The Impact of HIV and Aging on the Brain

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Adults with HIV are Aging but May Not Age Successfully



Smit, Lancet Inf Dis 2015, 15(7):810-8

Depp & Jeste, Am J Geriatric Psychiatry. 2006; 14: 6-20 Moore et al, J Clinical Psychiatry 2013, 74: e417-23

Unsuccessful Aging Can Affect Every Organ System in HIV+ Adults

- Nervous System
 - Cognitive Disorders
 - Depression
 - Neuropathy
 - Sleep Disorders
- Vascular System
 - Cardiovascular
 - Cerebrovascular
- Endocrine/Metabolic
 - Diabetes
 - Hypogonadism

• Liver

- $-\downarrow$ Drug Metabolism
- $-\downarrow$ Synthetic Function
- Kidney
 - \downarrow Drug Elimination
- Musculoskeletal
 - Osteoporosis
 - Frailty
- Pulmonary System

Cancer

Brooks et al, American Journal of Public Health 2012, 102(8): 1516-26 Onen et al, HIV Clin Trials. 2010;11(2):100-109; Womack et al, PLoS ONE. 2011;6(2): E17217; Desquilbet et al, J Gerontol A Biol Sci Med Sci. 2007;62(11):1279---1286.

HIV May Cause Premature Neurocognitive Decline



Modified from Valcour et al, Neurology 2004;63:822–827 Heaton et al, J Neurovirology, 2012, 18(Suppl 1): S46



Some Studies Do Not Clearly Support Premature CNS Aging



HIV May Accelerate White Matter Injury in the Brain



Unpublished CHARTER Data

Seider et al, J. Neurovirol. (2016) 22:201–212



HIV May Accelerate White Matter Injury in the Brain







Seider et al, J. Neurovirol. (2016) 22:201–212

HIV is Associated with Lower Subcortical Gray Matter Volumes and Cerebral Blood Flow



Ances et al, J Acquir Immune Defic Syndr 2012; 59: 469-77

Ances et al, Journal of Infectious Diseases 2010; 201:336–40

HIV and Age May Alter the Shape of Subcortical Gray Matter



HIV x Age Interaction, p < 0.001 (bilateral nucleus accumbens, amygdala, caudate, and thalamus)

Kuhn et al, Human Brain Mapping, 2016, DOI: 10.1002/hbm.23436

If Premature Aging Occurs, Multiple Mechanisms May Contribute

Cellular senescence

- Shortened telomeres
- Immune senescence
- Mitochondrial damage & oxidative stress
- Altered autophagy

Comorbidities

- Vascular disease
- Metabolic syndrome
- Frailty & sarcopenia
- Anemia & iron metabolism
- Other neurodegenerative diseases (e.g., Alzheimer's)

• Viral

- Compartmentalization and neurotoxic proteins
- Polypharmacy, Drug interactions, & Altered drug metabolism & distribution
 - Reduced elimination & drug binding
 - Altered blood-brain barrier permeability & molecular drug transporter functioning

Biomarkers of HAND May Differ in Younger and Older HIV+ Adults

- Similar in older and younger adults
 - HIV RNA (SCA)
 - Neurofilament light
 - sCD163
 - Neopterin
 - D-dimer, hsCRP

• Stronger in older adults

- HIV DNA
- Telomere length and other aging biomarkers
- IL-6, MCP-1, sCD40L
- Amyloid β1-42, p-Tau

	Correlation		Interaction	
	Age	GDS	Age x Biomarker	
Viral				
- HIV RNA (SCA)	×	X	-	
- HIV DNA	-	-	×	
Neuronal				
- Phospho-Tau (181)	×	X	×	
- Total tau	×	X	-	
 Neurofilament Light 	×	-	-	
Aging				
- Telomere Length	×	-	×	
 Mitochondrial Common Deletion 	×	X	-	
 Free Mitochondrial DNA 	×	-	×	
- 8-OHdG	×	X	×	
 Protein Carbonyls 	×	X	×	
- F2-isoprostanes	×	-	×	
Macrophage/Glial				
- MCP-1	X	X	×	
- sCD163	×	X	-	
- Neopterin	×	X	-	
- GFAP	×	-	-	
Metabolic/Vascular/Inflammation				
- IL-6	X	X	×	
- sCD40L	×	-	×	
- D-dimer	×	-	-	
- hsCRP	-	-	-	
- Amyloid β1-42	-	-	×	

Higher HIV DNA Levels are Associated with Older Age and HAND



Shiramizu et al, Int J Med Sci 2006, 6;4(1):13-8



Boulassel, Routy et al. J Clin Virol 2012, 53: 29– 32 Graph Courtesy Jean-Pierre Routy, McGill University



Oliveira et al, Sci Rep. 2015; 5: 17094

Shorter Lymphocyte Telomere Length is Associated with HIV and Inflammation



Leeansyah et al, JID 2013; 207:1157

Srinivasa et al, JAIDS 2014; 67: 414

र UC San Diego

Correlates of Shorter Telomere Length at UCSD

	Risk	Effect size	P value
Sex	Male	d = 1.6	0.005
Ethnicity	European	d = 1.0	0.001
Age	Older	r = -0.32	0.03
Duration of HIV	Longer	r = -0.31	0.06
Duration of Current ART	Longer	r = -0.27	0.08
Plasma HIV RNA	> 50 c/mL	d = 1.0	0.07
Global Deficit Score		r = 0.04	0.80
GDS Impairment		$X^2 = 0.09$	0.76

n = 47



0.00 Age

T/S Ratio

< 43

≥ 43

≥ 0.76

≥ 43

< 0.76

0

0.10-

0.05-

0.00-

Unpublished UCSD Data Copyright S. Letendre 2016

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Aging-Related Biomarkers Vary by HIV & Methamphetamine Use



Accelerated Aging in Blood and Brain Cells by DNA Methylation



22(3):366-75

212:1563-73



Gianella & Letendre, J Inf Dis 2016

Older Age and Lower Nadir CD4+ T-Cell Counts Correlate with Higher Anti-CMV IgG Levels



- Other correlates of higher anti-CMV IgG: AIDS diagnosis, ART use (p=0.005), and higher serum globulins (p=0.04). Trend with sCD163 (p=0.069).
- Among those with detectable HIV RNA in CSF, higher anti-CMV IgG in serum correlated with higher HIV RNA in CSF and higher CSF WBC counts (p=0.006)

Anti-CMV IgG is Associated with Worse Neurocognitive Performance



Letendre, et al, J Infect Dis, 2016, Submitted

HIV+ Adults Have Higher Risk of Vascular Disease



- HIV+ adults have greater 10-year risk of cardiovascular events (CVEs) and higher rates of atherosclerosis than HIVadults
 - HIV disease is associated
 with greater risk of
 atherosclerosis
 independent of viral load,
 type of ART, or severity of
 immunodeficiency

Hsue et al, AIDS 2006, 20: 2275-83; Brooks et al, American Journal of Public Health 2012, 102(8): 1516-26; Hsue et al, AIDS. 2009;23 :1059-1067; Kaplan et al, Clin Infect Dis. 2007;45(8):1074-1081; El-Sadr et al, Ann Intern Med. 2008;149(5):289-299; Triant et al, Clin Infect Dis. 2012; 54:408-413

Higher Risk of Acute Myocardial Infarction & Stroke in HIV+ Adults



 Hazard ratio for acute MI: 1.5 after adjusting for Framingham risk factors, comorbidities, and substance use

Freiberg et al, JAMA Intern Med. 2013;173(8):614-622



1,212 HIV+, 12,040 HIV- women

Chow et al, CROI 2016, Abstract 638

Vascular and Metabolic Disease Increase Risk for Neurocognitive Impairment

- 292 HIV+ adults in the START study
- Prior CVD was associated with NCI

Wright et al. Neurology 2010; 75: 864

- 130 HIV+ adults in the CHARTER study
- Diabetes and waist circumference were associated with NCI

McCutchan et al. Neurology 2012. 78: 485

	Risk	OR	р
Prior CVD	Yes	6.2	0.01
Total cholesterol	Higher	1.1	0.06
AIDS	No	0.41	0.08
Race	Black	2.2	0.08

	Risk	OR	р
AIDS	Yes	49.6	0.01
Diabetes	Yes	17.6	0.07
Waist circumference	Larger	1.3	0.001
Triglycerides	Lower	0.32	0.09
BMI	Smaller	0.69	0.04



Persistent Inflammation



Dyslipidemia Visceral Fat



Brain

Disease

Vascular

Disease

Blood-Brain Barrier Permeability Increases with Age and may Increase Drug Distribution into the CNS



Letendre et al, 18th CROI, 2011, Abstract 408

Croteau et al, 19th CROI, 2012, Abstract 592

Higher Concentrations of ART Drugs Can Injure Neurons in the Lab

- Fetal rat cortical neuron cultures exposed to increasing ARV concentrations
- At least mild injury was seen with all drugs
- Constructed dose-effect curves and calculated toxicity indices





EFV

NVP

5

3

Other Signs of CNS-Relevant ART Toxicity Have Been Accumulating

Longer Duration of Protease inhibitors Associated with Thicker Carotid Wall



LaBounty et al, HIV Medicine 2016, 17(7):516-23 Protease Inhibitors Associated with Cerebral Small Vessel Disease



Soontornniyomkij et al, AIDS 2014, 28:1297–1306

Higher NRTI Levels in CNS May Increase Mitochondrial and Telomere Toxicity



Torres & Lewis, Laboratory Investigation (2014) 94, 120–128

> Tenofovir was the most potent inhibitor of telomerase activity



Leeansyah et al, JID 2013; 207:1157

How can HAND be differentiated from other neurodegenerative diseases in older adults?

- In patients with HAND who are not on ART, CSF HIV viral load and markers of immune activation may be elevated (CEBM 2b; GOR B)
- Other biomarkers such as amyloid β1-42 and total tau can be abnormal in both HAND and Alzheimer's disease (CEBM 2b; GOR B). Soluble amyloid precursor protein may be able to differentiate the conditions (CEBM 2b; GOR B)
- Imaging is helpful in excluding other disorders
 - Magnetic resonance spectroscopy of the basal ganglia may be useful, since it is abnormal in HAND and rarely in other degenerative disorders (CEBM 2b; GOR B)

Mind Exchange Working Group, Clin Infect Dis. 2013; 56(7):1004-17

Older HIV+ APOE ε4 Carriers May be at Increased Risk for Brain Injury

-score



Morgan et al, J. Neurovirol. (2013) 19:150–156



Wendelken et al, J Acquir Immune Defic Syndr 2016;73:426–432

Aerobic Fitness & Exercise are Associated with Neurocognitive Performance





Exercise No Exercise

- Assessed 37 HIV+ adults older than 50 on a treadmill
- Peak VO2 (oxygen consumption) related to verbal and visual memory, visual perception, and language
- Lower peak VO2 associated with more HAND (p = 0.01)

Mapstone et al, Aging and Disease 2013, 4(6): 311-9

- 335 HIV+ adults with self-reported activity within 72 hours
- Exercisers had lower odds of global neurocognitive impairment (odds ratio = 0.38, p < 0.05)

Dufour et al, J Neurovirol 2013, 19(5):410-7

Stopping Smoking Reduces Risk for Cardiovascular Events

- More than 27,000 HIV+ patients had a total of 3,680 cardiovascular events or mortality
- Adjusted incidence rate ratio in patients who stopped smoking decreased from 2.3 within the first year to 1.5 after
 > 3 years compared with those who never smoked





Summary

- Premature aging of the brain in HIV+ adults is supported by most – but not all – reports
- Mechanisms of premature aging are being explored but may include cellular senescence with possible contributions by CMV, systemic vascular and metabolic disease, and perhaps the gut microbiome
- ART distribution into the CNS may increase with aging and could lead to greater neurotoxicity, which could in turn necessitate shifts in treatment regimens in older patients
- Interventions have not been identified but, in the short term, could include exercise and smoking cessation

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