

HIV, Aging, Exercise, the Brain, and a Relentless Epigenetic Clock

Report on the 8th International Workshop on HIV & Aging, 2-3 October 2017, New York

Written by Mark Mascolini

The 8th International Workshop on HIV & Aging offered reports on new research in three broad areas—exercise and aging, the central nervous system and aging, and epigenetic (or biological) aging. Under those broad umbrellas, attendees heard new data from rigorously planned studies on metformin suppression of cytomegalovirus, cognitive impairment in HIV-positive people over 60, declining lean mass in adults aging with HIV, step count as a predictor of health outcomes in an older HIV group, and an array of other topics.

EXERCISE AND AGING

Exercise can have profound impacts on the physical and psychological health of aging people with and without HIV, the University of Colorado's Wendy Kohrt reminded HIV & Aging Workshop attendees.¹ But low proportions of older people report physical activity as judged by the 2008 Physical Activity Guidelines for Americans.² Among people 65 and older, about 20% rate themselves highly active, 10% claim being sufficiently active, 20% admit being insufficiently active, and 50% say they are inactive.

Aiming to map molecular changes that occur in response to physical activity and relate these changes to benefits of such activity, Kohrt and collaborators launched MoTrPAC, the Molecular Transducers of Physical Activity Consortium.³ Under the aegis of the National Institutes of Health, the analysis will involve 2400 sedentary adults and 300 sedentary children randomized to start exercise or not and compared with 300 already highly fit adults.

At the HIV & Aging Workshop, attendees heard fresh findings on how several aspects of physical activity—or lack of physical activity—affects people aging with HIV infection, including studies of lean mass loss, step count as a health outcome predictor, and fatigue and frailty with HIV.

Lean mass drops steadily over 5 years in large HIV cohort

Appendicular lean mass declined steadily in both women and men with HIV who had repeat DXA scans through a median follow-up of 4.6 years.⁴ Regression modeling linked per-year use of tenofovir disoproxil fumarate (TDF) or integrase inhibitors to lower lean mass. But that analysis also linked longer overall antiretroviral therapy (ART) duration to greater lean mass.

Lean mass wanes with normal aging, and research ties significant loss to functional decline, falls, and mortality.⁵ To get an understanding of lean mass trajectories in people aging with HIV, and

to identify predictors of lean mass, collaborators from the University of Texas Health Science Center in Houston, the Modena HIV Metabolic Clinic, and other centers conducted this longitudinal analysis.

The study involved Modena HIV Metabolic Clinic patients who had DXA scans every 6 to 12 months for up to 10 years. The researchers charted changes in appendicular lean mass for the whole group and separately for women and men. They used mixed-effects regression models to pinpoint variables significantly associated with lean mass.

The study group included 839 women and 1759 men who had 2 or more DXA scans during the study period. The cohort had a median age of 44 years (35% of women and 46% of men older than 45), a median body mass index of 21.6 kg/m² for women and 23.5 kg/m² for men, and respective median pack-years smoking of 10.0 and 12.5. The study group had an HIV diagnosis for a median of 14 years and a median CD4 count of 528 cells/mm³. Two thirds of women (69%) and more than half of men (58%) reported no physical activity, while about one quarter of each group reported moderate activity and the rest vigorous activity.

Median baseline appendicular lean mass stood at 16.9 kg in women and 24.8 kg in men. Through a median 4.6 years of follow-up, lean mass fell by an average 231 g yearly in women and 322 g yearly in men. Lean mass declined steadily throughout follow-up in both women and men (**Figure 1**), regardless of age. The researchers noted that these losses exceed expected age-related loss in the general population.

Results

- ALM consistently decreased over the study period in both sexes
 - women: -231g per year, standard deviation [SD] 640g
 - men: -322g per year, SD 906g

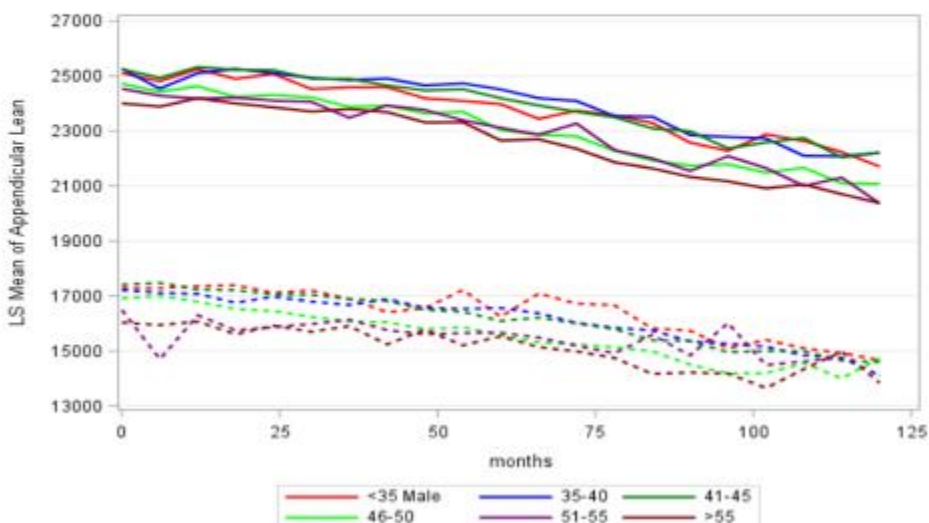


Figure 1. Through a median follow-up of 4.6 years, DXA-measured appendicular lean mass fell steadily in women and men with HIV at a rate faster than seen in the general population. (Source: Jordan Lake, University of Texas Health Science Center in Houston, and colleagues.⁴)

Mixed-effects modeling identified seven variables associated with less appendicular lean mass:

- Female sex: -4.5 kg
- Age older than 50 years: -1.05 kg
- Less than intensive regular physical activity: ≥ -419 g
- Tobacco use: -6.7 g per pack-year
- HIV RNA above 50 copies/mL: -270 g
- TDF use: -30 g per year
- Integrase inhibitor use: -0.6 g per year

Five factors were associated with greater appendicular lean mass:

- Increasing body mass index: 521 g per kg/m^2
- Metabolic syndrome: 151 g
- Male hypogonadism/postmenopausal status: 298 g
- Vitamin D insufficiency: 282 g
- Longer ART duration: 21 g per year

In a sex-stratified analysis, the associations between integrase inhibitor use or longer ART duration and lean mass lost significance in women. In an analysis limited to men, two additional factors were associated with lower appendicular lean mass: a history of AIDS wasting (-535 g), and CD4 nadir below 200 cells/ mm^3 (-269 g).

The researchers concluded that appendicular lean mass in this large HIV cohort declined steadily over time “at rates greater than expected for age-related change and across all age groups.” They encouraged further study of the association between TDF or integrase inhibitors and lower appendicular lean mass but did not speculate about mechanisms. The impact of integrase inhibitors on lean mass and weight appears complicated. A Vanderbilt University analysis of people switching from Atripla (single-tablet efavirenz/TDF/emtricitabine) to an integrase inhibitor, presented at IDWeek 2017, found that those who switched gained significantly more weight than those who stayed with Atripla, especially those who switched to single-tablet dolutegravir/abacavir/lamivudine.⁶

Step count predicts multimorbidity and frailty in aging HIV group

Step count recorded by a wearable fitness tracker predicted multimorbidity and frailty more consistently than demographic or HIV-related variables in a 114-person analysis of aging adults.⁷ The study also identified a strong trend linking step count to disability.

Plentiful research ties low physical activity to adverse health outcomes in people with HIV and the general population. To determine whether a measure of physical activity predicts such outcomes in an aging HIV population, Modena HIV Metabolic Clinic researchers and collaborators analyzed step count and other potential predictors in an older HIV population.

From October 2016 to June 2017, the investigators invited 175 HIV-positive people older than 50 years to join the study. They excluded 50 people (29%) without the computer literacy needed to participate. Eleven others declined for different reasons, leaving 114 study participants. Enrollees came from the My Smart Age With HIV (MYSAWH) cohort, which recruits people in Italy, Spain, Australia, and Hong Kong.

The researchers developed a Web application to record patient-related data, including step count collected by a fitness tracker (Garmin Vivofit2) intended to be worn 24 hours a day. Participants received instruction on using the app, and a dedicated online “coach” kept in touch with patients and answered questions. Besides step count recorded in the month after study entry, other covariates analyzed were age, waist circumference, and traditional HIV variables (including current and nadir CD4 count). The investigators used multivariable logistic regression analysis to assess the impact of those variables on three outcomes: multimorbidity (3 or more common comorbidities), frailty (assessed by a 37-variable index⁸ validated in the Modena HIV Metabolic Clinic), and disability determined by Instrumental Activities of Daily Living (IADL).

Ninety of 114 participants (79%) were men. Age averaged 56.7 years, waist circumference 92.1 cm, body mass index 24.4 kg/m², current CD4 count 690.5 cells/mm³, and nadir CD4 count 180 cells/mm³. Everyone was taking antiretroviral therapy, and all but 2 study participants had a viral load below 40 copies/mL. The researchers found that 19 participants (16.7%) had multimorbidity, 5 (4.4%) met frailty criteria, and median number of IADL deficiencies stood at 1.

Logistic regression analysis determined that each additional 1000 steps daily was associated with lower odds of multimorbidity (adjusted odds ratio [aOR] 0.72, 95% confidence interval [CI] 0.57 to 0.88, $P < 0.01$) (**Figure 2**) and lower odds of frailty (aOR 0.87, 95% CI 0.77 to 0.98, $P = 0.03$). More daily steps was also associated with lower odds of IADL disability, but that association stopped short of statistical significance (aOR 0.72, 95% CI 0.46 to 1.02, $P = 0.1$).

Results: Logistic regression analyses for prediction of MM

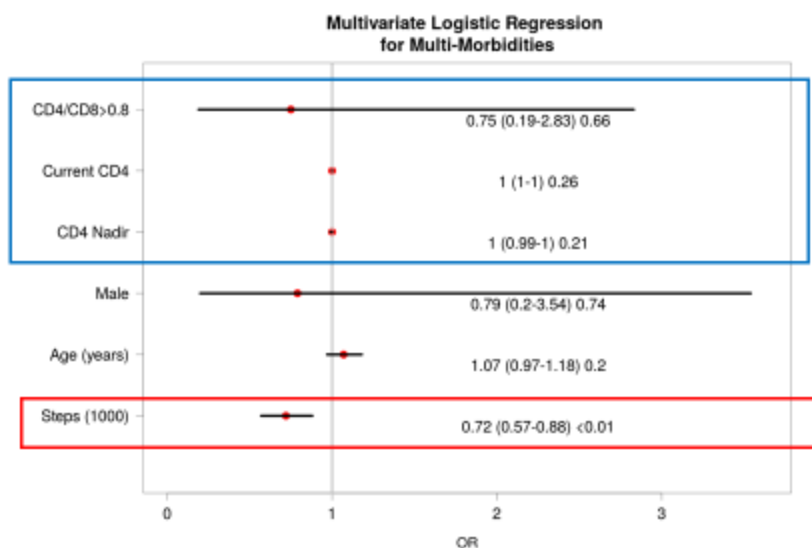


Figure 2. Step count recorded by a wearable fitness tracker predicted multimorbidity in a 4-country group of HIV-positive people older than 50 years. CD4 variables, gender, and age did not predict multimorbidity in this logistic regression analysis. (Source: Giovanni Guaraldi, University of Modena and Reggio Emilia, and colleagues.⁷)

In contrast, current or nadir CD4 count, gender, or age did not predict multimorbidity, frailty, or disability. A CD4/CD8 ratio above 0.8 was associated with almost 3-fold higher odds of frailty (aOR 2.78, 95% CI 1.16 to 7.02, $P = 0.03$) but not with multimorbidity or disability.

The MYSAWH investigators cited data showing that step count rose month by month through the first 6 months of analysis, even though the study did not include an intervention to encourage more walking. They believe that finding suggests wearing a fitness tracker “can empower older HIV patients in promoting healthy physical activity.” The researchers concluded that older people with HIV find a wearable fitness tracker easy to use and that such a device is a reliable way to record health predictors from daily life. They suggested that a physical function measure like daily steps should be used to monitor patients with HIV.

Subjective and objective fatigue greater with HIV in 50-to-75-year group

Certain baseline measures in an exercise trial enrolling sedentary HIV-positive and negative 50-to 75-year-olds found significantly greater fatigue in the HIV group, whether measured subjectively or objectively.⁹ The trial is now assessing the impact of exercise on fatigue.

Fatigue, a component of the standard frailty phenotype and a common marker of depression,

remains a frequent complaint among people with HIV infection. Exercise reduces fatigue among older adults in the general population, but the impact of exercise on fatigue in people with HIV is not well understood. And there are no consistent measures of fatigue in HIV populations.

To address these issues, researchers from the Colorado School of Public Health and the University of Colorado began a clinical trial of exercise in sedentary older adults with or without HIV. The report at the HIV & Aging Workshop compares baseline measures of subjectively and objectively measured fatigue.

All study participants were 50 to 75 years old. The HIV group had taken antiretroviral therapy for at least 2 years and had a viral load below 200 copies/mL and a CD4 count at or above 200 cells/mm³. Before the exercise program began, researchers assessed fatigue with two subjective measures (Short-Form 36 [SF-36] Vitality score and two fatigue questions on the Centers for Epidemiological Studies and Depression [CES-D] scale) and two objective measures (maximum oxygen consumption [VO₂max] during a graded treadmill test and 400-meter walk time).

The analysis included 36 people with HIV and 38 without HIV. The HIV-positive and negative groups were similar in average age (57.3 and 59.0 years) and proportion of men (86% and 95%). The HIV group included a lower proportion of whites (64% versus 82%) and a higher proportion of blacks (28% versus 11%) ($P = 0.003$), and people with HIV had a lower average body mass index (27.5 versus 29.8 kg/m², $P = 0.039$). A higher proportion of the HIV group was unemployed (19% versus 3%) and a lower proportion had full-time work (14% versus 66%) ($P < 0.001$). The HIV group included a higher proportion of current cigarette smokers (39% versus 13%, $P = 0.0105$) and a higher proportion of marijuana users (53% versus 14%, $P = 0.0004$).

Of the two subjective fatigue scales, the SF-36 Vitality score was significantly lower (worse) in the HIV group than in HIV-negative participants ($P = 0.010$) (**Table 1**). The HIV group also scored lower on the two CES-D fatigue questions, but the difference from the HIV-negative group was not significant. People with HIV walked 400 meters significantly more slowly than people without HIV ($P = 0.0004$) (**Table 1**). The HIV group also had a worse VO₂max, but the difference from the control group stopped short of statistical significance ($P = 0.0817$).

Table 1. Subjective and objective fatigue in older adults with or without HIV

	HIV-positive (n = 36)	HIV-negative (n = 38)	P
<i>Subjective measures</i>			
SF-36 Vitality score	48.1	53.6	0.010
CES-D fatigue questions	3.1	3.2	0.749
<i>Objective measures</i>			
VO ₂ max on graded treadmill	24.7 mL/kg/min	27.4 mL/kg/min	0.0817
400-meter walk time	254.6 sec	229.1 sec	0.0004

Source: DaLayna Goulding, Colorado School of Public Health, and colleagues.⁹

Neither subjective measure of fatigue correlated with either objective measure. But the two subjective measures correlated with each other ($r = 0.31$, $P = 0.007$), as did the two objective measures ($r = 0.46$, $P < 0.0001$).

The researchers believe their finding that some measures of perceived and physiological fatigue are significantly greater in people with HIV suggests that HIV infection has an independent effect on fatigue. Pending the exercise results of this trial, they proposed that “promoting exercise as a means to reduce fatigue may motivate adults with HIV to start and maintain physical activity habits as they grow older.”

T-cell responses to CMV could explain immune activation in nonfrail men

CD4 and CD8 T-cell responses to cytomegalovirus (CMV) correlated strongly with systemic inflammation and immune activation in nonfrail men with or without HIV infection.¹⁰ This Multicenter AIDS Cohort Study (MACS) analysis also yielded evidence suggesting that greater CMV-induced CD4-cell IL-2 responses could predict frailty in men without HIV.

Johns Hopkins University researchers who conducted this study noted that both aging and treated HIV infection are marked by low-level chronic inflammation and immune activation, which may contribute to morbidity and mortality. But the mechanism or mechanisms behind this inflammation/activation remain incompletely understood. The Hopkins team analyzed data from MACS men to test the hypothesis that CD4- and CD8-cell reactivity to CMV in HIV-positive and negative men who have sex with men (MSM) (1) contributes to systemic inflammation and immune activation and (2) can predict frailty.

The analysis involved 42 men in the Baltimore/Washington DC contingent of the MACS, an ongoing observational study in which HIV-positive and at-risk HIV-negative MSM make twice-yearly visits. Twenty-two study participants had HIV and 20 did not. Half of each group had frailty (assessed by standard Fried frailty phenotype criteria¹¹) and half did not. All HIV-positive men had an undetectable viral load.

To identify CMV-responsive T cells, the researchers stimulated cryopreserved lymphocytes overnight with overlapping 15-mer peptide pools spanning 19 CMV open reading frames. They used flow cytometry to quantify levels of IFN-gamma, TNF-alpha, and IL-2 responses in CD4 and CD8 cells. Electrochemiluminescence assessed 17 proinflammatory cytokines and chemokines, while a commercial lab measured levels of high-sensitivity C-reactive protein (CRP), an inflammation marker.

In HIV-positive and negative men without frailty, the researchers detected strong ($r = 0.60$ or greater) and statistically significant correlations between T-cell responses to CMV and serum markers of inflammation. Among HIV-negative nonfrail men, CD4 IL-2 responses to CMV correlated strongly with several markers of systemic inflammation, including IL-6 ($r = 0.66$), CRP ($r = 0.77$), and percent activated CD8 cells ($r = 0.84$).

Follow-up continued for 5.5 to 7.5 years (11 to 15 study visits) in the 9 nonfrail HIV-negative men. During that time, a greater CMV-induced CD4-cell IL-2 response predicted development of frailty (relative risk 1.24 per 1% response, $P = 0.027$).

The Hopkins investigators believe their findings “support the hypothesis that T-cell responses to CMV could explain much of the immune activation in nonfrail treated HIV-positive [men] and in HIV-negative men.” In men without HIV, they proposed, T-cell responses to CMV “may predict the onset of frailty.” They called for longitudinal studies, including treatment studies, to further explore these associations.

Only 30% provider/patient adherence to HIV geriatric consult recommendations

Primary HIV providers and their patients followed through on only about 30% of recommendations made during a Comprehensive Geriatric Assessment (CGA) by a geriatrician.¹² This study at a New York City HIV aging clinic could not identify reasons for the modest adherence.

The HIV clinic at Weill Cornell Medicine/New York Presbyterian Hospital established a dedicated HIV aging program in 2015. Every week comprehensive geriatric consultations are available to HIV patients referred by their primary provider. All referred patients undergo CGA, an interdisciplinary diagnostic process covering physical and mental health, social circumstances, daily functioning, and environment.¹³

Weill Cornell researchers conducted this study to determine the kind of recommendations that emerge from these CGA sessions and the percentage of recommendations followed within 6 months by providers or patients. Two reviewers not including the consulting geriatrician analyzed each consultation to itemize recommendations directed to the provider or the patient and to determine 6-month adherence.

The analysis focused on 66 patients, 45 of them (68%) men, with a median age of 67.2 years (range 50 to 84). Participants had been diagnosed with HIV for a median 21.9 years (range 4 to 36), two thirds had an undetectable viral load, and two thirds used Medicaid. HIV transmission risk was sex between men in 55%, heterosexual sex in 30%, and drug injecting in 15%. More than half of these people, 58%, lived alone. Median anxiety score (by PHQ-4) stood at 0.5 and depression score (by PHQ-4) at 1.

For these 66 HIV patients, the consulting geriatrician made 103 provider-directed recommendations, made 61 patient-directed recommendations, provided the patient information 47 times, and took 10 direct actions. Each patient had a median of 1 physician-directed recommendation, 1 patient-directed recommendation, and 2 total recommendations (**Figure 3**).

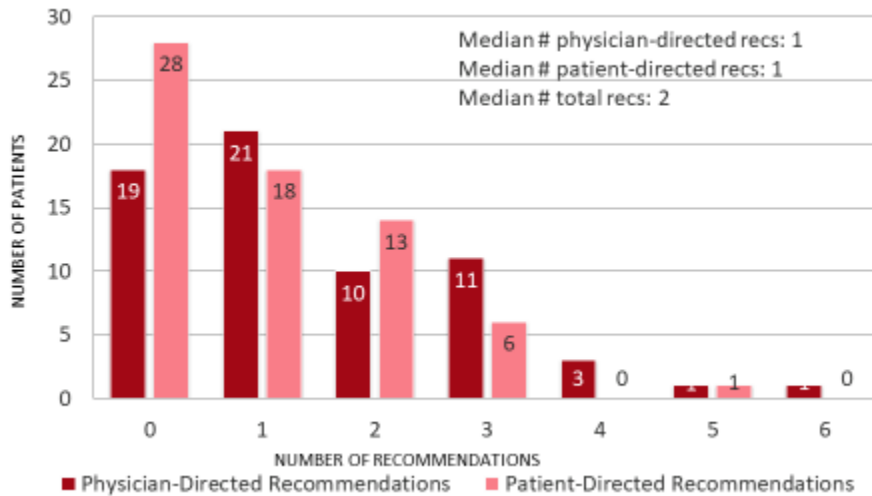


Figure 3. During 66 Comprehensive Geriatric Assessments with HIV patients, consulting geriatricians made 103 recommendations to providers, 61 recommendations to patients, and a median of 1 each to every patient. (Source: Christiana Bitas, Weill Cornell Medical College, and colleagues.¹²)

Within 6 months of the consultation, patients followed through on 19 of 61 recommendations (31%) while their HIV providers followed through on 27 of 103 (26%). The combined patient-provider adherence rate came to 28% (46 of 164 recommendations). Among patients who received 1 or more patient-directed recommendations, almost half followed at least 1 recommendation. No patient characteristics analyzed (age, gender, HIV risk, Medicaid use, viral load) predicted adherence. Nor did any CGA metric (such as anxiety or depression score, frailty, or VACS mortality score).

The researchers noted that their analysis is limited by the relatively small sample (more patient CGAs are being analyzed), potential bias of chart reviewers, and limited ability to discern adherence. At this point they cannot make recommendations about CGA because their analysis lacks a control group. They stressed that “further studies are needed to determine the utility of CGA in affecting patient outcomes long-term.”

AGING AND THE CNS

Accumulating research suggests that “early [antiretroviral] therapy alone may not be enough to protect the brain” from HIV infection, warned Yale University’s Serena Spudich in an HIV &

Aging Workshop invited lecture.¹⁴ But work so far has not pinned down where HIV replicating in the central nervous system (CNS)—but not in blood—comes from.

Workshop attendees pondered these issues and others in a session with four abstract-driven presentations on aging, HIV, and the CNS, including cognitive impairment over age 60; cognition, mood, and quality of life; monocyte activation and impaired cognition; and common single-nucleotide polymorphisms (SNPs) implicated in neurocognitive impairment.

Self-reported cognitive symptoms poor predictor of test-measured impairment

Symptoms of cognitive impairment reported by a group of older people with HIV proved poor predictors of impairment measured by standard tests.¹⁵ One third of these 127 people reporting cognitive symptoms had neuropsychological test results within expectations for their age and education.

Despite suppressive antiretroviral therapy, cognitive impairment remains frequent in people with HIV.¹⁶ As one would expect, cognitive symptoms become more common with age.¹⁷ But clinicians face challenges in predicting which older HIV patients are more likely to have HIV-associated neurocognitive disorder (HAND) without formal testing.

Researchers at the University of California, San Francisco (UCSF) Memory and Aging Center conducted this study to explore demographics and cognitive testing profiles of older HIV patients reporting cognitive symptoms. The analysis involved patients at least 60 years old enrolling in the HIV Elders Study, which tests mindfulness-based stress reduction as a way to reduce cognitive symptoms. All participants had an undetectable viral load for at least 6 months, had not used illicit drugs for 6 months, and had not tried mindfulness-based therapy.

Potential participants who report cognitive symptoms in a 10-minute phone or online interview are invited for detailed neuropsychological testing and clinical evaluation to assess objective impairment and rule out treatable causes. The testing battery addresses seven domains: memory, language, attention, executive function, processing speed, manual dexterity, and visuospatial perception. Reviewing test results, a staff conference determines whether a person has objective impairment in at least two domains and if they meet criteria for mild neurocognitive disorder (MND) or have normal cognition.

The UCSF team has evaluated 127 patients, 71 (56%) with MND, 37 (29%) within normal limits, and 19 (15%) with potential confounding conditions. The most frequent confounding conditions were major depression, substance use, and non-HIV neurologic conditions. People with MND did not differ from the normal group in age (median 64 and 65 years), gender (93% and 100% men), years of education (15.7 and 16.3), median HIV duration (27 and 29 years), or current CD4 count (mean 605 and 586 cells/mm³).

Further analysis indicated that the type of symptoms reported could not predict objectively measured cognitive impairment. For example, the MND group did not differ from the normal group in proportions reporting memory problems (92% and 87%), language difficulties (89% and 84%), or impaired executive function (59% and 54%). Excluding participants with confounding conditions, Pearson’s correlation analysis did identify a trend indicating that people with a higher symptom burden tended to have lower overall neuropsychological performance ($r = -0.262, P = 0.006$). And the cognitive testing profile showed a significant difference between the MND group and the normal group in every domain tested (**Figure 4**). The researchers noted that motor performance emerged as a weakness in both groups, while both groups had relatively preserved memory.

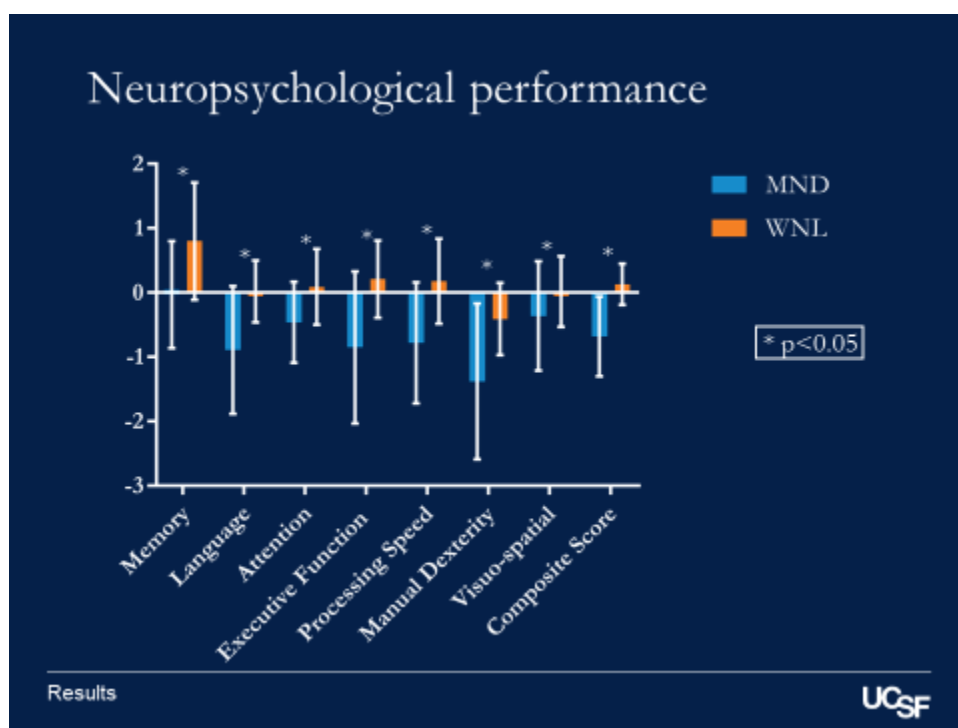


Figure 4. In 127 HIV-positive people 60 or older, neuropsychological testing distinguished those with mild neurocognitive disorder (MND) from those within normal limits (WNL) in every domain. But types of self-reported symptoms did not differ between the two groups. (Source: Shireen Javandel, University of California, San Francisco, and colleagues.¹⁵)

The researchers concluded that one third of older people with HIV reporting cognitive symptoms performed within normal limits on neuropsychological testing. They found that symptom characteristics “appear to be a poor predictor of impairment, while [symptom] burden may have some utility.” The UCSF investigators plan to explore other data they collected on geriatric syndromes, depression, and loneliness to see if they can identify factors that predict cognitive

impairment.

Depression, fatigue have greatest impact on QOL in men with HIV

Quality of life (QOL) in Canadian men aging with HIV could be largely explained by symptoms and impairments that can be addressed by evidence-based interventions, according to results of a 706-man study.¹⁸ Depression and fatigue emerged as the variables that most affect QOL.

Researchers from Montreal's McGill University who conducted this study noted that numerous factors can affect QOL in people with HIV. But analyzing these factors remains a challenge because their effects can be indirect and they can interact. In particular, the role cognition plays in QOL needs clarification—especially given the frequent co-occurrence of other factors, including mood symptoms. They planned this study “to estimate the extent to which cognition, mood, and other clinical factors influence QOL in Canadian men aging with HIV.”

Study participants came from the Positive Brain Health Now cohort,¹⁹ which aims to understand determinants and consequences of poor brain health in aging Canadians with HIV. Cohort members come from 5 cities, must be 35 or older, and must have HIV infection for at least 1 year. They make study visits every 9 months to update medical information and undergo cognitive testing. The researchers used the Wilson-Cleary model to assess the impact of life factors on QOL. They used structural equation modeling to discern interrelationships between variables affecting QOL.

The Brain Health Now cohort currently includes 840 people with HIV, 84% of them men, with an average age of 53 years. About 43% are working. The cohort does not include people with dementia or other neurological problems. The group averages an HIV infection duration of 17 years, a nadir CD4 count of 218 cells/mm³, and a current CD4 count of 623 cells/mm³. Most cohort members, 55%, had an AIDS-defining illness.

The QOL analysis involved 706 men. Variables of interest fell into three groups—symptoms, activity, and participation (**Figure 5**). The model explained 89% of the variance in QOL. Three variables had a direct impact on QOL: depression, social role, and health perception.

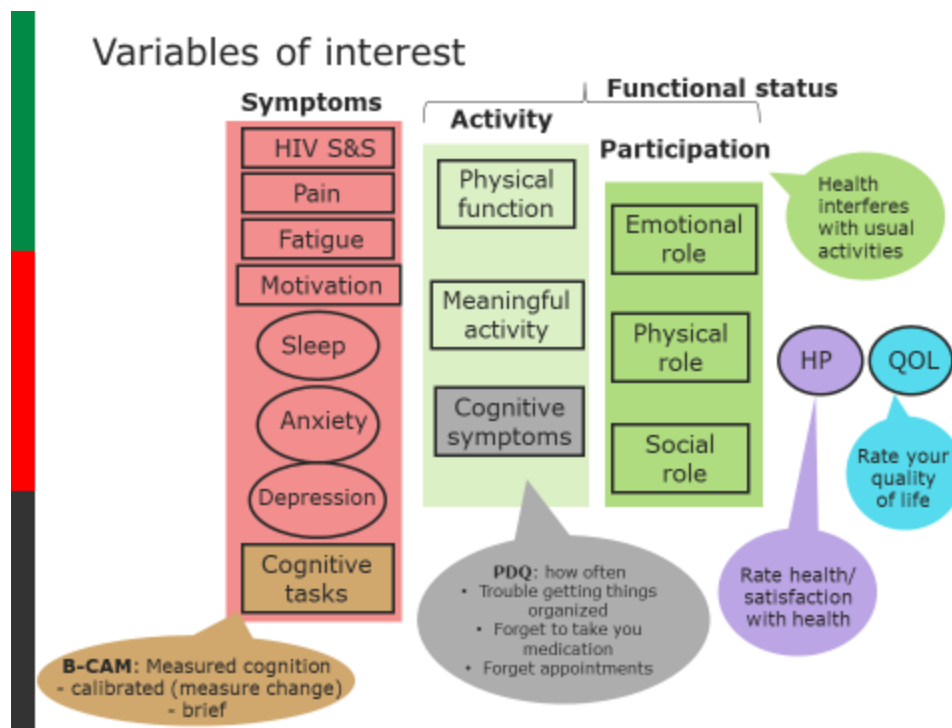


Figure 5. An analysis of factors affecting quality of life in 706 aging men with HIV considered variables in three areas. (**HP** means health perception.) (Source: Marie-Josée Brouillette, McGill University, Montreal, and colleagues.¹⁸)

Numerous factors had an indirect impact on QOL *through* health perception: HIV signs and symptoms, pain, fatigue, motivation, and depression (from the symptoms group), physical function (from the activity group), and all three variables in the participation group (see Figure 5). Two variables in the activity group—meaningful activity* and cognitive symptoms—had an indirect impact on QOL through the participation variables and health perception. Symptom variables that indirectly affected QOL through activity variables were HIV signs and symptoms, pain, fatigue, anxiety, depression, and performance on cognitive tasks. The researchers observed that performance of cognitive tasks had no direct impact on participation variables, health perception, or QOL. Overall, depressive symptoms had the biggest impact on QOL

*Meaningful activity includes working, reading, playing sports, and other worthwhile pursuits—excluding TV watching.

The McGill team noted that their analysis assesses “the vast majority” of constructs important to QOL in the absence of dementia. The researchers pointed out that they are not trying to devise a screening tool for HIV-associated neurocognitive disorder (HAND). Rather, “patients care about function and QOL, and we are interested in understanding the determinants of poor brain health.”

The Montreal investigators concluded that symptoms and impairments that can be addressed by evidence-based interventions largely explain variance in QOL and that depression and fatigue have the greatest impact on QOL in their model. Among aging Canadian men with HIV, they stressed, cognitive performance affects QOL only in the presence of cognitive symptoms.

Monocyte activation tied to cognitive impairment, lower brain volume with HIV

Among older adults with well-controlled HIV infection, monocyte activation correlated with test-measured cognitive impairment.²⁰ This 71-person study also linked monocyte activation to decreased hippocampal brain volume.

HIV-associated neurocognitive disorder (HAND) remains prevalent in populations with a sustained viral load below 50 copies/mL. Although antiretroviral therapy has reduced the severity of HAND, mild neurocognitive disorder and HIV-associated dementia may still affect nearly one quarter of people with HIV.²¹ Persistent central nervous system inflammation and aberrant monocyte activity may play roles in HAND persistence. In particular, CD14+CD16+ monocyte expansion has been linked to HAND and encephalitis. But most CD14+CD16+ expansion studies have involved younger people with HIV. Researchers at Temple University and colleagues at other centers mounted this study to assess the relationship between CD14+CD16+ monocyte activation and brain integrity (by neuropsychological testing and neuroimaging) in older people with well-controlled HIV.

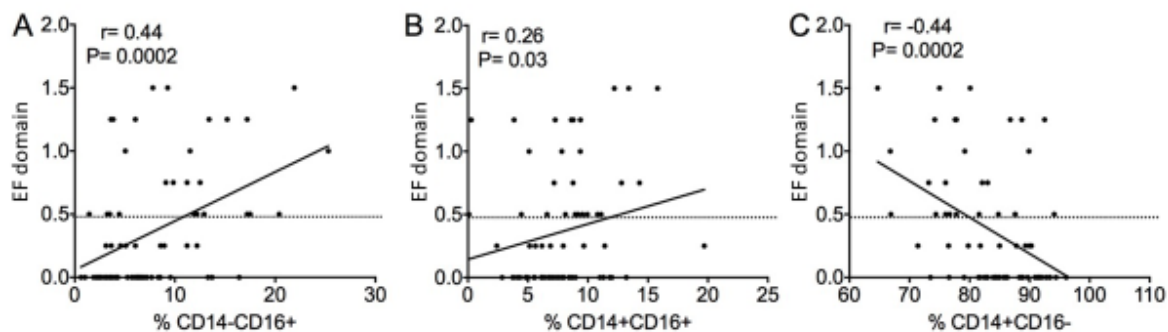
The study involved HIV-positive people more than 50 years old with a viral load below 50 copies/mL. They completed a neuropsychological test battery that yielded scores for psychomotor/processing speed (PM), executive functioning (EF), and learning and memory (LM), as well as a total global deficit score (GDS). The researchers excluded people with severe conditions, such as stroke, that may affect neuropsychological performance. They used magnetic resonance imaging to calculate brain volume from T1-weighted three-dimensional images. Imaging focused on 7 regions susceptible to both HIV & Aging, including the hippocampus.

Among the 71 study participants, 38 (54%) had neurocognitive impairment (GDS at or above 0.5) and 34 did not (GDS below 0.5). The impaired and unimpaired groups did not differ significantly in age (median 56 and 57.5 years), but they did in proportion of men (72% versus 94%, $P = 0.03$), proportion of blacks (71% versus 36% $P = 0.01$), and years of education (median 12 versus 15, $P = 0.002$). The two groups did not differ significantly on several HIV-related parameters, including plasma viral load, HIV duration, and current CD4 count (median 527 and 528 cells/mm³).

Levels of inflammatory CD14-CD16+ and CD14+CD16+ monocytes were significantly higher in people with versus without cognitive impairment determined by GDS and in the LM and EF domains, but not in the PM domain. But levels of nonactivated CD14+CD16- monocytes were

higher in people without neurocognitive impairment. Elevated monocyte levels correlated with worse impairment by GDS, in the LM domain, and in the EF domain (**Figure 6**), but again not in the PM domain. Neuroimaging determined that hippocampus volume was decreased in participants with greater neurocognitive impairment determined by GDS ($r = -0.23$, $P = 0.06$) and in those with higher levels of activated (CD16+) monocytes ($r = -0.35$, $P = 0.005$).


Elevated peripheral monocytes correlate with worse impairment

Monocytes correlate with EF, LM and Total GDS, but not PM.

Figure 6. In older adults with a viral load below 50 copies/mL, higher levels of activated peripheral monocytes were significantly associated with worse neurocognitive impairment determined by GDS and in the LM domain and the EF domain (pictured). (CD16+ monocytes are activated; CD16- monocytes are not.) (Source: Tricia Burdo, Temple University, and colleagues.²⁰)

The researchers believe their findings are consistent with persistent monocyte activation in older cognitively impaired people with well-controlled HIV infection. Monocyte-determined peripheral inflammation was higher in patients with global neurocognitive impairment and with impairment in the EF and LM domains. In addition, hippocampal brain volume was lower in participants with worse neurocognitive impairment, and decreased hippocampal brain volume correlated with increased peripheral monocyte activation.

The investigators suggested their observations “underscore the significance of monocyte/macrophage immune responses in chronic HIV, decreased brain integrity, and persistent monocyte activation during neurocognitive impairment.”

SNPs in hemochromatosis gene linked to symptomatic HAND

In two clinically distinct US cohorts, single-nucleotide polymorphisms (SNPs) in the hemochromatosis (*HFE*) gene were linked to increased risk of symptomatic HIV-associated neurocognitive disorder (HAND).²² These findings and others implicate iron dysregulation in the neuropathogenesis of HAND, according to collaborators at the Cleveland Clinic, the University of California, Los Angeles (UCLA), and other centers.

HAND persists in HIV populations with well-controlled HIV infection.¹⁶ Although mechanisms underlying HAND remain poorly understood, some work implicates disruption of iron transport and metabolism. Researchers who conducted this study pointed out that loss of iron homeostasis and mitochondrial dysfunction are linked to aging and to several non-HIV-related neurocognitive disorders. In addition, common SNPs in the *HFE* gene have been tied to neurocognitive disorders. The investigators planned this study to test the hypothesis that *HFE* SNPs influence brain structure, neurodegenerative processes associated with aging, and susceptibility to HAND in adults with HIV. *HFE* SNPs are most prevalent in European-ancestry populations.

The analysis involved US adults with HIV enrolled in the CHARTER cohort, all of whom underwent extensive neurocognitive testing. Of the 1047 CHARTER participants analyzed in this study, 243 (23%) had neuroimaging and all had genotyping at both *HFE* SNP loci (*G845A* and *C187G*). The study excluded individuals with severe neuro-confounding comorbidities such as traumatic brain injury. The researchers used multivariable logistic regression or multiple linear regression to identify associations with *HFE* variants.

Of the 1047 patients studied, 568 (54%) had no neurocognitive impairment, 359 (34%) had asymptomatic neurocognitive impairment (ANI), 90 (9%) had mild neurocognitive disorder (MND), and 30 (3%) had HIV-associated dementia (HAD). Age averaged 43 years in all four groups, and about 23% of all groups were women. Nonwhites made up 60% of the unimpaired group, 58% of the ANI group, 50% of the MND group, and 40% of the HAD group. Respective proportions with significant comorbidity were 29%, 41%, 45%, and 77%; proportions on antiretroviral therapy (ART) were 68%, 74%, 78%, and 90%; and median nadir CD4 counts were below 200 cells/mm³ in all 4 groups.

The second study group included 164 decedents in the National NeuroAIDS Brain Bank (NNTC Study), 161 of whom had neurocognitive assessment before they died, all of whom had *HFE* genotyping at the *C187G* locus, and subsets of whom also had neuropathological scoring of amyloid *beta* (abeta) plaque accumulation (n = 101) and synaptodendritic loss (n = 35) in several brain regions affected by HAND. The group had a median CD4-count nadir of 27 cells/mm³. Their age averaged 48 years at death, 82% were taking ART, and 32% were nonwhite.

In the CHARTER cohort proportions with 1 or more *HFE* SNPs were 20% without neurocognitive impairment, 19% with ANI, 30% with MND, and 30% with HAD. In the NNTC,

proportions with the rs1799945, G SNP were 17% without impairment, 14% with ANI, and 28% in the combined MND and HAD groups.

In the entire CHARTER sample, presence of one or more *HFE* variants was associated with all HAND (OR 1.60, $P = 0.04$) as well as with symptomatic HAND (OR 2.0, $P = 0.02$) before adjusting for potential confounding factors. These findings indicated an approximate doubling of the likelihood of having HAND. Similarly, in ancestry-stratified analyses adjusted for nadir CD4 count, plasma viral load, comorbidity, and ART status, having one or more *HFE* minor allele(s) was associated with approximately twice higher odds of MND plus HAD versus ANI plus no HAND in 440 self-reported whites, particularly among those under 50 years of age (**Figure 7**). However, the researchers noted that older age groups were underrepresented in this study. In 243 CHARTER participants with neuroimaging, *HFE* minor alleles were independently associated with (1) lower total cerebral volume ($P < 0.05$), (2) lower cerebellar white matter volume ($P < 0.05$), and (3) increased brain atrophy indicated by ventricular size ($P < 0.01$) and increased volumes of sulcal and cerebellar cerebrospinal fluid (both $P < 0.05$).

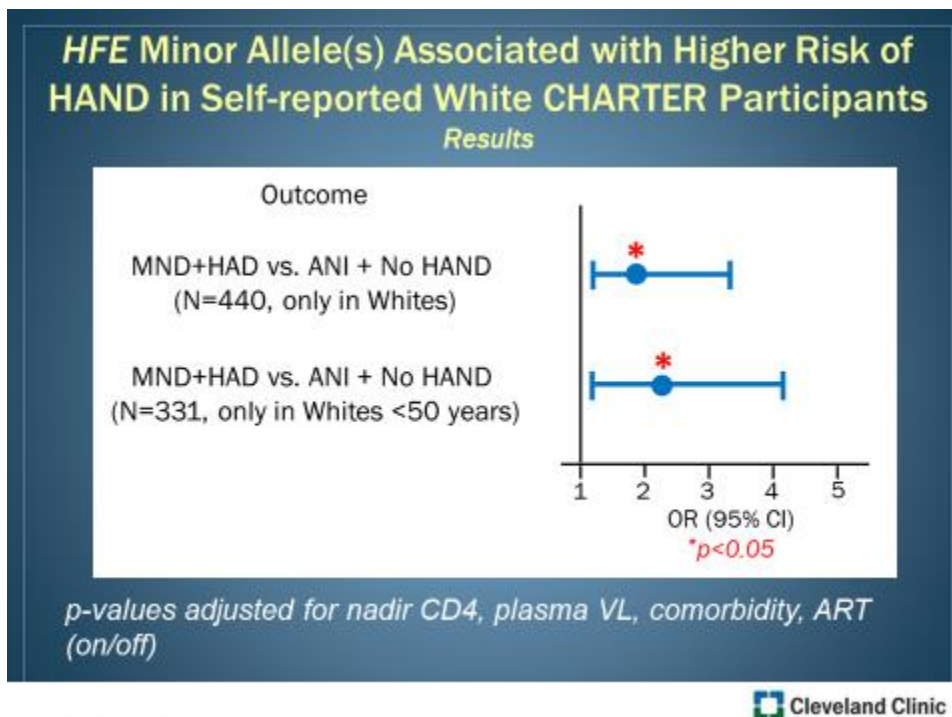


Figure 7. Multivariable analysis determined that whites with minor *HFE* alleles in the CHARTER cohort had approximately 2-fold higher odds of MND plus HAD versus ANI plus no HAND. (Source: Harpreet Kaur, Cleveland Clinic Foundation, and colleagues.²²)

In multivariable analyses of the NNTC group, the *HFE C187G* SNP was associated with a significantly increased prevalence of HAND versus no HAND (OR 3.9, $P = 0.05$), with MND plus HAD versus ANI plus no HAND (OR 4.2, $P = 0.01$), with loss of synaptodendritic

complexity in the striatum ($P = 0.02$), and with greater abeta plaque accumulation in the frontal cortex ($P = 0.03$).

The researchers concluded that these findings represent the first demonstration that *HFE* SNPs are associated with symptomatic HAND, and the findings come from two distinct HIV cohorts. They proposed a strong biological plausibility for this association because (1) both *HFE* SNPs disrupt protein processing, (2) *HFE C187G* has been associated with white matter loss in HIV-negative people, and (3) *HFE* and *APOE* e4 may interact to promote mitochondrial dysfunction and apoptosis.

The investigators proposed that the associations they demonstrated may indicate that iron dysregulation is an important factor “in these key mechanism underlying progression from asymptomatic to symptomatic neurocognitive impairment” in people with HIV infection.

BIOLOGICAL VERSUS CHRONOLOGICAL AGING

Everyone on Earth shares one aging trait: we all do it at the same pace. Every 365.25 days (roughly) we age exactly 1 year. But that rule holds only if you’re talking about chronological age. *Biological* age is a different beast entirely.

We owe this discovery to a UCLA scientist named Steve Horvath, who showed that biological—or epigenetic—aging measured by DNA methylation often does not run in tandem with chronological age. *Epigenetic* links the prefix *epi* (meaning “besides,” as in *epiphenomenon*) to *genetic* to indicate nongenetic influences on gene expression—like methylation. Measuring methylation at two DNA cytosines creates an “epigenetic clock,” a timepiece for biological aging.²³ For example, by calculating epigenetic age in brain and blood of people with HIV, Horvath estimated that HIV boosts epigenetic age in brain tissue by 7.4 years and in blood by 5.2 years.²⁴ Two studies at the HIV & Aging Workshop used Horvath’s epigenetic clock to see whether antiretroviral therapy slows epigenetic aging in people with HIV.

ART does not reset epigenetic clock in adults with HIV

Starting antiretroviral therapy (ART) did not restore epigenetic age in men with HIV infection.²⁵ This comparison of 15 men with HIV and 15 matched HIV-negative men also produced evidence that accumulation of highly differentiated CD8 cells represents a biomarker of overall biological age.

ART contributes to longer life expectancy with HIV, approaching that seen in the general population. But prior work by researchers from the University of California, Los Angeles (UCLA) found that DNA methylation patterns predict people with HIV have an epigenetic age 14 years older than their chronological age.²⁶ Epigenetics, the UCLA team noted, involves “alteration of DNA through modifications that do not change the underlying nucleotide

sequence, yet are important in controlling gene expression.”²⁶ These modifications include methylation of cytosine residues.

To determine whether starting ART resets the epigenetic clock to a time closer to chronological age, these investigators conducted a longitudinal comparison of 15 HIV-positive men and 15 age- and ethnicity-matched HIV-negative men in the Multicenter AIDS Cohort Study (MACS). All men were 39 to 50 years old, and all men with HIV reached an undetectable viral load with ART. The UCLA investigators calculated epigenetic age by assessing DNA methylation patterns 1 year before ART began and 1 and 2 years after treatment started—and at the same MACS visits in HIV-negative men. The researchers used weighted gene comethylation network analysis (WGCNA) to find changes in global methylation patterns linked to ART initiation and to determine whether ART affects such changes. WGCNA works by identifying clusters (modules) of interrelated genes that respond in a similar manner to the variable in question. The researchers used flow cytometry to determine T- and B-cell differentiation on the same samples used for epigenetic analysis.

Before ART began, epigenetic age was approximately 8 years older in men with versus without HIV infection ($P = 0.00062$) (**Figure 8**). Two years of ART only partially evened the epigenetic imbalance between HIV-positive and HIV-negative men, leaving the HIV group with a still significantly older epigenetic age ($P = 0.017$) (**Figure 8**).

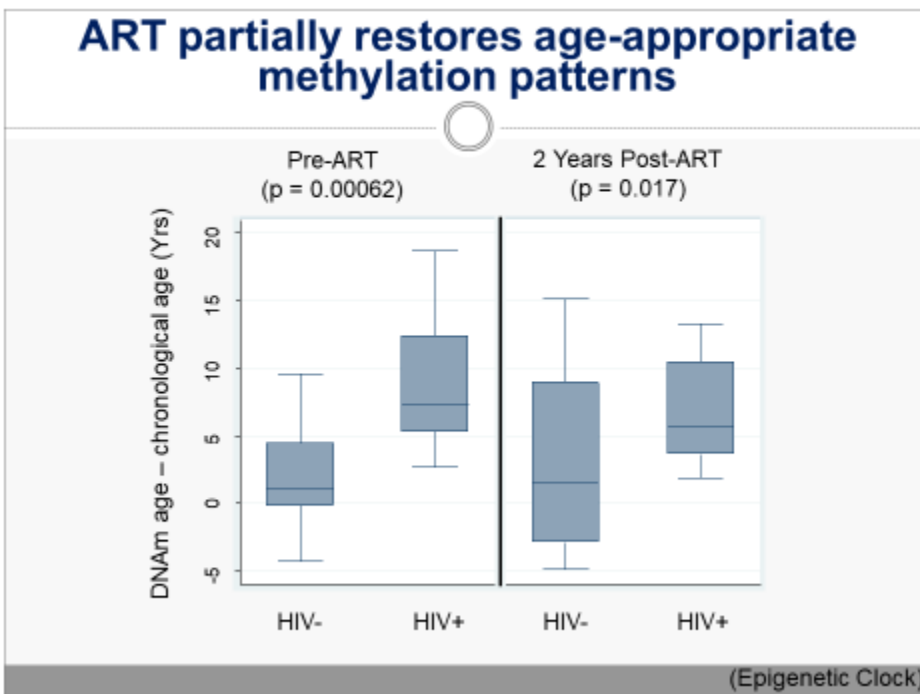


Figure 8. Before antiretroviral therapy began, 15 men with HIV had a significantly older

epigenetic age (assessed by DNA methylation patterns) than a matched group of men without HIV. Two years of ART only partially restored age-appropriate epigenetic age in the HIV group. (Source: Beth Jamieson-Karavodin, University of California, Los Angeles, and colleagues.²⁵)

WGCNA identified 14 modules significantly associated with aging and HIV status. Only 1 of these 14 modules demonstrated a trend toward an association with ART initiation. This analysis detected no consistent network of genes significantly associated with ART, a finding “demonstrating that ART did not have a strong global impact on HIV-induced age-accelerated epigenetics.”

Total, senescent, terminally differentiated, and activated CD8 cells were strongly associated with accelerated epigenetic aging after ART began—the older the epigenetic age, the greater the CD8-cell elevation. The researchers reminded workshop attendees that senescent (CD8+CD57+CD28-) cells are linked to age-related diseases such as frailty, osteoporosis, diabetes, cardiovascular disease, and Alzheimer’s disease.

The UCLA investigators concluded that HIV accelerates epigenetic age and that 2 years of ART do not completely restore age-appropriate DNA methylation patterns. These findings, they believe, suggest that “HIV and aging work through partially overlapping mechanisms.” The study also yielded evidence that epigenetic age is associated with accumulation of senescent and activated CD8 cells and that 2 years of ART do not restore levels to those seen in people without HIV.

Mixed evidence on biological age in children starting ART early

South African children who began antiretroviral therapy (ART) within the first 3 years of life did not have accelerated biological (epigenetic) aging when compared to HIV-negative children by DNA methylation age.²⁷ But telomere length proved significantly shorter in children with HIV or exposed to HIV than in HIV-unexposed uninfected children.

Research documents accelerated biological aging in antiretroviral-naïve adults with HIV,²⁶ and 2 years of ART did not restore biological age to that measured in HIV-negative adults.²⁵ Biological age can be calculated by measuring DNA methylation (the method used in the just-reported adult studies^{25,26}) or by telomere length.²⁸ Until this new study by collaborators at New York’s Columbia University and Johannesburg’s University of the Witwatersrand, these biological-age clocks saw limited use in children with HIV. The New York/Johannesburg team aimed to compare these aging markers in three groups—HIV-infected children who began ART within the first 3 years of life, HIV-exposed uninfected (HEU) children, and HIV-unexposed uninfected (HUU) children.

Study participants came from CHANGES, an ongoing longitudinal cohort study in Johannesburg

that enrolls HIV-infected and uninfected children 4 to 9 years old. In the HIV group, the researchers also assessed the impact of six variables on biological aging—sex, time on ART, pretreatment CD4 percent, pretreatment viral load, current CD4 percent, and exposure to cigarette smoke in the house.

The analysis included 120 children with HIV and 60 uninfected children (33 HEU, 25 HUU, 2 status unknown). In the HIV, HEU, and HUU groups, age averaged 6.4, 6.1, and 6.9 years ($P = 0.07$). The proportion of boys did not differ significantly between the three groups (46.7%, 54.6%, 44.0%, $P = 0.67$); nor did the proportion exposed to cigarette smoke (34.2%, 33.3%, 36.0%, $P = 0.98$). Children with HIV had a viral load below 400 copies/mL and averaged 5.7 years of follow-up.

Chronological age correlated positively with DNA methylation age ($r = 0.57$, $P < 0.01$) but not with telomere length ($r = -0.01$, $P = 0.9$). The researchers noted that lack of a correlation with telomere length may reflect a plateau in telomere shortening seen in children at the age of this study group.^{29,30} The positive association between chronological age and DNA methylation age did not differ much between the HIV, HEU, and HUU groups.

Age-adjusted DNA methylation age did not differ between the three groups of children ($P = 0.96$). Telomere length was statistically similar in the HIV and HEU groups ($P = 0.43$) but significantly shorter in the HIV group than in the HUU group ($P = 0.05$) and significantly shorter in the HEU group than in the HUU group ($P = 0.03$) (**Figure 9**).

Telomere Length, by Group

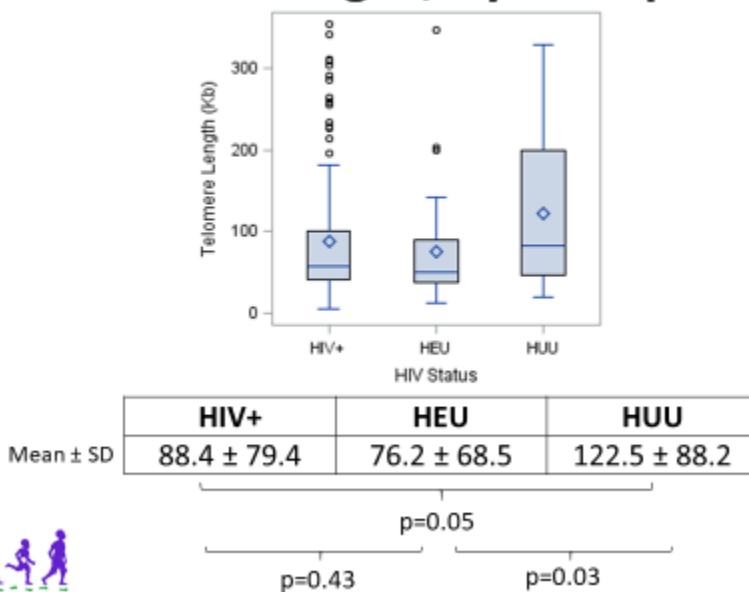


Figure 9. In a comparison of Johannesburg children with HIV (HIV+), HIV-exposed uninfected (HEU) children, and HIV-unexposed uninfected (HUU) children, the HIV and HEU groups had significantly shorter telomere length—indicating older biological age—than the HUU group, even though all three groups had similar chronological ages. (Source: Stephanie Shiao, Columbia University, New York City, and colleagues.²⁷)

Exposure to household smoke was associated with significantly older age-adjusted DNA methylation age (mean 0.71 versus -0.38 for smoke versus no smoke, $P = 0.05$) but with statistically similar telomere length ($P = 0.31$). Current CD4 percent correlated negatively with age-adjusted DNA methylation age—higher CD4 percent meant lower DNA methylation age ($r = -0.36$, $P < 0.01$). But current CD4 percent did not correlate with telomere length ($r = 0.07$, $P = 0.43$).

The Columbia/Witwatersrand collaborators concluded that biological age measured by DNA methylation does not differ between HIV-positive children who start ART in the first years of ART and HIV-negative children. Only continuing follow-up can determine how long that benefit of early ART persists as children age. Telomere length was significantly shorter in HIV-infected children and HEU children than in HUU children. Whether that difference reflects *in utero* HIV exposure, *in utero* antiretroviral exposure, or other factors, the investigators said, requires further study.

mtDNA variation linked to gait speed drop in older white men with HIV

A study of non-Hispanic HIV-positive white men over 50 years old linked mitochondrial DNA (mtDNA) haplogroup J to slower gait speed and faster yearly drop in gait speed.³¹ This analysis of 455 men in the Multicenter AIDS Cohort Study (MACS) appears to be the first to assess the impact of mitochondrial genetics on physical function in people with HIV.

Research indicates faster drops in physical function with HIV infection. Gait speed, a simple and much-used way to measure physical function, predicts functional decline, hospital admission, disability, and death in older adults in the general population. Gait speed wanes more quickly in HIV-positive MACS men than in their HIV-negative MACS counterparts.³² Johns Hopkins University researchers who conducted this study noted that mtDNA haplogroups can affect inflammation and apoptosis pathways and so may influence functional decline. Previous research also links mitochondrial genetic variation to frailty and mortality in the general population and to aging and disease risk in people with HIV.

The Hopkins team planned this study to explore the potential impact of common European mtDNA haplogroups on gait speed decline in aging non-Hispanic white men with HIV infection. The study group included 455 HIV-positive MACS men older than 50 who had twice-yearly gait

speed measures between October 2007 and September 2016. Health workers measured gait speed as time to walk 4 meters at a usual pace and defined slow gait as walking speed less than 1 meter/second (m/sec). The researchers extracted data from multiple genotyping panels and determined mtDNA haplogroups; they categorized haplogroups into four common European mtDNA haplogroups—H, J, T, and Uk—and they combined all remaining haplogroups into “others.”

To compare rates of gait speed decline, the investigators used random-effects mixed linear models adjusted for cumulative viral load (viremia copy years), AIDS history, HCV infection, peripheral neuropathy, college education, and smoking. They used mixed-effects logistic regression models controlling for the same variables to assess odds of slow gait speed.

Among the 455 study participants, 41.3% had mtDNA haplogroup H, 9.7% haplogroup J, 11.7% haplogroup T, 23.7% haplogroup Uk, and 13.6% other haplogroups. Overall age averaged 52.9 years with little difference between haplogroups. Baseline CD4 count stood at 561.4 cells/mm³. Most participants (70%) had an undetectable viral load at baseline.

For the whole group, baseline gait speed was 1.15 m/sec and was slightly and nonsignificantly lower with haplogroup J than with other haplogroups. Gait speed waned at a rate of 0.017 m/sec/year in haplogroup J versus 0.011 m/sec/year in other haplogroups ($P = 0.02$). The interaction between haplogroup and age was statistically significant only for haplogroup J (–0.006 m/sec/year, $P = 0.017$).

The adjusted logistic regression model determined that belonging in haplogroup J nearly tripled the odds of slow gait speed after age 50 (**Table 2**). Other variables independently associated with slow gait speed in this model were older age, history of AIDS, and cumulative viral load. There was a trend toward higher odds of slow gait speed with peripheral neuropathy ($P = 0.058$). Having a college degree was independently associated with lower odds of slow gait speed. HCV infection and ever smoking were not independently associated with slow gait speed in this analysis.

Table 2. Odds of slow gait speed among white MACS men over age 50

	Adjusted odds ratio	95% CI	<i>P</i>
mtDNA haplogroup J	2.73	1.08 to 6.91	0.034
Older age	1.14	1.09 to 1.19	<0.001
History of AIDS	1.90	1.01 to 3.57	0.046
Cumulative viral load (viremia copy years)	1.29	1.05 to 1.58	0.015
Peripheral neuropathy	1.31	0.99 to 1.73	0.058
College degree	0.33	0.18 to 0.59	<0.001

Adjusted for HCV infection, AIDS diagnosis, viremia copy years, college education, smoking, peripheral neuropathy.

Source: Jing Sun, Johns Hopkins Bloomberg School of Public Health, and colleagues.³¹

The Hopkins researchers believe their findings suggest that “difference in mtDNA haplogroup may be predictive of mitochondrial function and present a potential pathway to understand the pathophysiology of physical function decline in an HIV population.” They proposed that continuing research into genetic variation and physical function could lead to development of new medications or management strategies for aging people with HIV infection.

CMV suppression may explain antiaging impact of metformin

Metformin, the much-used antidiabetic agent, suppressed human cytomegalovirus (HCMV) in cell studies at Johns Hopkins University (**Figure 10**).³³ Because of multiple links between chronic HCMV infection and age-related processes and diseases, the findings suggest that anti-HCMV activity may explain why metformin appears to retard the aging process.

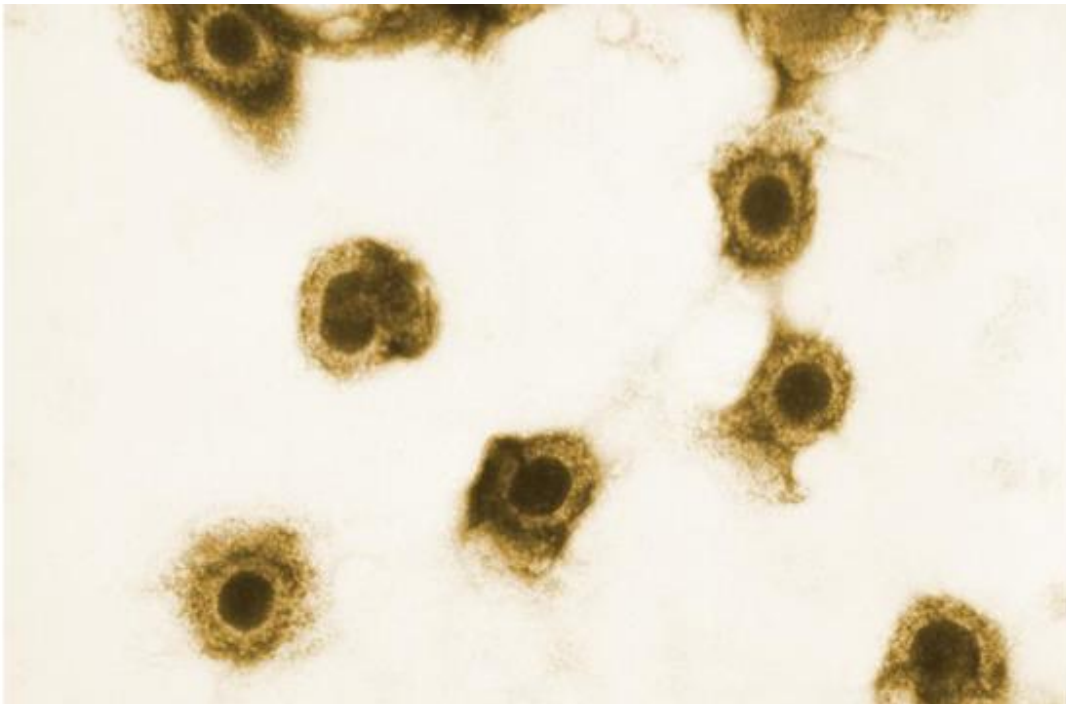


Figure 10. Metformin controlled replication of cytomegalovirus in human fibroblasts, a result suggesting the mechanism underlying the apparent antiaging effect of metformin. This transmission electronmicrograph shows cytomegalovirus virions in a tissue sample. (Source: CDC/Sylvia Whitfield.)

Chronic HCMV infection is highly prevalent in aging populations and in people with HIV

infection.³⁴ Abundant research links HCMV to age-related T-cell immunosenescence, chronic inflammation, and immune activation, notably in people with HIV infection.³⁵ In addition, HCMV infection may heighten the risk of frailty, disability, cardiovascular disease, and mortality. The Hopkins investigators conducted their cell study to test the hypothesis that metformin suppresses HCMV replication and viral protein expression in human fibroblasts, an effect that may contribute to the antiaging properties of metformin.³⁶

The Hopkins team added metformin to MRC-5 human fibroblasts at concentrations of 0.5, 1, 3, or 5 mM. Two hours later they inoculated the fibroblast cultures with HCMV Towne strain at a multiplicity of infection (MOI) of 0.01. This low MOI, the researchers explained, mimics chronic HCMV infection in people with a healthy immune system. They cultured these cells for up to 5 days after infection. The Hopkins investigators measured HCMV-induced cytopathic effect by microscopic observation of viral plaques. They used quantitative PCR to evaluate HCMV replication and Western blot to assess HCMV protein expression.

At 3 and 5 days after infection, metformin suppressed HCMV-induced cytopathic effect. The drug lowered HCMV replication in a concentration-dependent manner, on average by 70% at 0.5 mM, 80% at 1 mM, and more than 90% at 3 or 5 mM. At 3 mM metformin suppressed HCMV replication by more than 85% 2, 3, and 5 days postinfection.

In a dose-dependent manner, the antidiabetic agent suppressed expression of HCMV immediate early 2 protein and delayed expression of early protein pp52. At the lowest concentration, 0.5 mM, metformin completely suppressed expression of HCMV late protein pp28. The drug exerted suppressive effects at HCMV MOIs up to 1.0.

The researchers concluded that their findings demonstrate a “potent anti-HCMV property of metformin,” which may explain its “geroprotective” effect. They also believe their results “suggest potential repurposing of metformin as a safe and effective treatment for HCMV infection.” The Hopkins investigators aim to conduct longitudinal studies to assess the impact of metformin on HCMV and HCMV-related immune parameters in established HIV cohorts.

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