55)	46.54 (9.61)	.38	.16	48.56 (6.62)	44.05 (8.13)	4.09*	.61
Attention/ WM [a]	40.69 (8.04)	42.71 (7.79)	2.00	.26	46.12 (10.41)	41.50 (8.55)	2.66	.49
Learning [a]	38.63 (12.97)	34.73 (10.46)	.66	.35	46.00 (9.74)	35.24 (10.06)	4.30*	1.09
Memory [a]	38.08 (12.97)	37.19 (11.54)	.02	.07	47.00 (10.36)	34.98 (10.60)	3.84+	1.15
Motor	39.84 (10.32)	42.85 (11.23)	1.06	.27	41.68 (7.95)	41.26 (9.67)	.02	.05

Notes. WM= working memory; [a]controlled for WRAT-3 Reading subtest score within the Older group comparisons; *p<.05 level; +*p*=.05-.09

*Rivera Mindt et al. (2014)

A study of 82 HIV-positive Caribbean Latinx adults fluent in English demonstrated the potential impact of acculturation on cognitive function [7]. In this 65% male, 92% Puerto Rican group with a median age of 47, correlational and multivariate analyses both determined that **higher acculturation to US culture** (measured on the Abbreviated Multidimensional Acculturation Scale) was **associated with better global neuropsychological function, verbal fluency, processing speed, and attention/working memory**. That both linguistic *and* nonlinguistic cultural factors affected neuropsychological functioning among HIV-positive Latinx people, the researchers wrote, "further reinforces the theory that the influence of acculturation extends beyond the effects of language" [7].

Studying 134 US adults with HIV, 74% Latinx and 26% non-Hispanic Whites, these same investigators found that **average neuropsychological test raw scores were significantly higher among non-Hispanic whites than in Latinx people on measures of verbal fluency, attention/working memory, learning, memory, and processing speed** [8]. Latinx people had significantly higher raw scores for executive functioning.

Socioeconomic status correlated positively with verbal fluency, attention/concentration, learning, memory, processing speed, and executive functioning in bivariate analyses [8]. Estimated childhood socioeconomic status significantly predicted measures of verbal fluency, processing speed, and executive functioning. Linear regression analysis showed that controlling for socioeconomic status significantly attenuated the neuropsychological test score differences between Latinx people and non-Hispanic Whites, a finding confirming the importance of socioeconomic status in estimating neurocognitive function. Binary logistic regression singled out socioeconomic status as the only independent predictor of HAND.

AMAS U.S. American Scores & Average NC T-scores

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Psychology Press
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Multidimensional effects of acculturation on English-language neuropsychological test performance among HIV+ Caribbean Latinas/os

Alyssa Arentoft[1,2], Desiree Byrd[3,4], Reuben N. Robbins[5], Jennifer Monzones[1,6], Caitlin Miranda[1], Ana Rosario[1,7], Kelly Coulehan[1], Armando Fuentes[1], Kaori Kubo Germano[1], Erica D'Aquila[1], Jacob Sheynin[1], Felicia Fraser[1], Susan Morgello[3,8], and Monica Rivera Mindt[1,3,4]

[1]Department of Psychology, Fordham University, New York, NY, USA
[2]Department of Psychology, West Los Angeles VA Healthcare Center, Los Angeles, CA, USA

	Language Competence	*Cultural Competence*	*Cultural Identity*	*Overall U.S. American Identity*
Fluency	**.43****	0.14	**.23***	**.32****
Executive Function	0.20	-0.14	0.06	0.03
Processing Speed	**.29****	0.06	0.21	**.23***
Attention	**.30****	0.00	0.18	0.18
Learning	**.24***	0.09	0.10	0.17
Memory	0.21	0.09	0.14	0.18
Motor	0.12	0.07	0.11	0.12
Global NC	**.36****	0.09	0.21	**.26***

N = 82 HIV+' Latinx Abbreviated Multidimensional Acculturation Scale (AMAS; Zea et al., 2003); *p<.05; p<.001

Socioeconomic Status

Adult SES (Hollingshead) mediated the relationship between ethnicity w/ Learning & Memory.

Learning: ISP $R^2\Delta$=.08, β=.30, *SE* β=.09, p<.01, ethnicity ns

Memory: ISP $R^2\Delta$=.09, β=.34, *SE* β=.10, p<.01, ethnicity ns

The Clinical Neuropsychologist, 2015
Vol. 29, No. 2, 232–254, http://dx.doi.org/10.1080/13854046.2015.1029974
Routledge
Taylor & Francis Group

Socioeconomic Status and Neuropsychological Functioning: Associations in an Ethnically Diverse HIV+ Cohort

Alyssa Arentoft[1,2], Desiree Byrd[3,4], Jennifer Monzones[1,5], Kelly Coulehan[1], Armando Fuentes[1], Ana Rosario[1], Caitlin Miranda[1], Susan Morgello[3,6], and Monica Rivera Mindt[1,3,4]

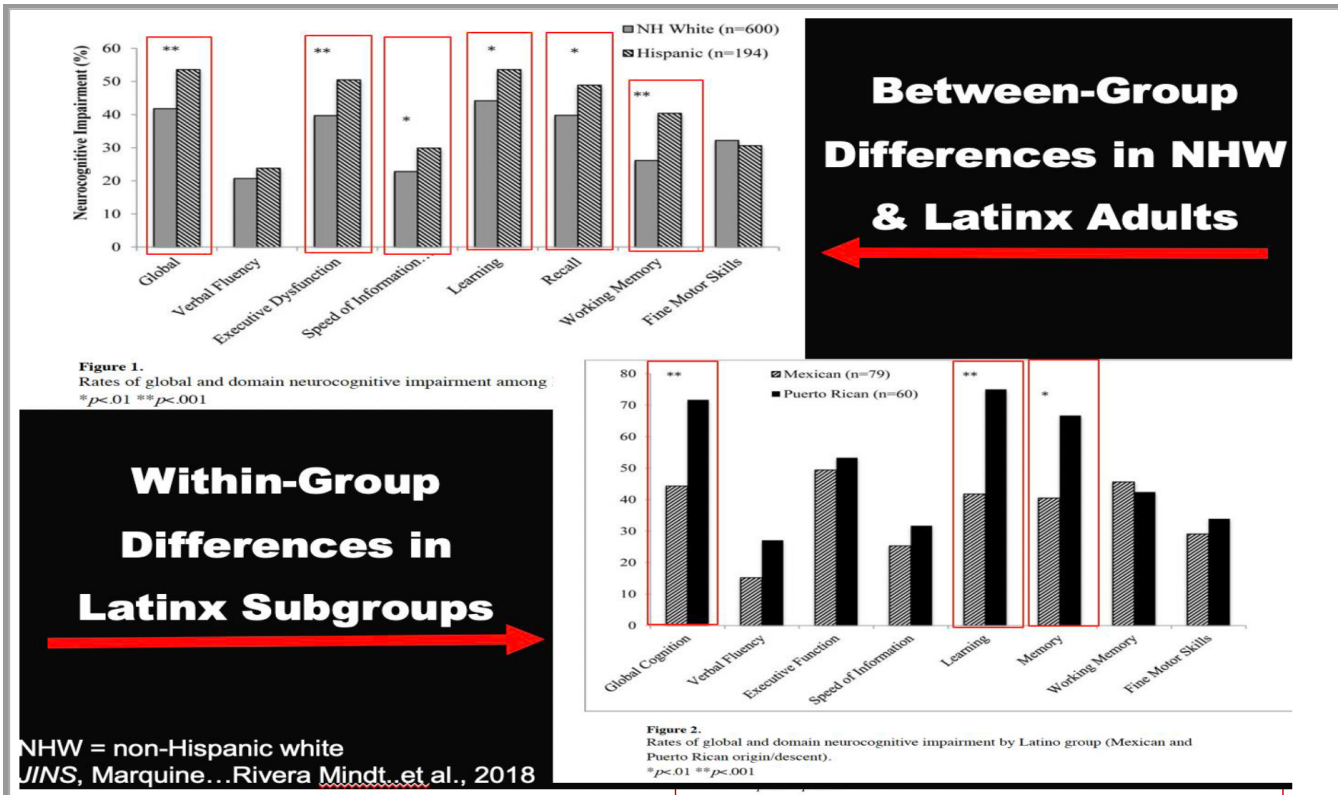
[1]Department of Psychology, Fordham University, Bronx, NY, USA
[2]Department of Psychology, California State University, Northridge, Northridge, CA, USA

Table 4. Correlations between SES estimates and neuropsychological raw scores (N = 128)

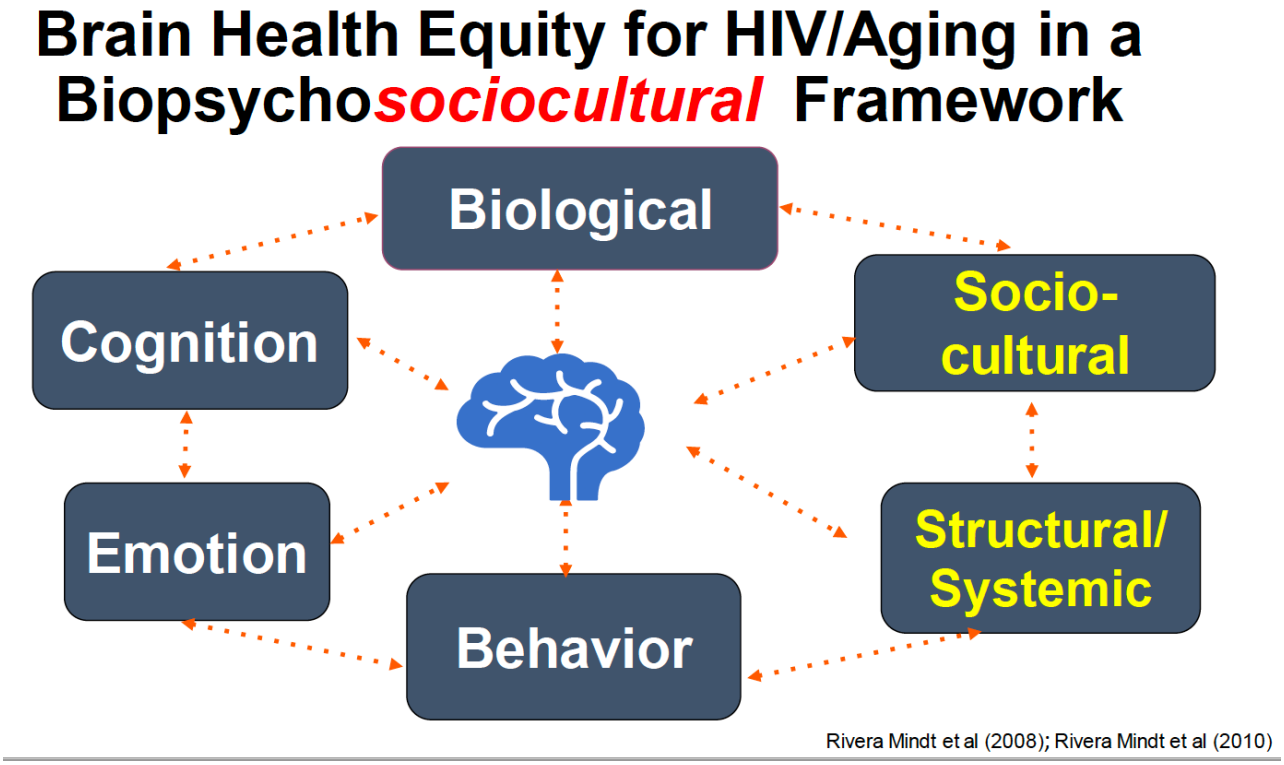
	Adult SES	Childhood SES
Verbal fluency		
COWAT (FAS) total	.27***	.19*
Animals total	.14	.31***
Attention/working memory		
WAIS-III LNS[b]	.31***	.14
PASAT[b]	.25**	−.02
Learning		
HVLT total[b,c]	.40***	.29***
BVMT total[c]	.20**	.13
Memory		
HVLT delay[c]	.39***	.15
BVMT delay[c]	.21**	.13
Processing speed		
WAIS-III digit symbol	.18**	.09
WAIS-III symbol search	.26***	.16
Trails A[a,b]	−.15*	−.22**
Executive functioning		
WCST perseverative responses[a]	−.03	.03
WCST perseverative errors[a]	.13	.25**
Trails B[a]	−.22**	−.12
Motor		
Grooved Pegboard—dominant hand[a,b,d]	−.01	−.06
Grooved Pegboard—non-dominant hand[a,e]	.06	−.05

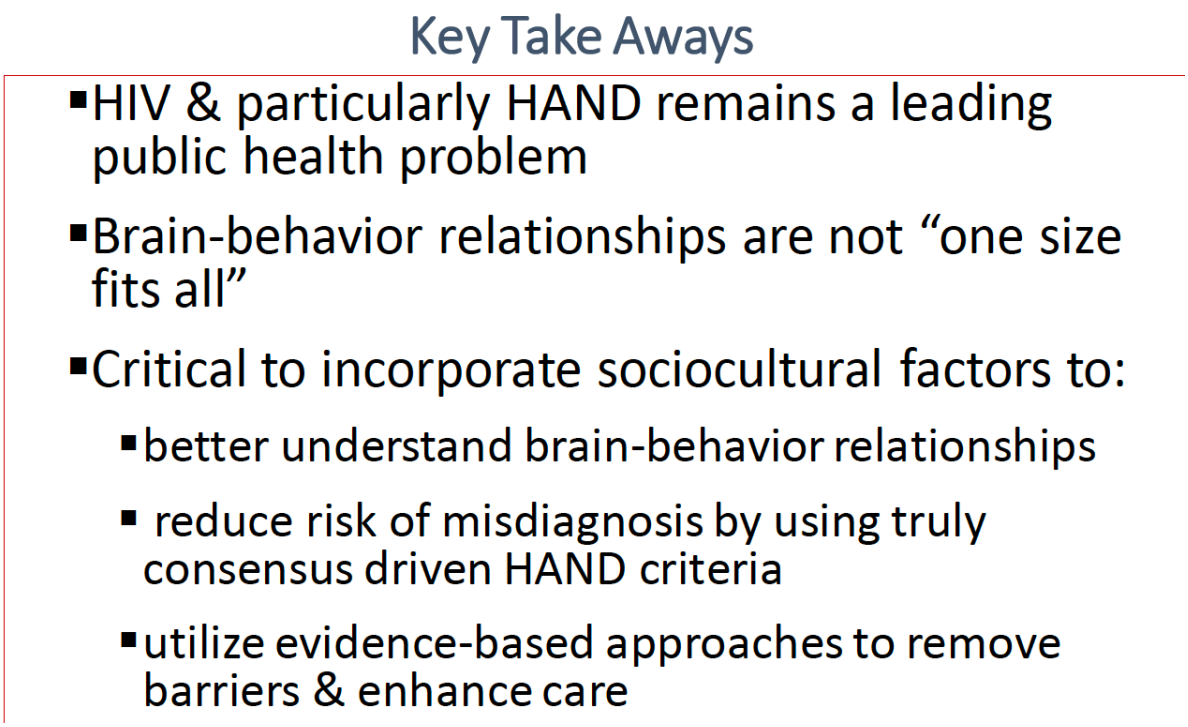
[a]log transformed, after controlling for BDI.
[b]BDI.
[c]Substance abuse/dependence.
[d]Age.
[e]Gender.
*p < .10; **p < .05; ***p < .01.

The CHARTER team used baseline data from their 6-center study to compare neurocognitive function in 194 Latinx adults (average age 41.3, 78% men) and 600 non-Hispanic Whites (average age 43.1, 88% men) [3]. C**ompared with Whites, Latinx cohort members had a higher rate of global neurocognitive impairment (54% vs 42%) and worse HIV-associated impairment in executive function, learning, recall, working memory, and processing speed.** After statistical adjustment for significant variables, Latinx people had almost 60% higher odds of global neurocognitive impairment (odds ratio 1.59, 95% confidence interval 1.13 to 2.23, P < 0.01). Among Latinx groups, a **higher proportion of Puerto Ricans than Mexicans had impaired neurocognition (71% vs 44%).**



Rivera Mindt argued that consistent findings of health disparities between Latinx (and other marginalized groups) and non-Hispanic whites underscores the need for Brain Health Equity—"the fair distribution of brain health determinants, outcomes, and resources within and between segments of the population, regardless of social standing."





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Aging and Cardiometabolic Comorbidities Among Individuals With HIV

John Koethe, MD, Vanderbilt University School of Medicine, Nashville, Tennessee
NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

Because so many HIV-related and non-HIV factors can contribute to cardiometabolic disease risk in people with HIV, Vanderbilt University's John Koethe told workshop attendees, easing the cardiometabolic disease burden requires work on several fronts: traditional risk factors, gradual physiologic alterations, direct antiretroviral therapy (ART) effects, and direct viral and immunologic effects.

The HIV community has known for decades that cardiometabolic disease rates climb faster with age in people with than without HIV

[1,2]. Earlier, more effective, and less toxic ART has towed a raft of benefits in its wake, Koethe noted, but normal cardiometabolic disease risk is not among them. One model of multimorbidity among antiretroviral-treated people with HIV in the United States projects that in 2030, only 28% of people will have no physical comorbidities, 27% will have 1, and 45% will have two or more [3].

Koethe posited four kinds of short- and long-term factors that can contribute to cardiometabolic comorbidities:

1. Traditional risk factors such as diet, smoking, and genetics, which range from short-term modifiable factors to immutable factors
2. Gradual physiologic alterations such as weight gain and fat partitioning, which tend to be long-term and probably only partially modifiable
3. Direct ART effects, such as tenofovir DF's impact on bones, which are modifiable and partially to fully reversible
4. Direct viral and immunologic effects, which have a largely unknown modification and reversal potential

Traditional risks, altered physiology, ART effects, and viral factors may interact in a complex web and, despite reasonable therapies, could culminate in cardiometabolic diagnoses like atherosclerotic cardiovascular disease (ASCVD) (**figure**).

Vanderbilt University's John Koethe proposed a web of risk factors for cardiometabolic comorbidities in people with HIV, in this example culminating in atherosclerotic cardiovascular disease (ASCVD).

Weight gain remains a fraught and elusive variable in the evolution of cardiometabolic comorbidities, one that deserves particular attention in people with HIV infection because of ART's impact on weight. An illuminating case-control study in the Kaiser-Permanente healthcare system matched 8256 people with HIV to 129,966 HIV-negative people by age, sex, race/ethnicity, clinic, and year [4]. People with HIV started follow-up with a lower body mass index (BMI) than HIV-negative controls (25.8 vs 28.7 kg/m2). But through 12 years of follow-up, the HIV group gained BMI more than 3 times faster than controls (0.22 vs 0.06 kg/m2 per year).

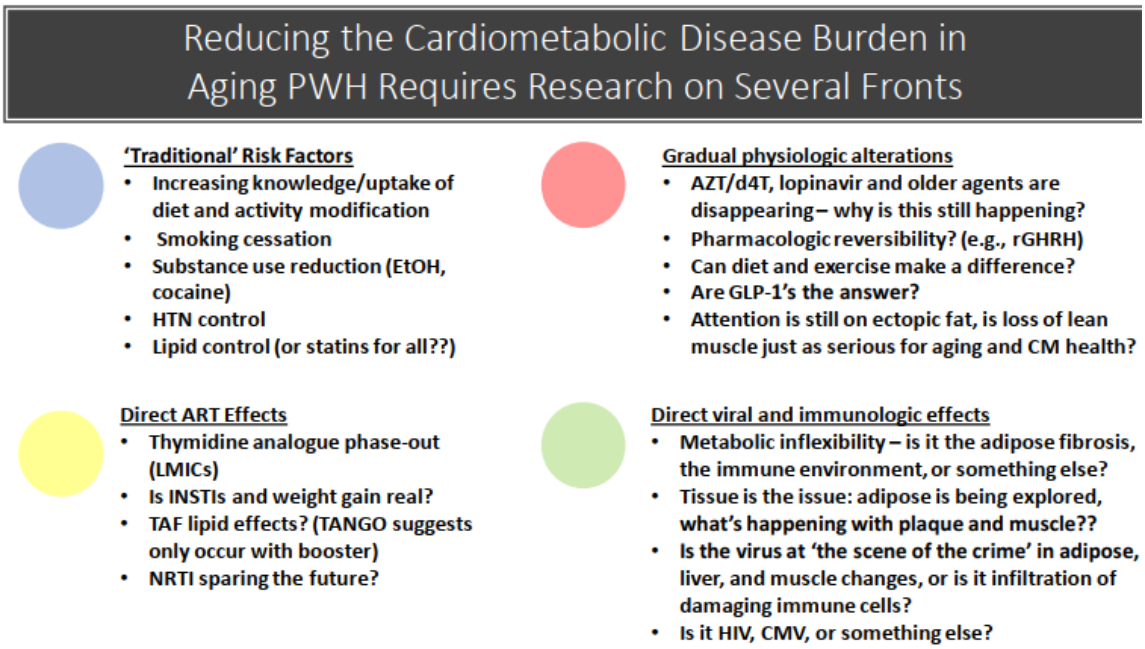
Koethe argued that "weight gain really does matter" clinically in people with HIV, citing as evidence analyses of the D:A:D cohort (in which a 1- to 2-unit BMI upticks conferred a significantly higher risk of a new diabetes diagnosis regardless of pre-ART weight [5]) and the VACS cohort (in which incremental weight gains in the first year of ART boosted diabetes risk almost 2-fold compared with HIV-negative controls [6]).

Analysis of other studies led Koethe to the following conclusions:

- HIV reshapes adipose tissue compartments over time.
- Cardiometabolic disease risk is affected by *where* weight is regained on ART.
- Subcutaneous adipose tissue (SAT) T-cell profile changes with progressive glucose intolerance in people with HIV.
- Changes in the SAT macrophage profile promote fibrosis and ectopic fat deposition in people with HIV.

Koethe underlined the scarcity of "data on the immunologic and viral environment of coronary plaque, despite major alterations in many of the component cell types in long-term HIV."

He closed with specific suggestions and lingering questions on the four fronts that must be addressed to ease cardiometabolic disease burden in people with HIV (**table**).



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Optimizing HIV and Aging Care: Gaps in Current Clinical Practice

Jacob Walker, MD, University of Colorado Anschutz Medical Campus, Aurora, Colorado
NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

HIV-related problems rarely emerged as gaps in care for older people with HIV infection, according to analysis of two integrated HIV-aging clinics and other data by Jacob Walker of the University of Colorado. Rather, providers believe the two areas of greatest need for HIV-aging clinics are geriatric syndrome management and care coordination.

The University of Chicago's HIV and Aging Clinic featured providers dually trained in HIV infection and geriatric medicine. Clinic enrollees were offered the option of a geriatrics consultation or transfer of HIV care. The HIV and Aging Clinic, which lasted 2 years, got funded as an extension of the University of Chicago's geriatrics clinic.

Clinic attendees had to be at least 50 years old. At a median age of 69 years, clinic attendees had a high geriatric syndrome burden marked by polypharmacy (use of multiple non-HIV drugs), cognitive impairment, osteoporosis, and functional decline and falls.

Walker listed 5 successes at the Chicago HIV and Aging Clinic:

- High patient interest

- Dementia diagnosis and management
- Excellent pharmacy support
- Insurance and drug coverage support
- Nursing home care coordination

Barriers to care involved durable medical equipment and home health services, difficulty getting referrals to dementia specialists, and getting patients to primary care/geriatrics providers.

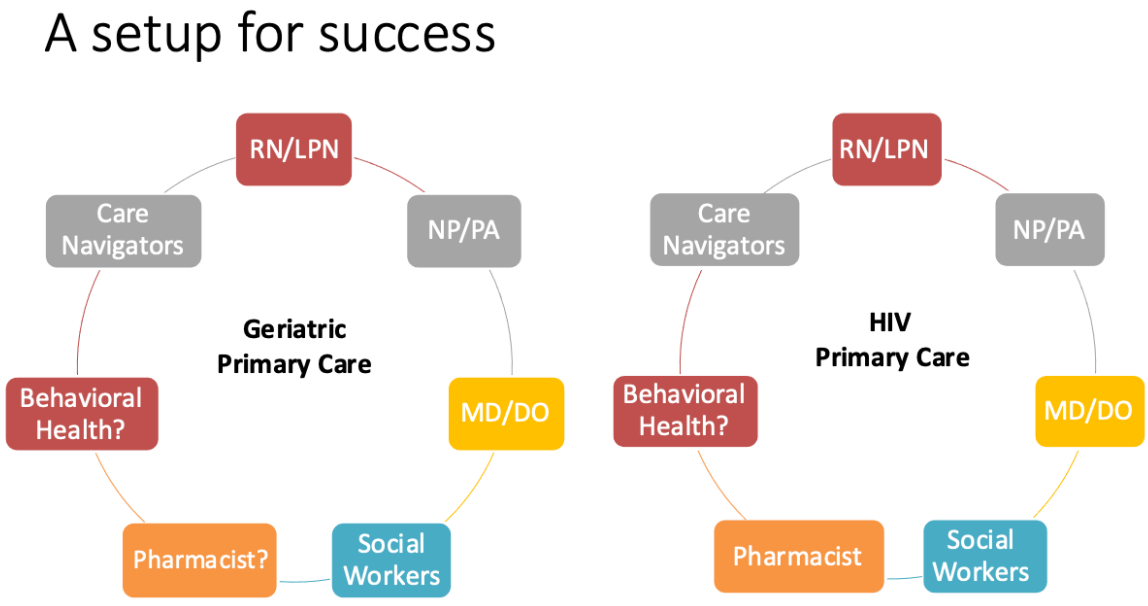
At the University of Colorado's Anschutz Medical Campus, a Positive Aging *Consultation* evolved into a Positive Aging *Clinic*—both for HIV-positive people 50 or older. The Positive Aging Consultation began with a geriatrics clinic visit and medication review by a pharmacist. Problems with this approach were referral barriers, provider billing barriers, and people with HIV not liking the transfer to a different clinic, even though it was in the same building as the HIV clinic.

The Positive Aging Clinic features a geriatrician working *in* the HIV clinic as a consultant or a primary HIV provider. Visits last 60 minutes for new patients and 30 minutes for returning patients. Early problems include initial billing barriers. Providers listed geriatric syndrome management and care coordination as areas of greatest need. But Walker noted that the clinic population is growing fast.

Before and during the COVID pandemic, people with HIV older than 50 reported several barriers to care: transportation, wait times, communication with their provider, and a need for help connecting to other resources [1]. Clinic users noted that access to telehealth helped them more than care navigators, home visits, or longer appointment times.

Walker listed provider-reported barriers to care of 50-or-older people with HIV from a 2018 survey of 226 American Academy of HIV Medicine members, 54% of them MDs or DOs, 27% nurse practitioners or physician assistants, and 19% PharmDs [2]. Only 14% of these providers felt strongly prepared to care for older people with HIV, though 42% rated themselves somewhat prepared. The rest were neutral in preparedness (15%), somewhat unprepared (25%), or strongly unprepared (4%). These HIV providers picked HIV-associated neurocognitive disorder (HAND) and geriatric symptom screening as topics of greatest interest, followed by polypharmacy, palliative care, frailty, and cardiovascular disease.

Walker proposed that staffing for a geriatric primary care HIV clinic would do well to mirror that of a traditional HIV primary care practice (**figure**).



Some authorities believe that geriatric primary care for people with HIV should take as its model standard HIV primary care.

Opportunities to improve geriatric HIV care abound, Walker suggested, including establishing advance care planning, screening for osteoporosis, cognitive testing in the primary care office, setting up physical therapy and exercise programs, smoothing transitions across care settings, improving communication and access to urgent care, integrating specialty services (including dental, vision, and

hearing), and promoting recruitment of older people with HIV for research.

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Aging Concerns, Serious Illnesses, and Caring for Vulnerable Older Patients

William Dale, MD, PhD, City of Hope, Duarte, California
NIH HIV and Aging Research Workshop, September 5, 2023

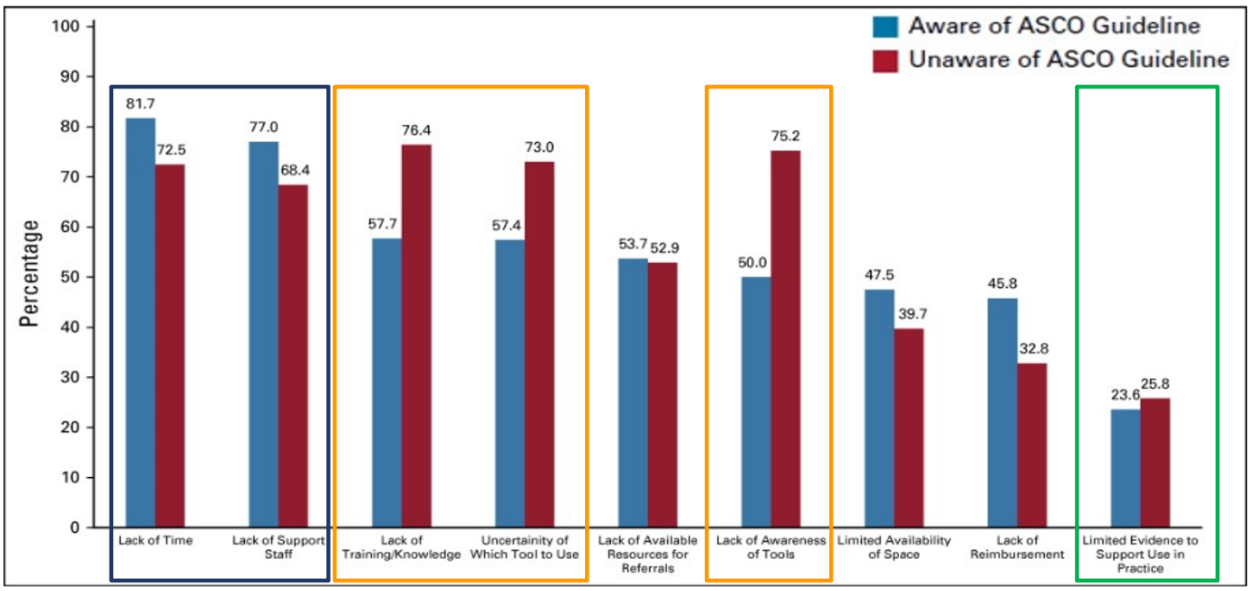
(Reported by Mark Mascolini for NATAP)

William Dale, Director of the Center for Cancer and Aging at the City of Hope in Duarte, California, offered HIV-centric aging experts and advocates a view of concerns about caring for older people with cancer—and two initiatives that address these concerns: (1) the American Society of Clinical Oncology (ASCO) guidelines and updates on Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy, and (2) the Cancer and Aging Research Group (CARG), which aims to link aging and cancer researchers with the goal of "designing and implementing clinical trials to improve the care for vulnerable older adults."

In May 2018 ASCO released its first evidence-based advice on improving care in older people with cancer [1]. These guidelines reflected the deliberations of a national panel of experts in cancer and aging proposing a new standard of care for people 65 or older receiving chemotherapy. The document stressed that " **geriatric assessment** should be used to identify vulnerabilities or aging-associated impairments that are not routinely captured in oncology." At the time fewer than 25% of people with cancer who were 65 or older got such assessments. ASCO most recently updated the guidelines in July 2023 [2].

A 2021 survey of 1277 oncologists found that 57.3% of respondents never or rarely did geriatric assessments [3]. Only 14.1% did such assessments most of the time and 6.7% always. Yet 25.9% of oncologists always assessed older patients differently from younger people, 37.0% did so most of the time, and 27.8% did so some of the time. Among respondents who assessed older people differently from young people, 69% did so without a formal assessment and 29% with a formal assessment. Only about half of oncologists caring for older adults, 52%, voiced awareness of the ASCO guidelines. Providers aware of the guidelines were 2 to 4 times more likely to conduct a geriatric assessment.

Among respondents either aware or unaware of the ASCO guidelines, reasons most cited for not following ASCO guidelines in practice were lack of time (81.7% aware of guidelines, 72.5% unaware), lack of support staff (77.0% aware, 68.4% unaware), lack of training or knowledge (57.7% aware, 76.4% unaware), and uncertainty about which tool to use (57.4% aware, 73.0% unaware) (**figure**). Among oncologists unaware of ASCO guidelines, 75.2% cited lack of awareness of tools as a reason for not applying ASCO guidelines (**figure**).



A survey of 1277 oncologists in 2021 found lack of time, support staff, and training the most-cited reasons for not applying ASCO guidelines for geriatric assessment in practice.

To make it easier for clinicians to implement ASCO-endorsed assessment of geriatric patients, ASCO developed an Action Chart for Practical Geriatric Assessment [4]. Most of the domains addressed—such as physical function, functional status, social support, and comorbidities—apply equally well to aging people with HIV.

To plan and conduct clinical trials aimed at improving care of aging cancer patients, clinical researchers at the City of Hope founded the Cancer and Aging Research Group (CARG) in November 2006 (https://www.mycarg.org/) From its original 10 members, CARG has grown to include more than 620 international members at 75 institutions in 22 countries. The group's primary goal is to connect researchers on aging and cancer to devise and run clinical trials addressing improved care for older adults with cancer. That goal has four facets—increasing high-impact research, developing effective interventions, mentoring the next generation of aging and cancer researchers, and widely disseminating findings to inform clinical practice.

Since its inception, CARG has (1) received and addressed about 250 research inquiries, (2) awarded 9 pilot grants for a total $175,000, (3) fostered mentoring through 87 CARG Buddy Program matches, (4) published 118 articles, and (5) received $25 million in grant funding for CARG members using CARG.

Dale encouraged all to join CARG if they meet a single requirement—the desire to help vulnerable older adults. Inquiries about joining CARG may be sent to https://www.mycarg.org/?page_id=150 or to CARinG@coh.org.

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Targeting Cellular Senescence to Prevent or Alleviate Frailty Among Older Adults With HIV

Mary Clare Masters, MD, Northwestern University Feinberg School of Medicine, Chicago, Illinois
NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

Despite improvements in the lifespan of people with HIV infection, noted Northwestern University's Mary Clare Masters, they still have a reduced *healthspan* compared with the general population because they endure earlier and more frequent noninfectious comorbidities, as well as higher rates of geriatric syndromes and multimorbidity.

Plentiful evidence indicates that aging is a major risk factor for most chronic diseases, including heart disease, stroke, cancer, emphysema, pneumonia, diabetes, kidney disease, and Alzheimer's disease. That age remains the greatest risk for so many conditions gave rise to the field of geroscience, which rests on the hypothesis that "therapeutically targeting fundamental aging biology will have a significantly greater impact on overall human disease than treating individual diseases."

Research on the biology of aging, Masters explained, led to recognition of hallmarks or *pillars* of aging that drive the physiology of aging, including cellular senescence, impaired proteotasis (protein regulation within cells), and altered metabolism. Aging pillars linked to accelerated aging in people with HIV infection are advanced epigenetic age, declining telomere length, and mitochondrial dysfunction. Recent research suggests these aging hallmarks are not independent of each other but, rather, intimately linked, a state suggesting that improving one hallmark will improve others.

Progress in HIV geroscience would be furthered by answering a critical question: How much inflammaging driven by cellular senescence overlaps with chronic inflammation in HIV infection. (Inflammaging is an age-related rise in proinflammatory markers in blood or tissue [1].) Geroscience supports the premise that interventions aimed at biological aging processes will also exert a positive impact on age-associated morbidities attributed to HIV, Masters said.

Stressors like oncogenic mutations, radiation, chemotherapeutic drugs, DNA damage, and metabolic insults can cause cellular senescence. Piling up in aging tissues, senescent cells feature cell-cycle arrest, resistance to apoptosis, and higher production of beta-galactosidase and p16(INK4a). Senescent cells secrete pro-inflammatory, pro-apoptotic, and pro-fibrotic compounds, which yield a senescence-associated secretory phenotype (SASP).

Senescence experts have a name for pharmacologic agents that target cellular senescence: senotherapeutics. These agents can be either senolytics (selective killers of senescent cells) or senomorphics (senescent phenotype modulators). Some work suggests that senotherapeutics may affect HIV reservoirs.

Transplanting small numbers of senescent cells into young mice caused persistent physical dysfunction and spread cellular senescence to other tissues [2]. Transplanting even fewer senescent cells into older mice had the same effects and also shortened survival. Giving dasatinib and quercetin (D + Q) to mice transplanted with senescent cells eased physical dysfunction and increased post-treatment survival by 36%. Dasatinib is a tyrosine kinase inhibitor licensed for certain leukemias. Quercetin is an over-the-counter flavonoid antioxidant.

The first-in-human senolytics trial gave D + Q (100 + 1250 mg daily) to 14 people with idiopathic pulmonary fibrosis and to 9 with diabetic kidney disease [3]. In people with pulmonary fibrosis, treatment for 3 weeks improved physical function (walk distance, gait speed, chair-stand) and yielded a trend toward some lower SASP measures. In people with diabetic kidney disease, D + Q lowered expression of senescence markers in adipose tissue and reduced SASP factors. D + Q did not improve pulmonary function, lab chemistries, or frailty index. Masters added that other studies of D + Q in humans are now underway, but they exclude people with HIV infection.

ACTG protocol A5426, the first trial of senolytics in people with HIV, will randomize 40 people to D + Q (100 + 1250 mg daily) for 2 days every 14 days for 12 weeks or to placebo. Participants must be taking antiretrovirals for at least 2 years and diagnosed with HIV for at least 10 years. They must be at least 50 years old, have a viral load below 200 copies, be frail or prefrail according to the Fried frailty phenotype, and have a life expectancy of at least 2 years. The primary physical endpoint is change in gait speed at 12 weeks.

Masters proposed that senolytics "are a promising geroscience-guided intervention for impaired physical function and frailty in people with HIV."

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Trained Immunity Likely Exacerbates Age-Related Comorbidities in People With HIV

Nick Funderburg, PhD, Ohio State University College of Medicine, Columbus, Ohio
NIH HIV and Aging Research Workshop, September 5, 2023

(Reported by Mark Mascolini for NATAP)

Ohio State University's Nick Funderburg asked what mechanisms drive development and progression of age-related comorbidity in people with HIV. Whether the blame lies with mechanisms unique to HIV or with accelerated versions of the usual aging process remains uncertain. Perhaps, he suggested, certain inflammatory, cellular, lipid, and other profiles linked to specific comorbidities hold the key to explaining comorbidity mechanisms in people with HIV.

Funderburg proposed that trained immunity* probably exacerbates age-related comorbidities in people with HIV. As an example of age-related comorbidities in people with versus without HIV, he offered coronary artery calcium (CAC) scores as a marker of cardiovascular disease. Prior research found that CAC scores and arterial age are directly related to monocyte activation and inflammation in a multiethnic group in the US general population [1]. CAC scores were also positively related to chronological age in this general-population group ($r = 0.713$, $P < 0.001$). People with HIV, Funderburg noted, have higher CAC scores and older arterial ages (determined by CAC, age, sex, total and HDL cholesterol, smoking, and hypertension) than demographically similar people without HIV. Arterial age can be 20 years older than chronological age in people with HIV, whereas HIV-negative people have similar arterial and chronological ages.

* "**Trained immunity** describes the immunological process by which innate immune cells acquire immunological memory. After exposure to certain stimuli, innate immune cells can adjust their response to subsequent insults, resulting in an enhanced response to previously encountered infectious agents." ·

Ochando J, Mulder WJM, Madsen JC, Netea MG, Duivenvoorden R. Trained immunity — basic concepts and contributions to immunopathology. Nature Reviews Nephrology. 2023;19:23-37. https://www.nature.com/articles/s41581-022-00633-5

"The de facto innate immune memory that is trained immunity is different from the immune memory in **adaptive immunity**. First, trained immunity is dominantly mediated by myeloid cells, whereas adaptive immune memory is a unique characteristic of lymphocytes, mainly T cells and B cells."
Hu Z, Lu SH, Lowrie DB, Fan XY. Trained immunity; a yin-yang balance. Wiley.com. Online library. https://onlinelibrary.wiley.com/doi/pdf/10.1002/mco2.121

An array of biological mechanisms may influence inflammation and promote age-related comorbidities in HIV populations, Funderburg reminded attendees: microbial translocation, HIV products, copathogens, antiviral therapy toxicities, altered lipid profiles, and lifestyle factors. All these variables may contribute to monocyte/macrophage activation. Trained immunity, he proposed, may drive several inflammatory conditions, including aging. Viral, bacterial, and fungal products, proinflammatory lipids, and myeloid cells could all contribute to this process.

Recent research showed that immune cells from people with versus without HIV infection pump out higher levels of inflammatory cytokines in responding to microbial products [2]. Funderburg [3] and several other researchers confirmed different responsiveness to toll-like receptor (TLR) ligands (bacterial products) [4] in cells from people with versus without HIV. Other work showed that monocyte-derived macrophages (MDMs) from people with HIV have different patterns of gene expression than MDMs of HIV-negative people [5]. And in people with HIV, MDMs are activated, proinflammatory, and potentially proatherogenic. Gene patterns after exposure to TLR ligands also differ between people with and without HIV.

Funderburg noted that research by Mark Cameron and Cheryl Cameron at Cleveland's Case Western Reserve University determined that myeloid cell proportions and CD14 gene expression in reactive oxygen intermediates (ROIs) are higher in people with than without HIV. Compared with ROIs of people without HIV, those of people with HIV differ in gene and pathway expression in arterial tissue samples. Differential pathway expression may involve innate immune activation, mitochondrial dysfunction, wound healing, senescence, and antioxidants.

Finally, Funderburg reviewed research in Uganda showing that adolescents who acquired HIV perinatally have gene expression signatures of trained immunity.

Funderburg concluded his talk with a question rather than a conclusion or hypothesis: Is trained immunity exacerbated/altered in

aging people with HIV and what interventions may reduce this process? He addressed a broader question—what can be done about increased age-related comorbidities in people with HIV?—by posing three components of this question, and then by suggesting further questions raised by these three component questions (**table**):

What can be done about increased age related comorbidities in PWH?

How do clinicians best identify individuals at elevated risk for comorbidities or multi -morbidity?

- Traditional risk factors?
- Biomarker/immune profiles? Blood versus tissues?
- Best imaging/measurement techniques?

What are the mechanisms driving comorbidity development and progression?

- Unique mechanisms or accelerated versions of aging processes?
- Are certain inflammatory, cellular, lipid, etc. profiles associated with specific comorbidities which may provide insight into mechanisms?

Intervention strategies?

- Smoking cessation, dietary and/or exercise interventions?
- Polypharmacy/ drug:drug interactions
- Modulate individual "drivers" or common pathways they use?

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