HIV and the Aging Brain

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Disclosures

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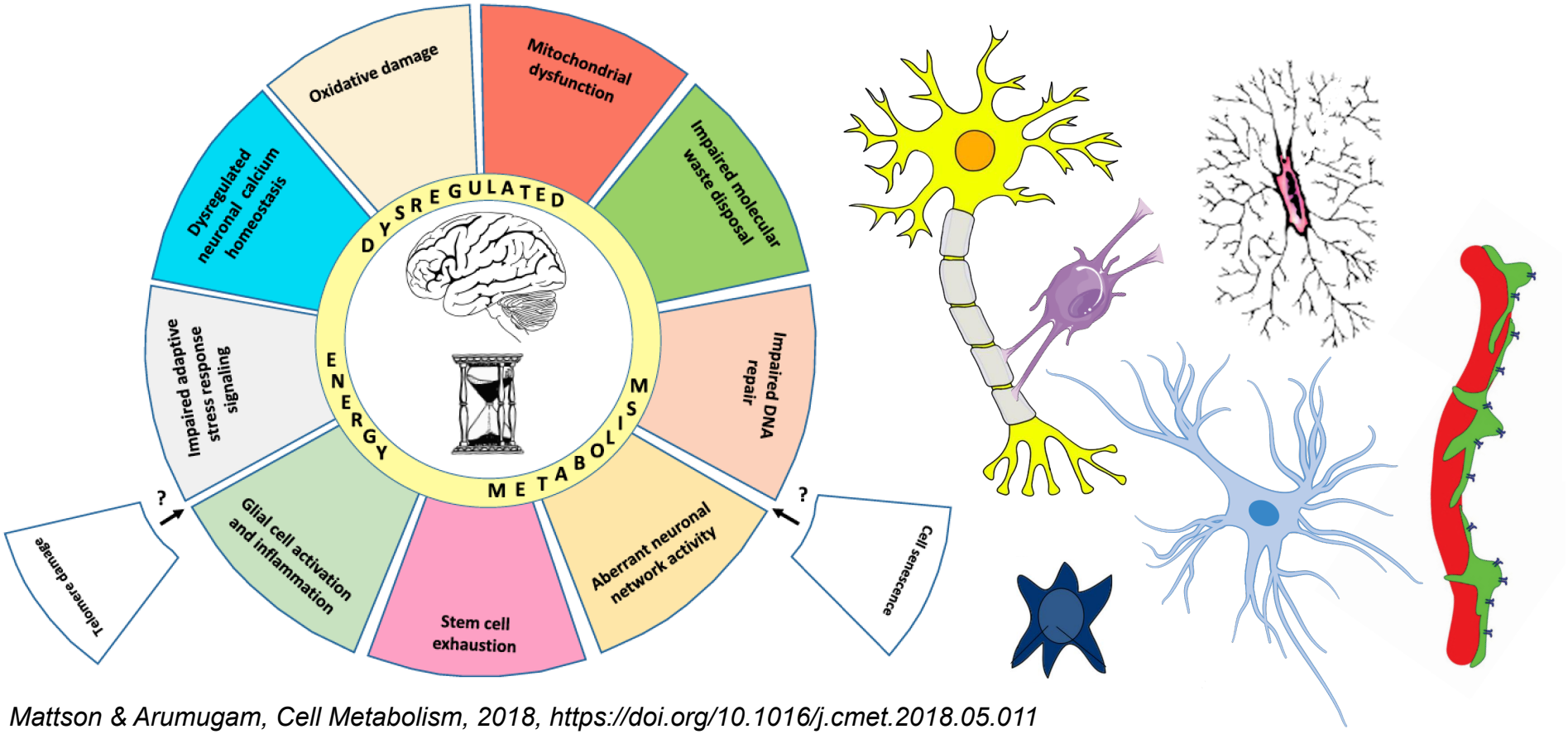
- National Institutes of Health
- Merck & Co., Inc.

Overview

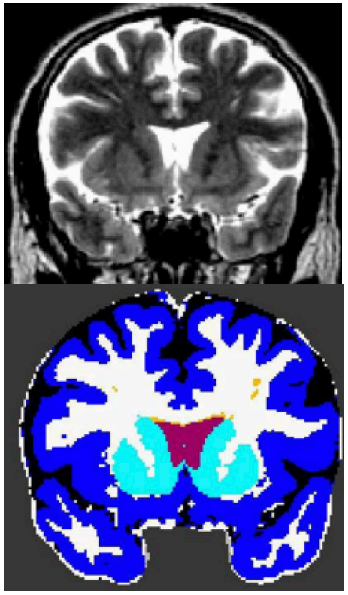
- **Premature Brain Aging in PWH**
  - **Brain Imaging**
  - **Cognitive and Mental Health**
  - **Successful Brain Aging**
- **Mechanisms of Premature Aging in PWH**
  - **Cerebrospinal Fluid Biomarkers**
  - **Biomarkers of Biological Aging**
  - **Neurotoxicity of Drugs**
- **Interventions**

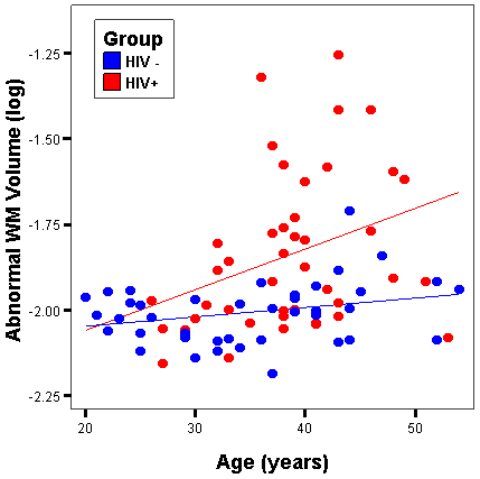
Hallmarks of Brain Aging



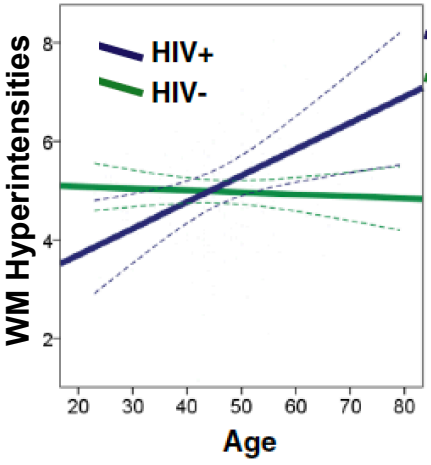
Mattson & Arumugam, Cell Metabolism, 2018, https://doi.org/10.1016/j.cmet.2018.05.011

HIV May Accelerate White Matter Injury

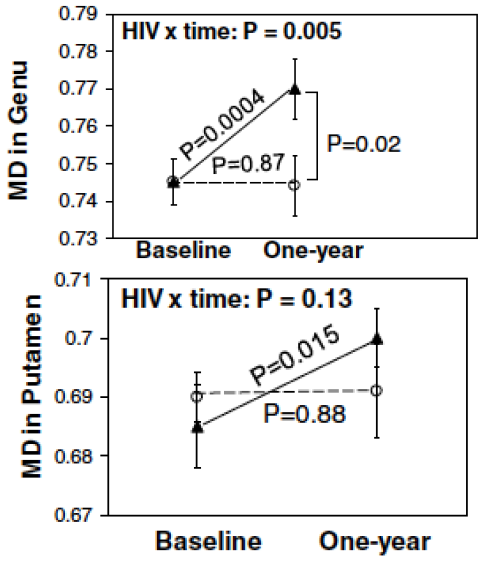




HIV x Age Interaction p = 0.003



HIV x Age Interaction p = 0.01



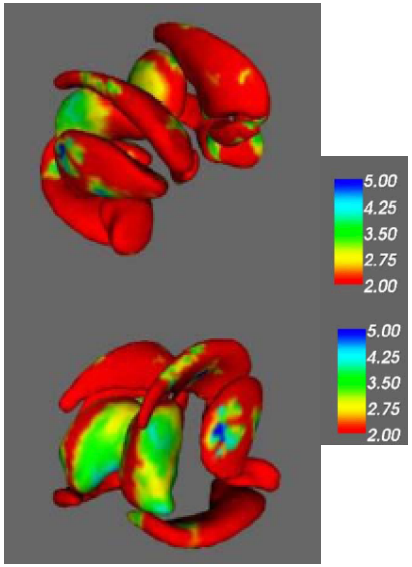
Archibald et al, J. Neurovirol. 2014; 20: 603–611

Fennema-Notestine et al, J Neurovirol, 2013; 19 (4), 393-401

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

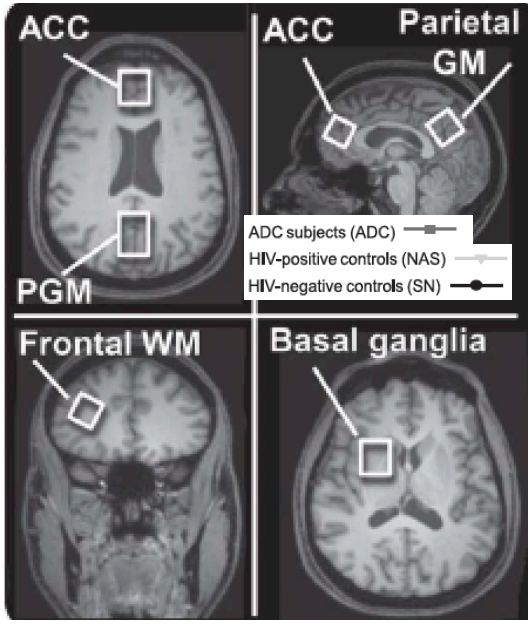
Holt et al, J. Neurovirol. (2012) 18:291–302

HIV May Accelerate Subcortical Gray Matter Changes, Gliosis, and Neuronal Injury

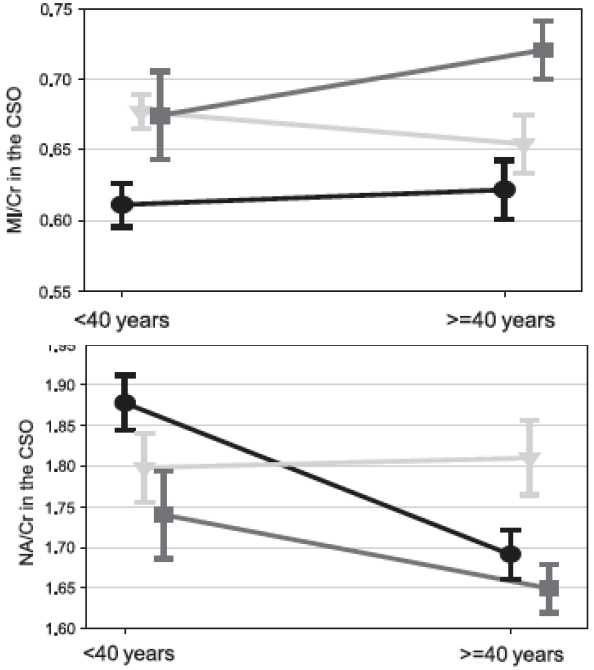


HIV x Age Interaction, p < 0.001 (bilateral nucleus accumbens, amygdala, caudate, and thalamus)

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

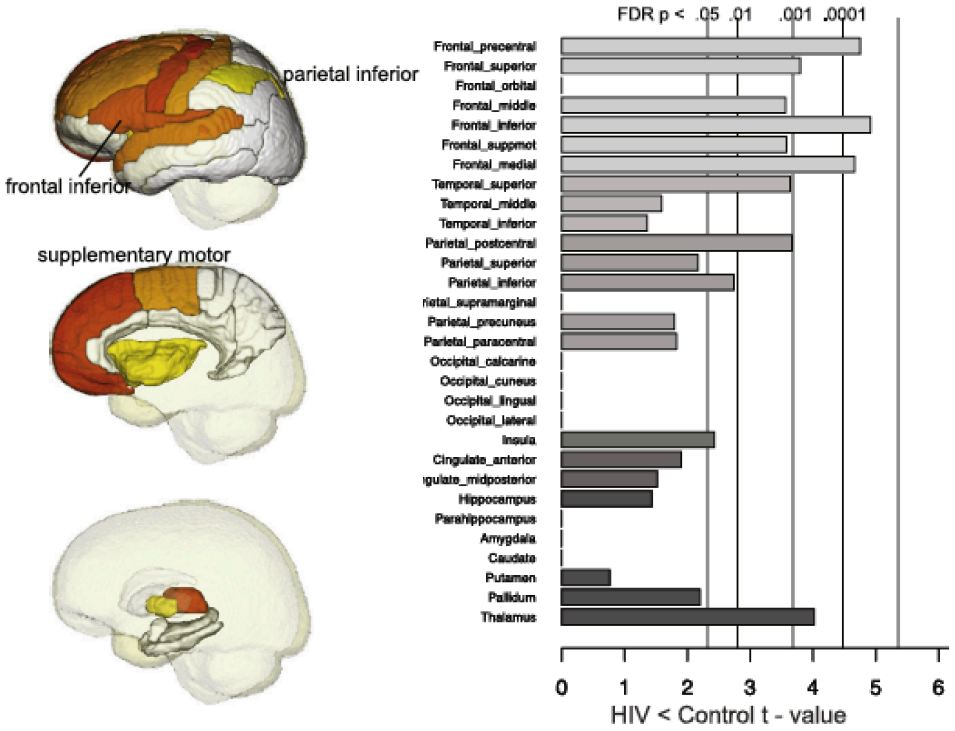


Chang et al, Neurology 2014; 82: 2213–22

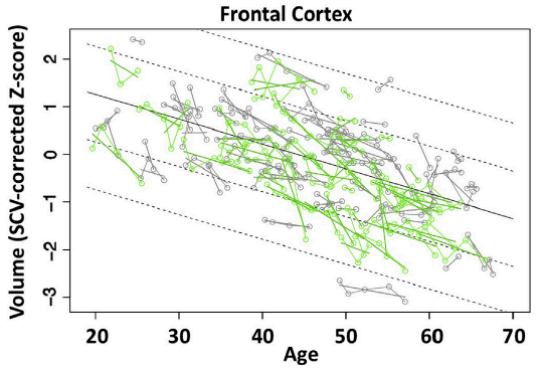


Chang et al, NeuroImage 2004; 23: 1336-47

Longitudinal Evidence Supports Differential Vulnerability of Brain Regions



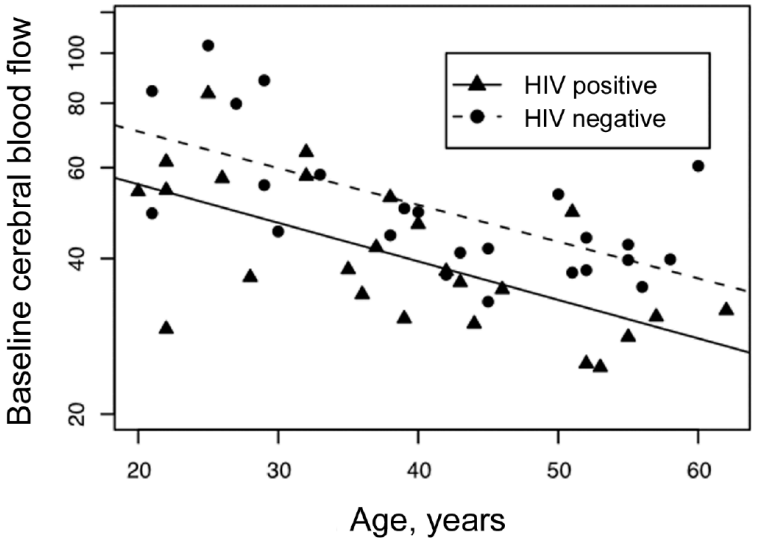
Pfefferbaum et al, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2018; 3:844–859



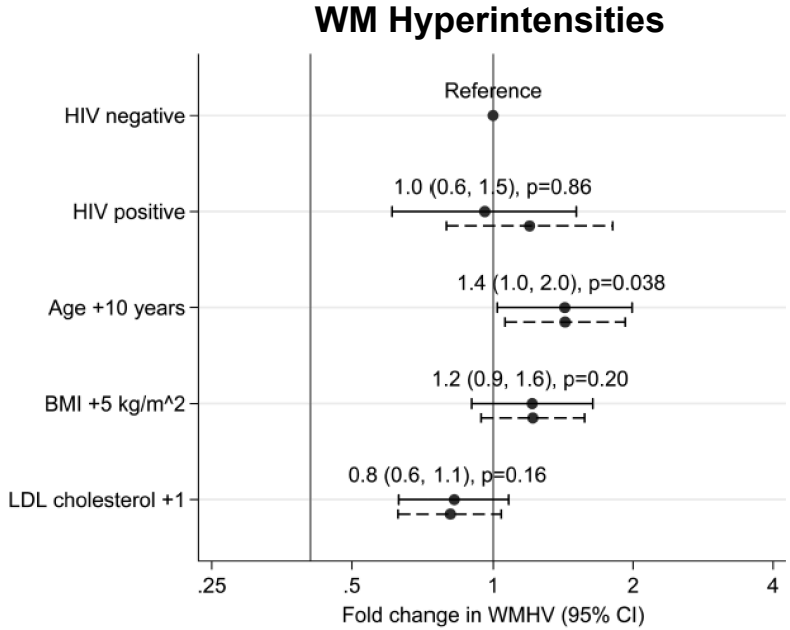
ROI	Volume differences		Trajectory differences		Acceleration (slope) with age	
	t	*p*	*t*	*p*	*t*	*p*
Lateral ventricles	1.3111	0.1925	2.5715	0.0108	1.7101	0.0900
Sylvian fissures	2.1708	0.0320	1.7452	0.0823	1.4851	0.1403
Frontal cortex	−1.4266	0.1565	−1.0916	0.2761	−2.5370	0.0126
Sensorimotor cortex	−0.2914	0.7713	0.1812	0.8563	−2.3352	0.0213
Temporoparietal cortex	−1.8728	0.0637	−0.7269	0.4680	−2.2728	0.0250
Cingulum	−2.0626	0.0414	−0.9936	0.3214	−1.3730	0.1725
Insula	−3.3542	0.0011	−1.9828	0.0486	−1.8737	0.0636
Thalamus	−3.6202	0.0004	−1.6656	0.0972	−2.6255	0.0099
Hippocampus	−2.4597	0.0154	−2.8136	0.0053	−0.8254	0.4109
Amygdala	−1.3382	0.1835	−0.5882	0.5570	0.6580	0.5119
Basal ganglia	−0.6206	0.5361	0.4741	0.6359	−0.5426	0.5885

Pfefferbaum et al, Neurobiology of Aging 35 (2014) 1755e1768

Some Imaging Studies Have Not Found Evidence of Premature Aging

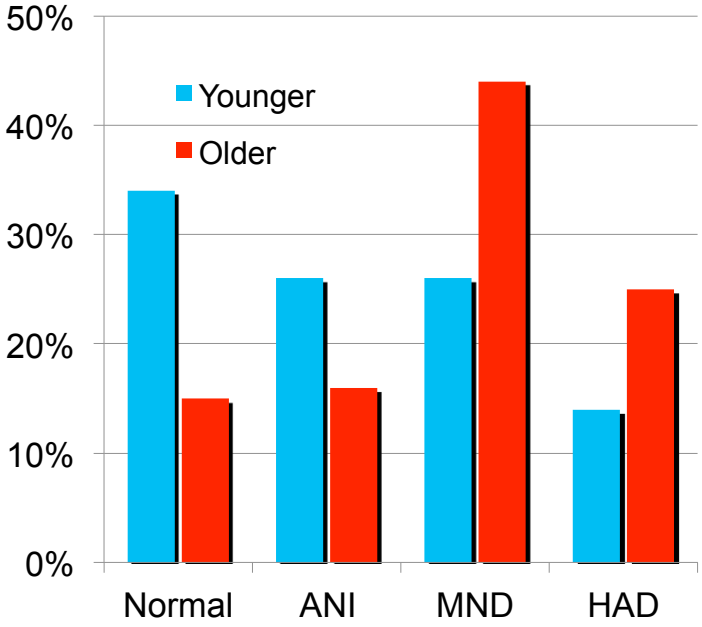


Ances et al, J Infect Dis 2010; 201:336–40

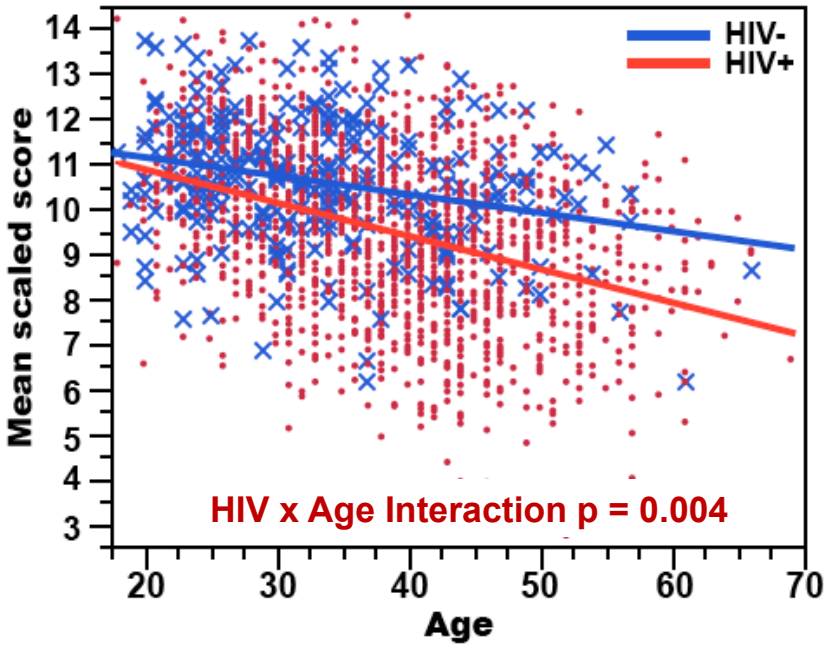


Haddow et al, AIDS Res Hum Retrovir 2019; 35(5): 453-60

HIV May Cause Premature Cognitive Decline

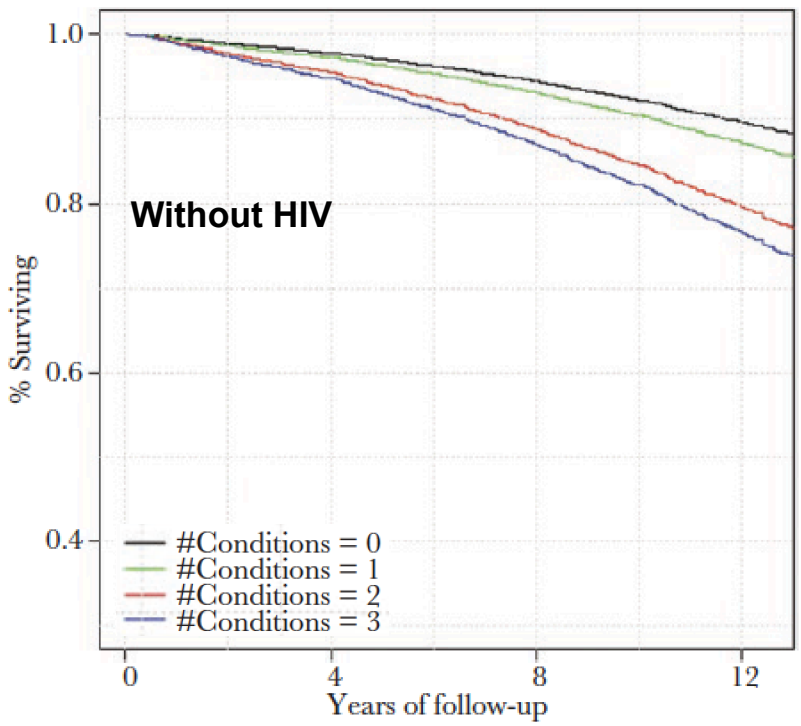


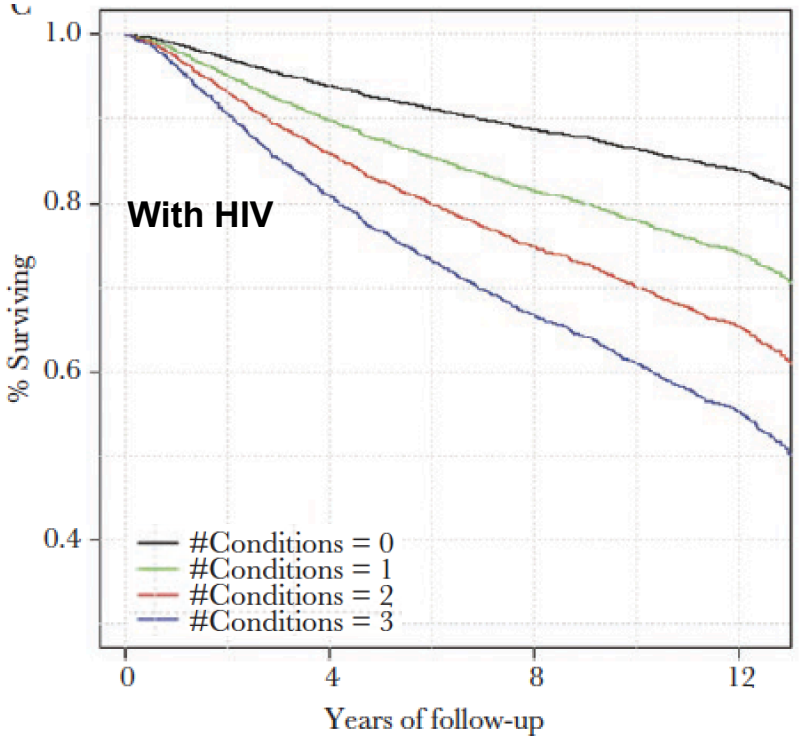
Adapted from Valcour et al, Neurology 2004;63:822–827



Heaton et al, J Neurovirology, 2012, 18(Suppl 1): S46

Greater Influence on Mortality of Depression in PWH

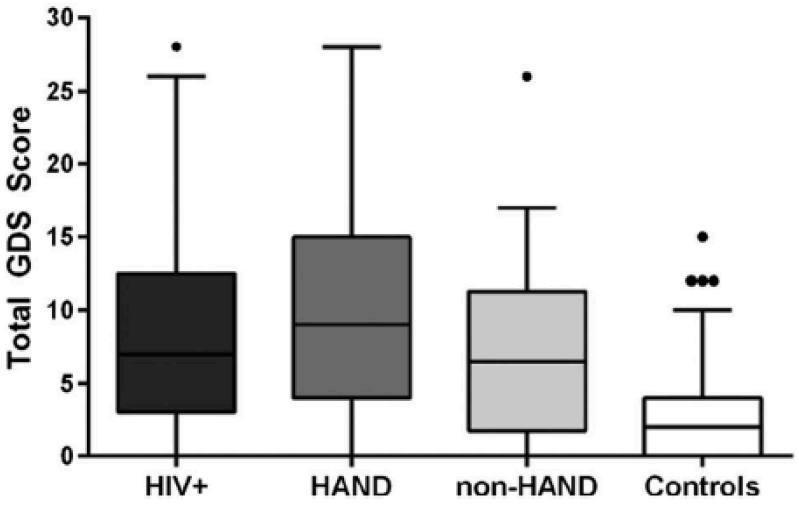




Conditions: Depression, Alcohol Use, Cigarette Smoking

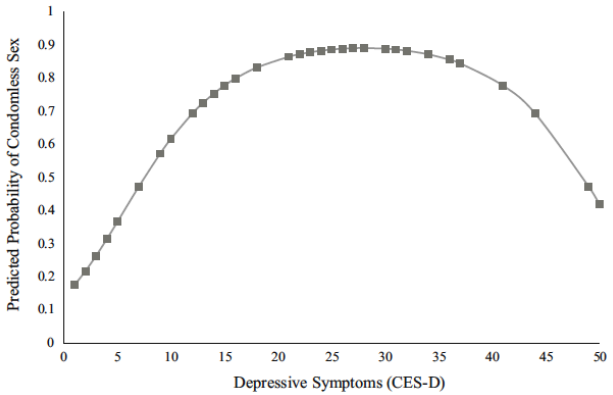
Chichetto et al, Open Forum Infectious Diseases, 2019; 1-8

Overlap Between Cognition and Depression



Milanini et al, AIDS Care, 2017; 29(9): 1178–1185

GDS: Geriatric Depression Scale

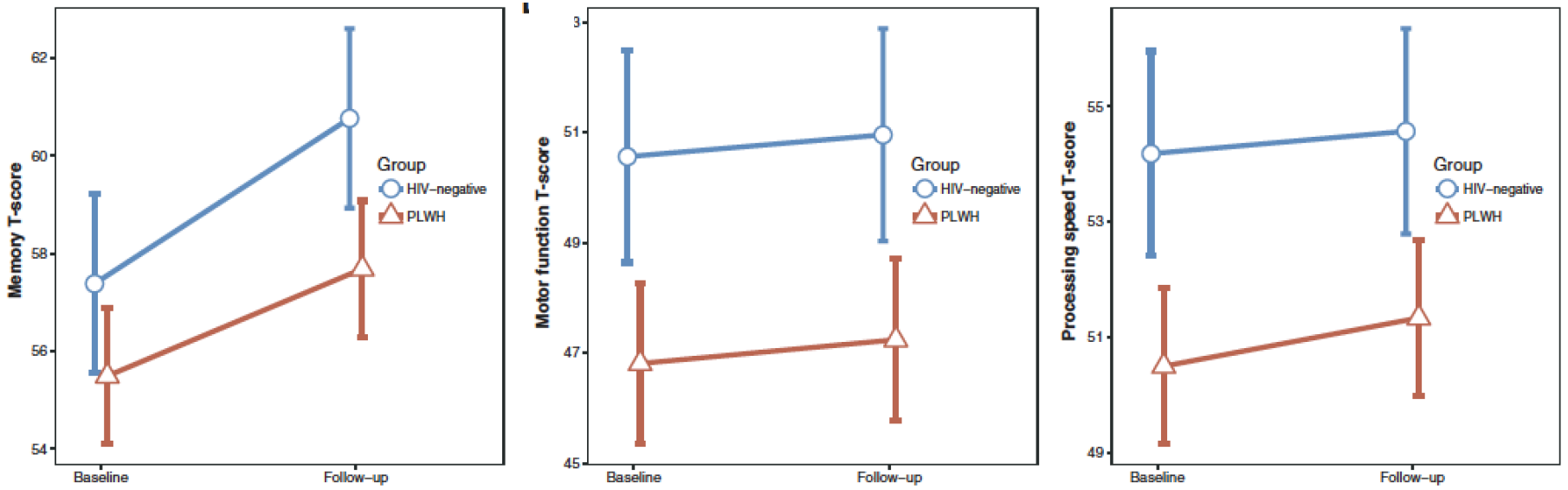


Babowitch et al, Arch Sex Behav (2018) 47:2035–2040

Outcome[a]	Effect Estimate (95% CI)	
	Per 25% Increase in % of Days With Depression	Comparing Those Always Depressed With Those Never Depressed
All-cause mortality, hazard ratio[b]	1.19 (1.05-1.36)	2.02 (1.20-3.42)
Risk of missing a scheduled appointment, risk ratio[c]	1.08 (1.05-1.11)	1.37 (1.22-1.53)
Risk of having an unsuppressed viral load, risk ratio[c]	1.05 (1.01-1.09)	1.23 (1.06-1.43)

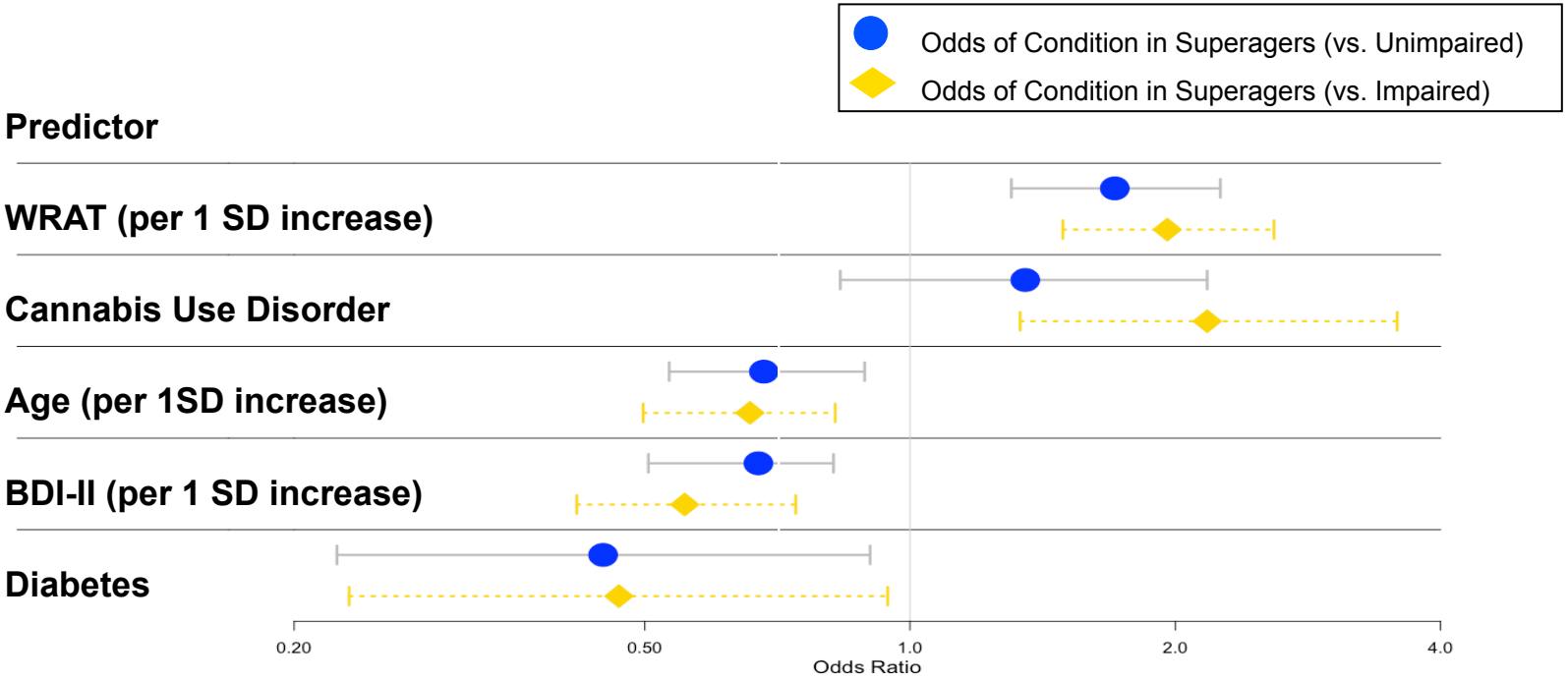
Arseniou et al, Psych Clinic Neurosci 2014; 68: 96–109

Some Cognitive Studies Have Not Found Evidence of Premature Aging



Cole et al, Clin Infect Dis, 2018; 66(12):1899–909

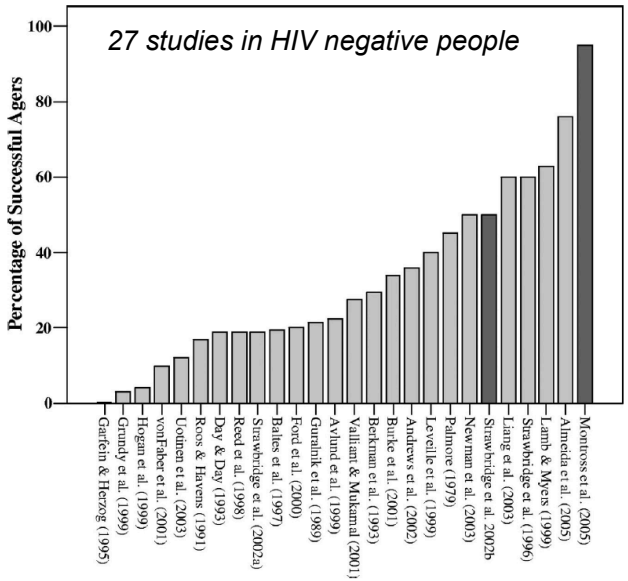
Correlates of Cognitive SuperAging in PWH



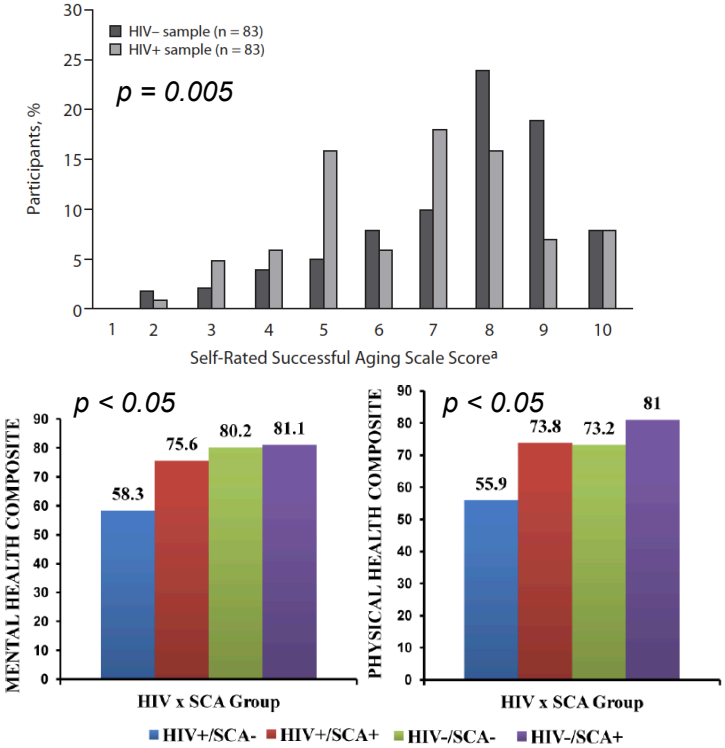
Saloner et al., 2019, PMID: 30890191

Successful Aging in 36% of the General Population: May be Lower in PWH

- **Common elements of successful aging**
  - Avoidance of disease and disability
  - Maintenance of high physical and cognitive function
  - Sustained engagement in social and productive activities
- **Subjective quality of life** may be more important than the absence of disease

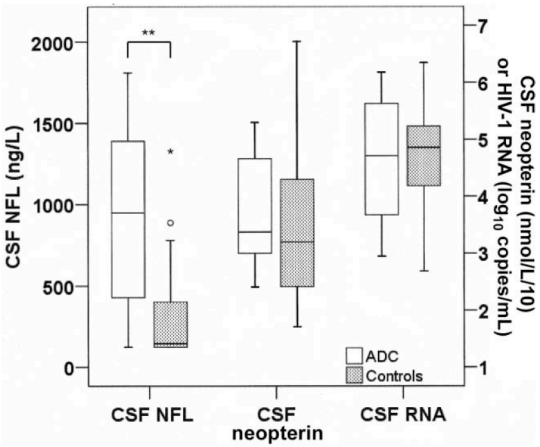


Most frequent correlates of SA: Nonsmoking and absence of disability, arthritis, and diabetes

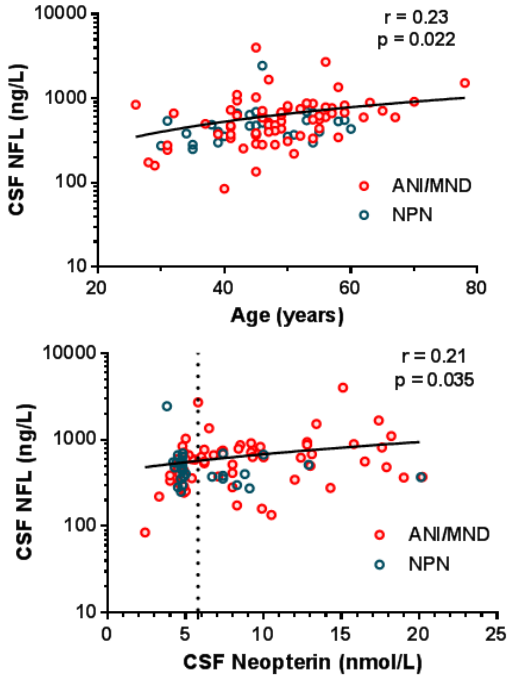


Rowe & Kahn, Gerontologist. 1997;37(4):433-40; http://en.wikipedia.org/wiki/Successful_Aging, Accessed 8 November 2013; Depp & Jeste, American Journal of Geriatric Psychiatry. 2006; 14: 6-20; Moore et al, J Clinical Psychiatry 2013, 74: e417-23; Moore et al, AIDS Behav. 2018 ; 22(5): 1551–1561

Older Age is Associated with Higher Concentrations of Many Biomarkers in PWH



Gisslen et al, J Infect Dis, 2007; 195: 1774-8

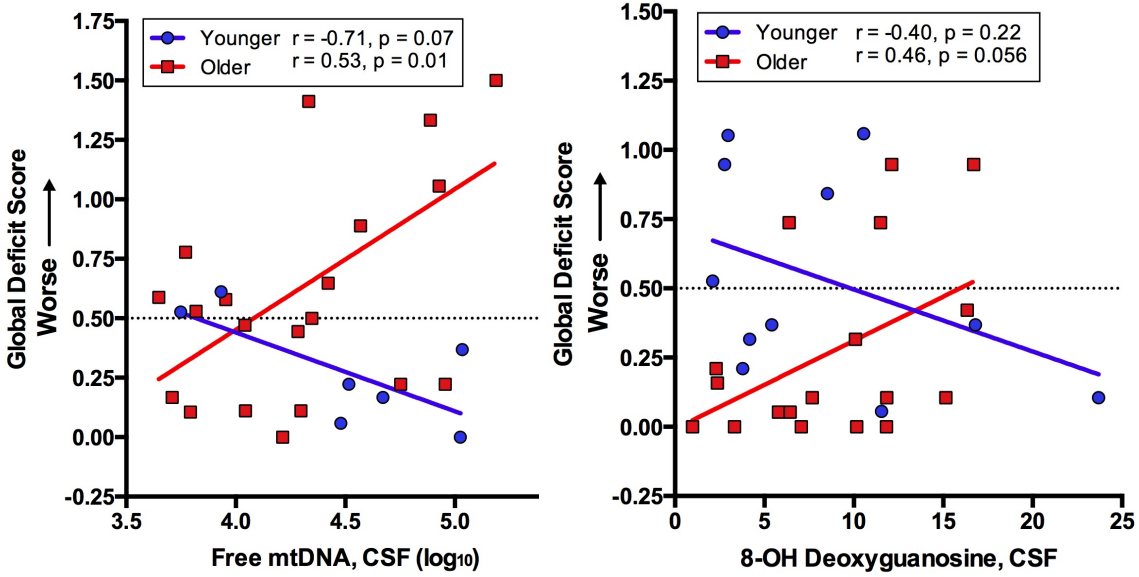


Eden, et al, PLoS One, 2016; 11 (6), e0157160

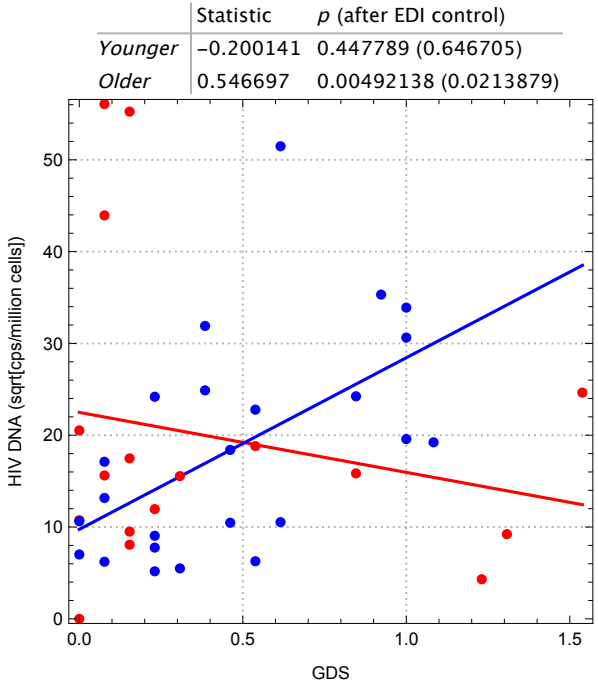
	Correlation		Interaction
	Age	GDS	Age x Biomarker
Viral			
- HIV RNA (SCA)	✗	✗	-
- HIV DNA	-	-	✗
Neuronal			
- Phospho-Tau (181)	✗	✗	✗
- Total tau	✗	✗	-
- Neurofilament Light	✗	-	-
Aging			
- Telomere Length	✗	-	✗
- Mitochondrial Common Deletion	✗	✗	-
- Free Mitochondrial DNA	✗	-	✗
- 8-OHdG	✗	✗	✗
- Protein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

Unpublished UCSD Data

Aging Alters Associations Between Some Biomarkers and Cognition

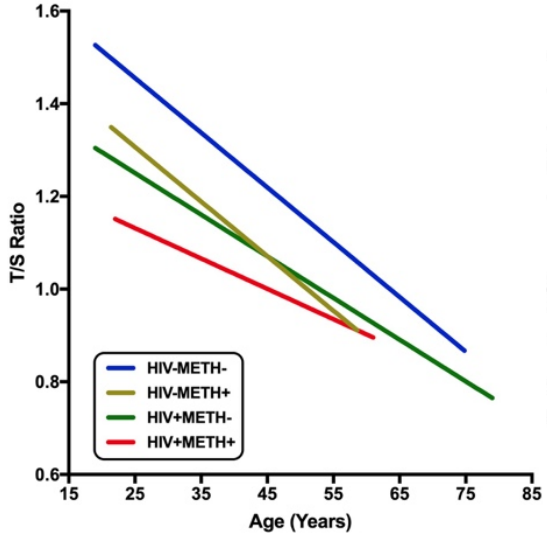


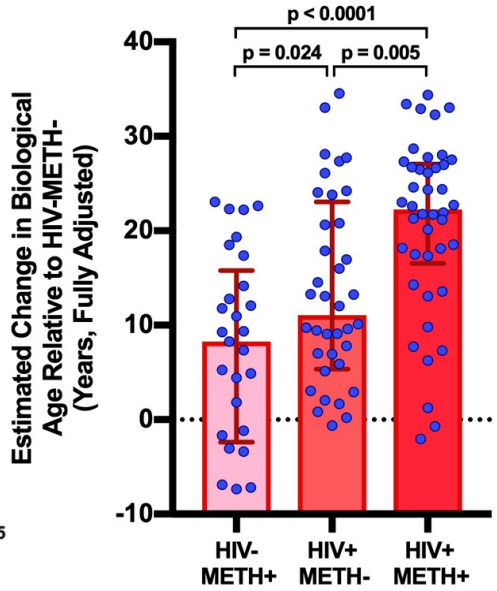
Unpublished UCSD Data
Free mtDNA Data Courtesy Sanjay Mehta



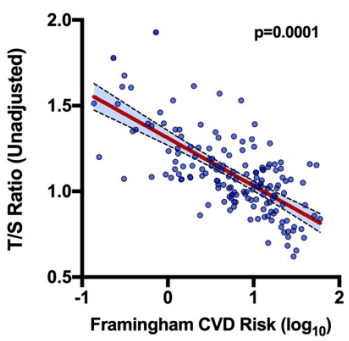
Oliveira et al, Sci Rep, 2015; 5, 17094

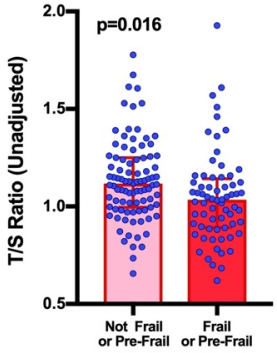
HIV, Methamphetamine, & Shorter Telomeres

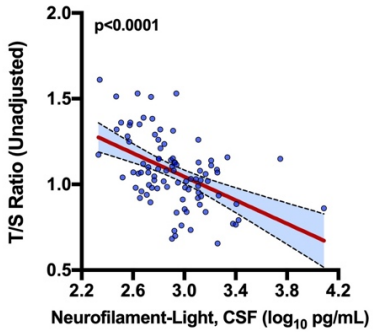


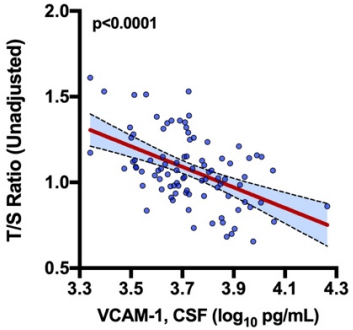


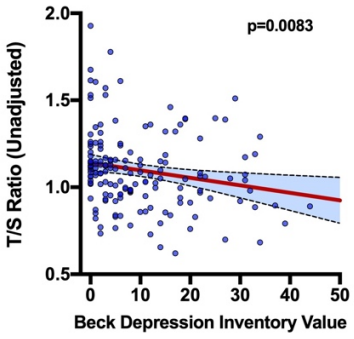
Mehta, Letendre, et al. Manuscript Submitted, 2019

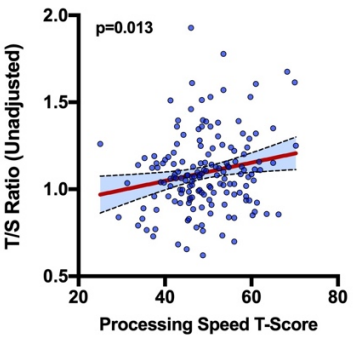




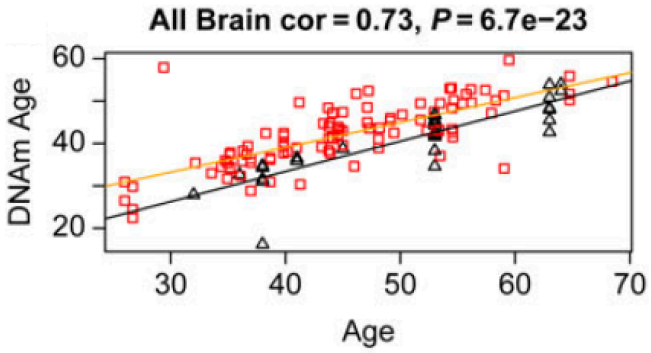


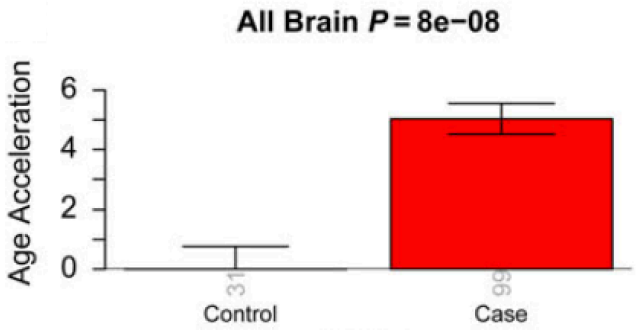




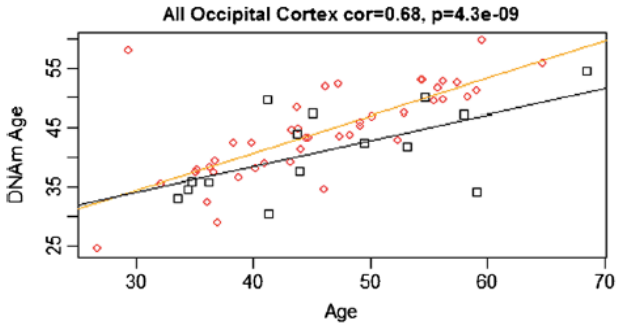


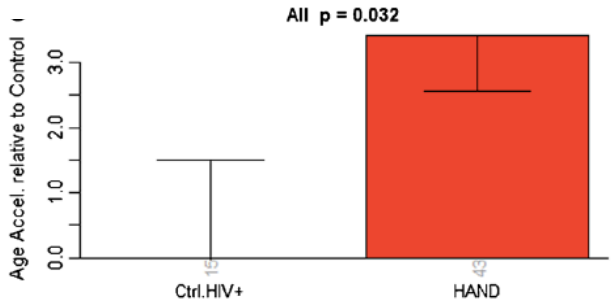
Evidence of Premature Brain Aging by the Epigenetic Clock Method





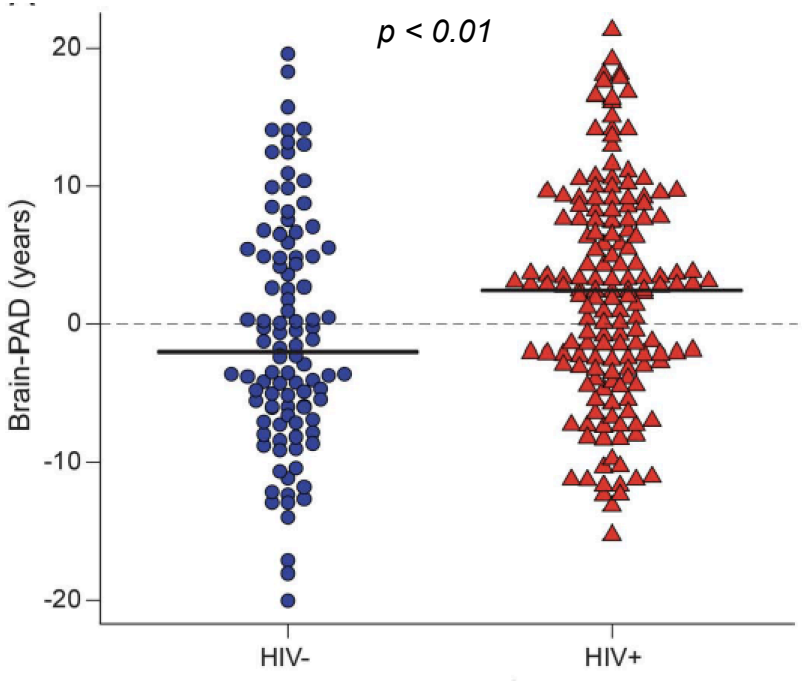
Horvath & Levine, J Infect Dis 2015; 212:1563–7

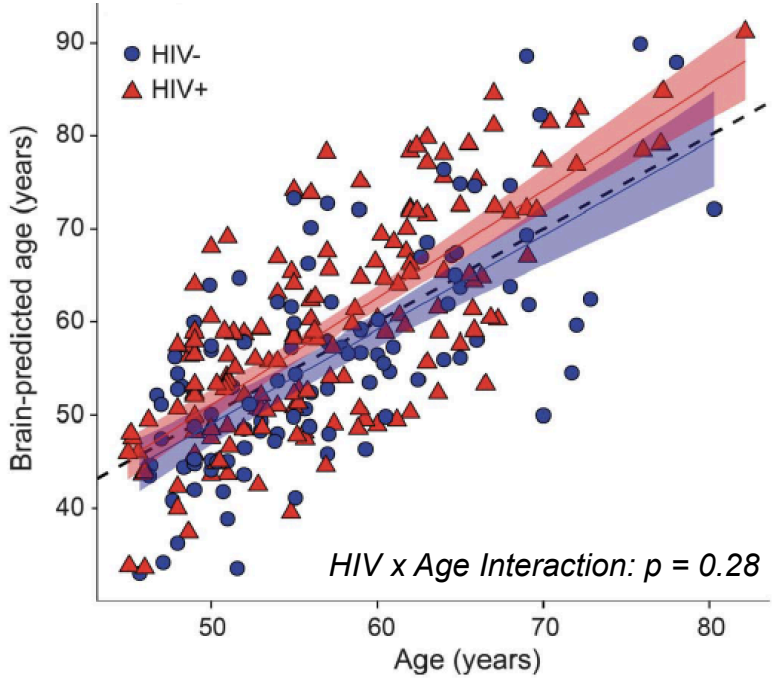




Levine et al, J Neurovirol 2016, 22(3):366-75

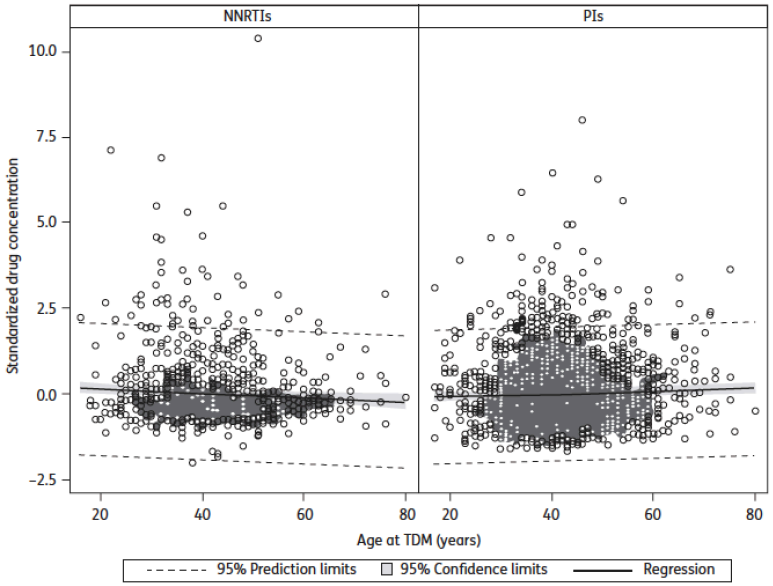
Imaging-Based Brain-Predicted Age is Older in PWH



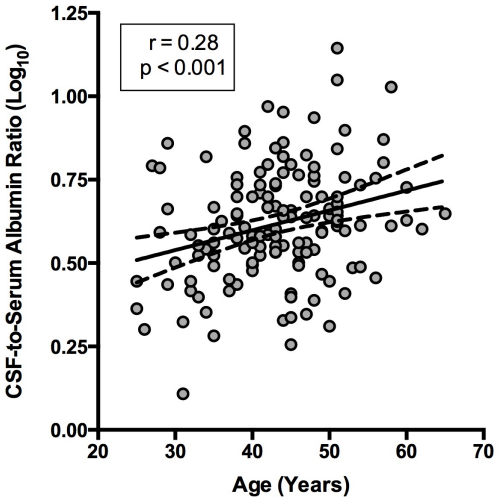


Cole, et al, Neurology 2017; 88:1349–1357

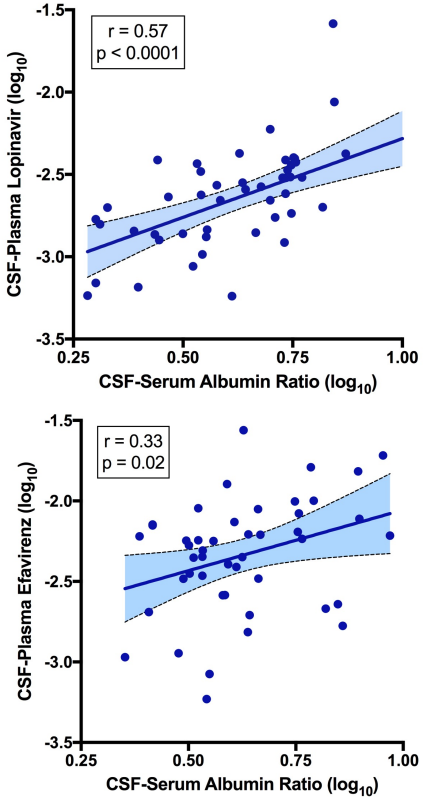
Older Age May Alter Drug Metabolism and Distribution into the CNS



Winston et al, J Antimicrob Chemother 2013; doi:10.1093/jac/dkt029

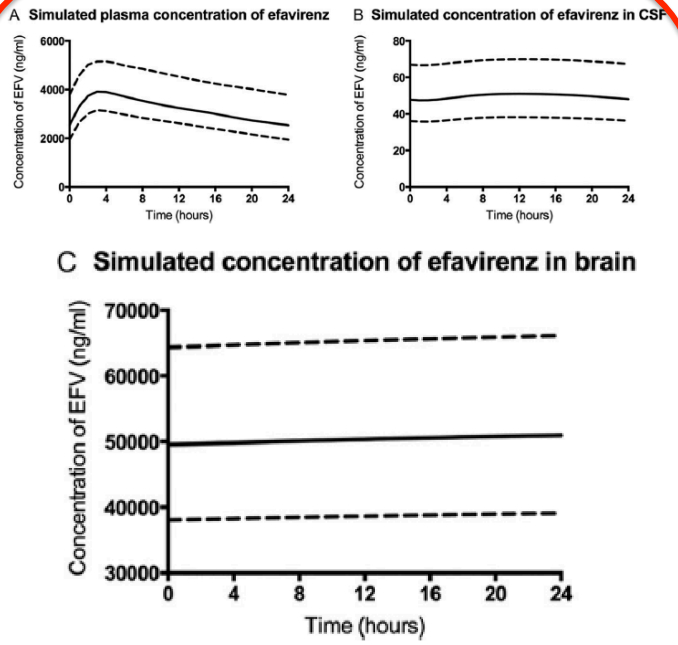


Letendre et al, 18th CROI, 2011, Abstract 408

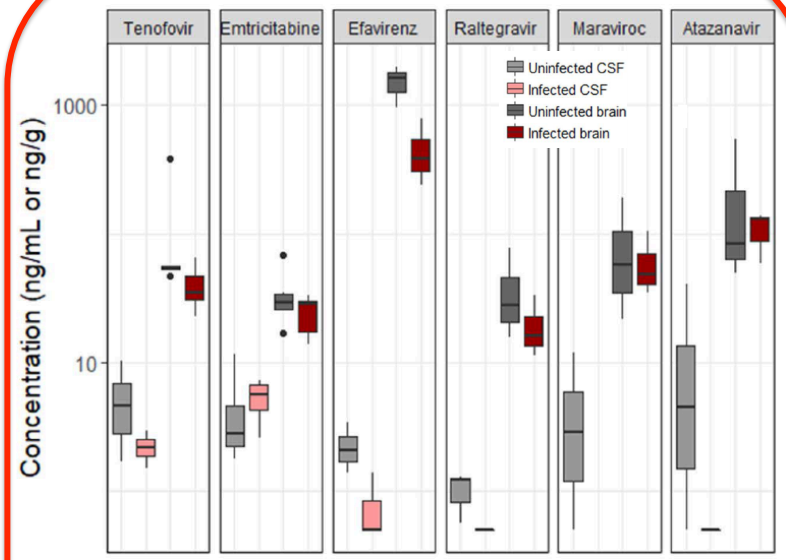


Croteau et al, 19th CROI, 2012, Abstract 592

Animal Models Support That ART Concentrations in Brain Are Much Higher Than in CSF

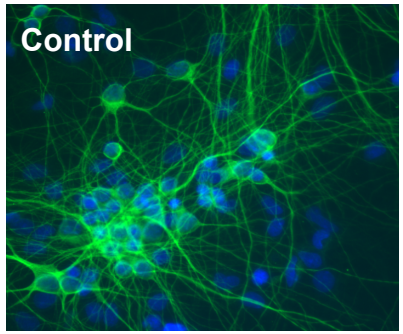


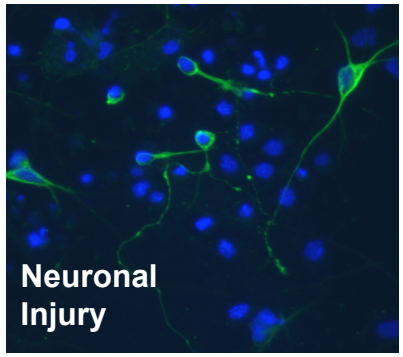
Curley et al, AAC 2017, 61(1): e01841-16

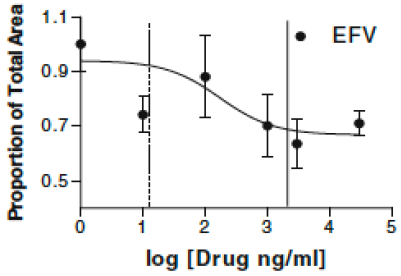


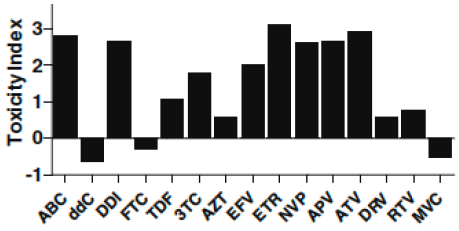
Srinivas et al, IAS 2017, Abstract WEAB0105
Srinivas et al, Xenobiotica 2018, 17:1-10

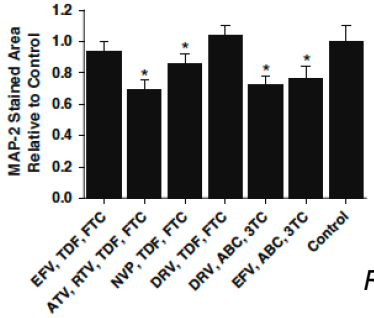
In Vitro Evidence of ART Toxicity in Neuronal Cell Culture











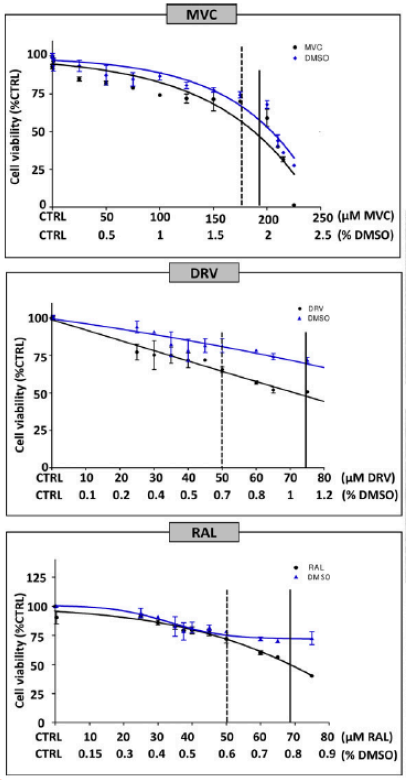
	Mitochondrial Assay			Neurite Outgrowth Assay				
	MMP	ROS	Cytotx	Outgrowth		Retraction		Cytotx
				length	branch	length	branch	
Abacavir	1.6	1.1	-0.2	1.1	1.0	0.1	-0.2	-0.6
Tenofovir	1.6	0.0	-0.5	0.5	0.5	-1.6	-1.0	0.4
Efavirenz	-13.6	0.5	-6.8	2.9	1.1	-3.3	-0.6	-2.6
Rilpivirine	-6.2	1.0	-0.7	1.3	1.0	-2.8	-1.9	-2.2
Elvitegravir	-10.4	2.1	-1.5	0.8	0.5	-1.5	-1.2	-1.7
Dolutegravir	1.0	0.5	-0.5	3.2	4.0	-0.5	0.3	-0.5
Atazanavir	-2.4	1.9	-0.5	1.4	1.0	-0.5	-1.3	-0.5
Darunavir	2.1	0.4	-0.4	1.2	0.8	0.0	-0.3	-0.8
Ritonavir	-5.2	2.8	-0.4	0.2	0.3	-1.7	-0.5	-0.8
Cobicstat	-12.0	7.7	1.0	1.1	1.1	-1.6	-2.4	-1.7
Menadione	-12.0	10.6	-20.9					
Staurosporine				7.1	9.6	-0.9	0.2	-1.2
BIO				-2.2	-0.4	-3.6	-2.2	0.6

Hinckley et al, CROI 2016, Abstract 395

Robertson et al, J Neurovirol 2012, 18: 388-299

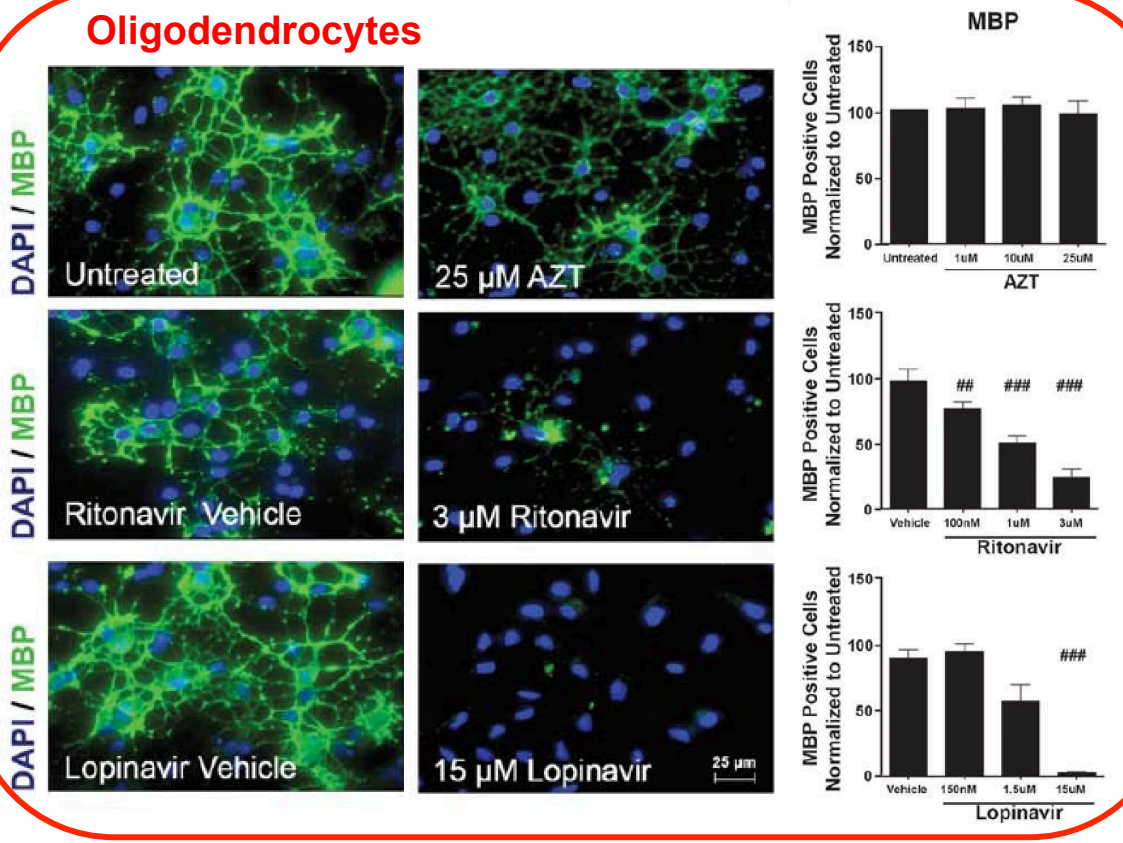
ART Toxicity in Other Glial Cells

Astrocytes



Latronico et al, J Neurochem 2018, 144: 271-84

Oligodendrocytes



Jensen et al, J Neuropathol Exp Neurol 2015, 74(11): 1093-1118

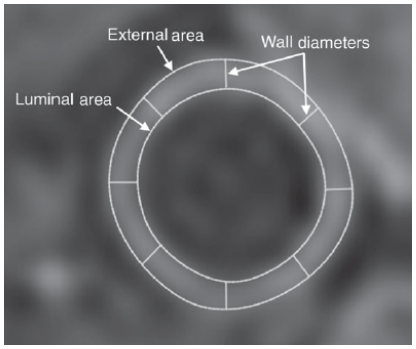
Evidence of Clinical Neurotoxicity Has Been Accumulating

Efavirenz is Associated with HAND

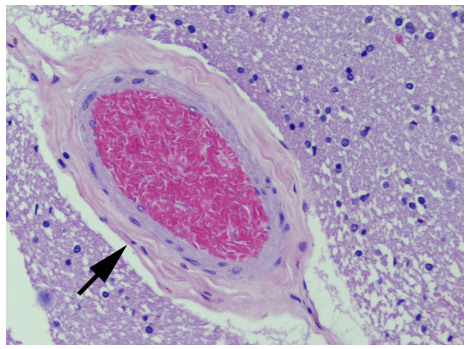
Risk Factor	Odds Ratio	P Value
Age (per 10 years)	0.83	0.29
Education (per 1 year)	0.85	0.002
Non-Italian Born	3.5	0.056
Efavirenz use	**4.0**	**0.008**

Ciccarelli et al, Neurology 2011, 76: 1403

PIs are Associated with Carotid Thickening and Cerebral Small Vessel Disease



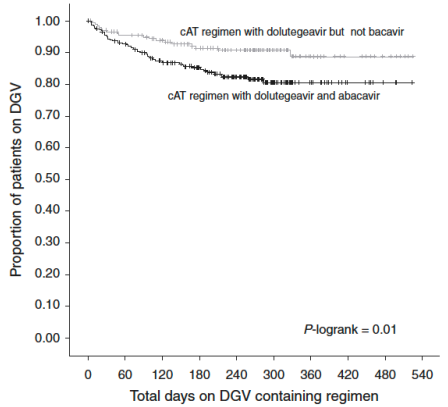
LaBounty et al, HIV Medicine 2016, 17(7):516-23



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

Dolutegravir, NP AEs, & Discontinuation

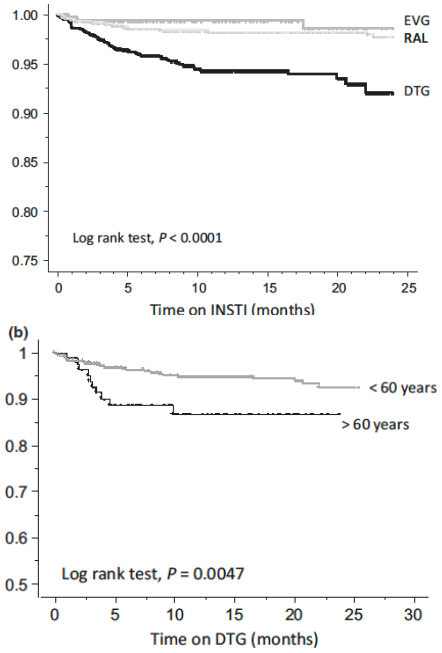
N=565
DTG Only



Adverse drug reaction	*n* (%)
Sleep disturbance, insomnia	31 (5.6)
Gastrointestinal complaints	21 (3.8)
Joint, tendon and/or muscle pain	11 (2.0)
Psychological/psychiatric symptoms[b]	14 (2.5)
Neurologic symptoms	10 (1.8)
General malaise (headache and severe fatigue)	24 (4.3)
Respiratory tract complaints	5 (0.9)
Other	9 (1.6)

de Boer et al, AIDS 2016, 30:2831–2834

N=1,950
InSTIs Only



Hoffmann et al, HIV Medicine 2017, 18, 56--63

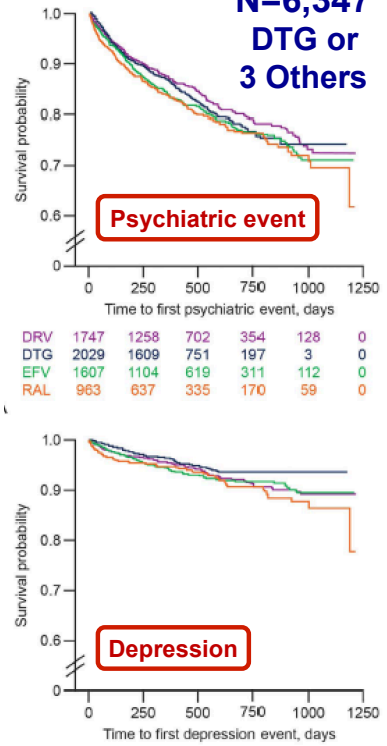
N=4,041
DTG vs. RAL

Variable	HR[a]	*P* value
Female	1.98	<0.001
Age, per 10 years older	0.93	0.319
Nonwhite ethnicity	0.75	0.172
Prior AIDS-defining condition	0.89	0.513
HCV-coinfection	0.80	0.221
$CD4^+$ cells per μl		
<350		
350–500	0.98	0.880
>500	1.07	0.735
HIV RNA >100 000 copies per ml	1.53	0.149
Treatment naive	1.05	0.858
Backbone		
Abacavir–lamivudine		
Tenofovir–emtricitabine	0.91	0.626
Other	0.97	0.902
Raltegravir versus dolutegravir	1.30	0.140

Toxicity:
RAL 4.3%
DTG 3.6%

Elzi et al, AIDS 2017, 31:1853–1858

N=6,347
DTG or 3 Others



Fettiplace et al, J AIDS 2017;74:423–431

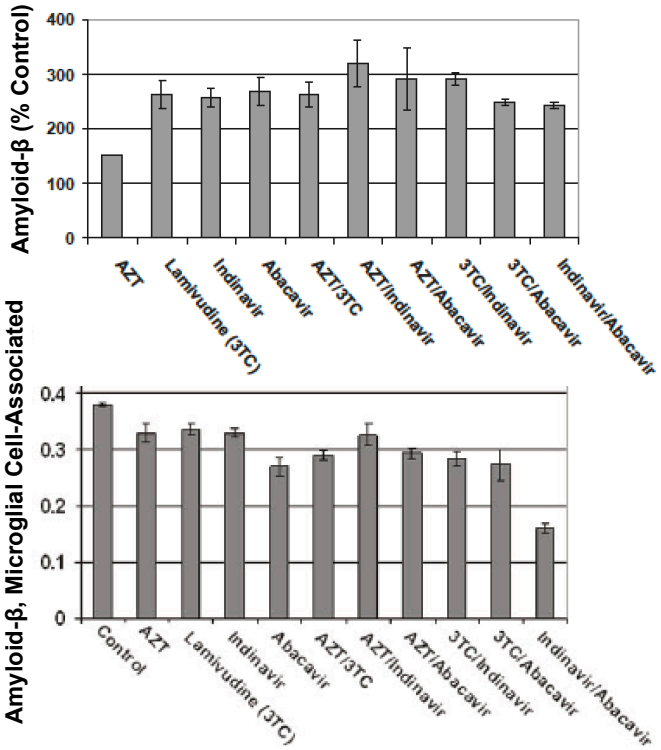
Summary of *in vitro* Evidence of Mechanisms of Neurotoxicity

Drug	Effect
Maraviroc	↑ Microglial activation
Raltegravir	↑ IL-8 in brain macrophages
Efavirenz	↑ TNF-α and IL-1β
	Dendritic spine injury
	Mitochondrial alterations
	↑ Autophagy
	↑ β-Secretase expression, ↑ amyloid-β, ↑ ROS
	↑ Endoplasmic reticulum stress
	↓ ATP stores; ↓ neural stem cell proliferation
Etravirine	↓ MAP-2 density in rat neurons

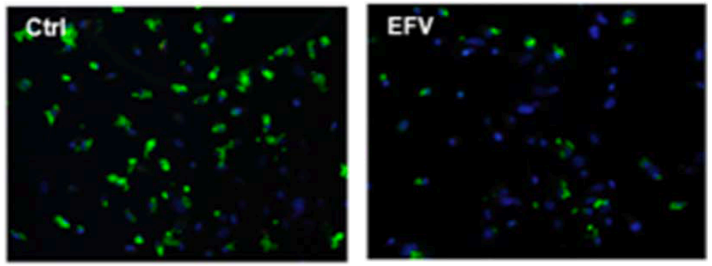
Drug	Effect
Zidovudine	↓ Mitochondrial DNA in cortical neurons
	↑ Amyloid-β production
Lamivudine	↓ Mitochondrial DNA in cortical neurons
	↑ Amyloid-β production
Abacavir	↑ Amyloid-β production
Indinavir	↑ Amyloid-β production
Lopinavir	↓ Myelin basic protein, ↓ galactocerebroside in oligodendrocytes
	↑ Oxidative stress, ↑ ER stress, ↑ IL-6 and TNF-α in macrophages
	↓ Tight junction proteins, ↓ synaptic proteins, ↑ TNF-α, IL-6 and IL-1β
Atazanavir	↑ Oxidative stress, ↓ MAP-2, ↓ synaptophysin

Shah et al, Neurotox Res (2016) 30:677–697 691

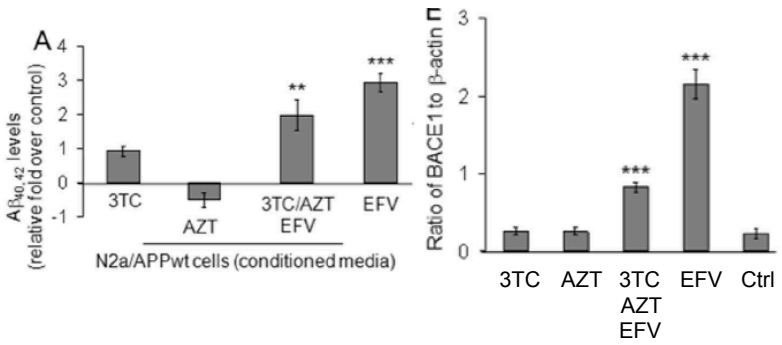
ART Drugs Can Increase Amyloid-β & Reduce Microglial Phagocytosis



Giunta et al, Molecular Brain 2011, 4:23

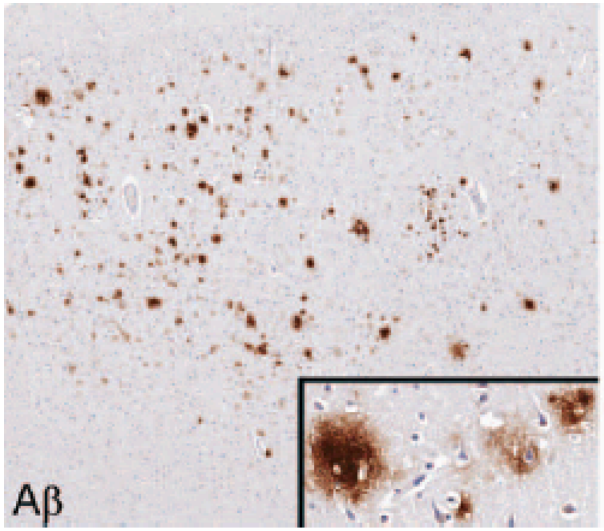


EFV Reduces Microglial Phagocytosis of $A\beta_{1\text{-}42}$

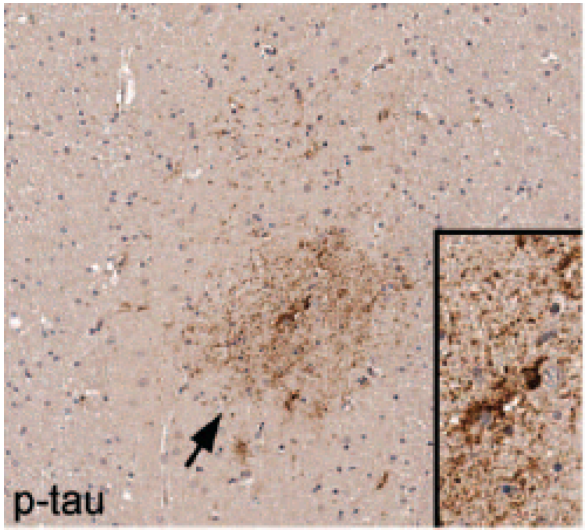


Brown et al, PLoS ONE 2014, 9(4): e95500

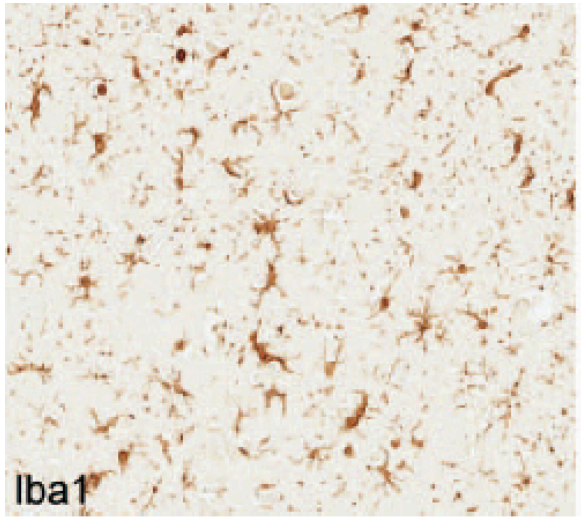
Amyloid and Phospho-Tau Neuropathology May be Influenced by Antiretrovirals



Tenofovir use prior to death associated with lower odds of amyloid β plaque deposition
(OR 0.13, p=0.012)



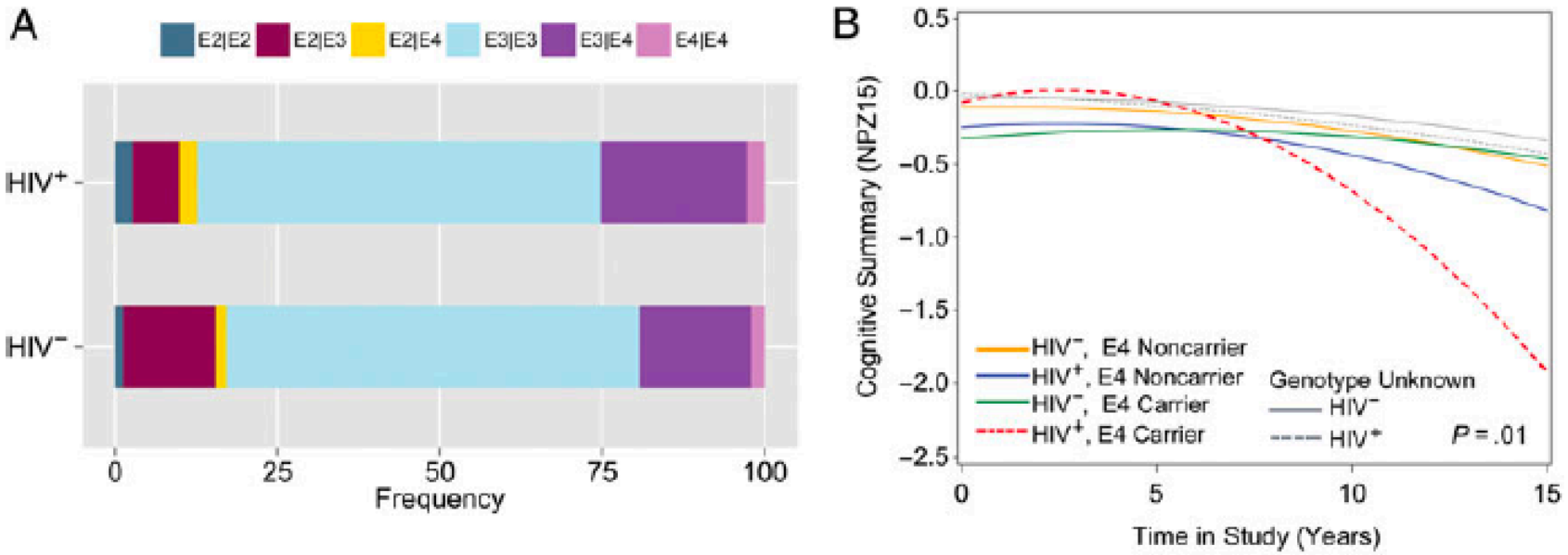
Darunavir use prior to death associated with higher odds of phopho-tau deposition in neurons
(OR 15.3, p=0.0005)



Ritonavir use prior to death associated with higher odds of microgliosis
(OR 4.96, p=0.023)

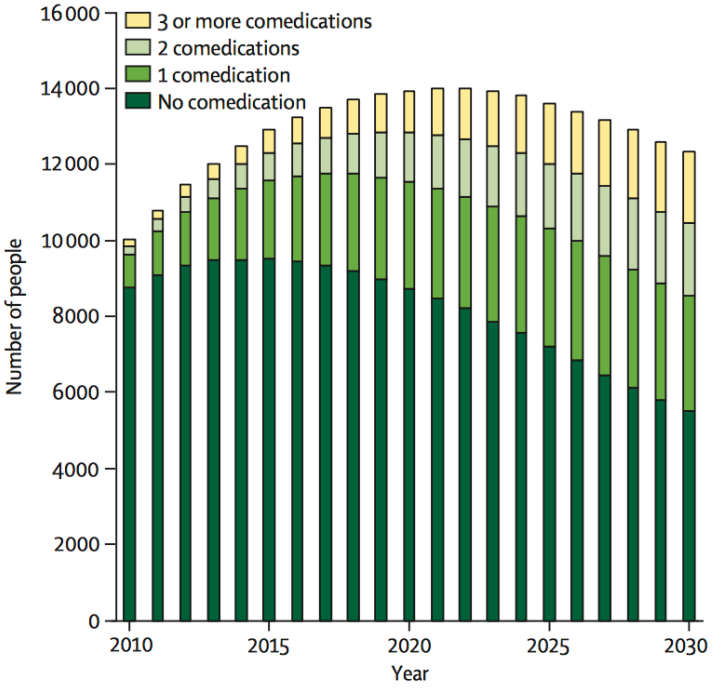
Soontornniyomkij et al, AIDS 2018, 32: 2005–2015

APOE ε4 is Associated with Cognitive Decline in Men with HIV in MACS

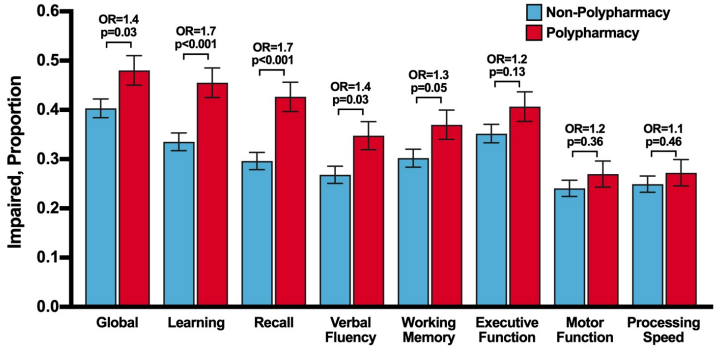


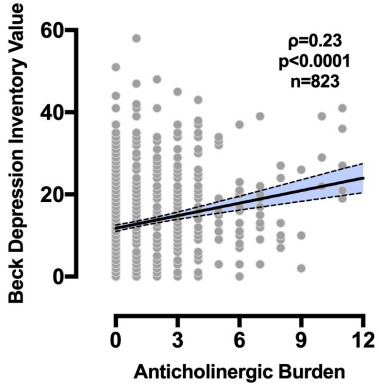
Mukerji et al, Clinical Infectious Diseases 2016;63(8):1130–9

Risks of Polypharmacy in Aging PWH



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



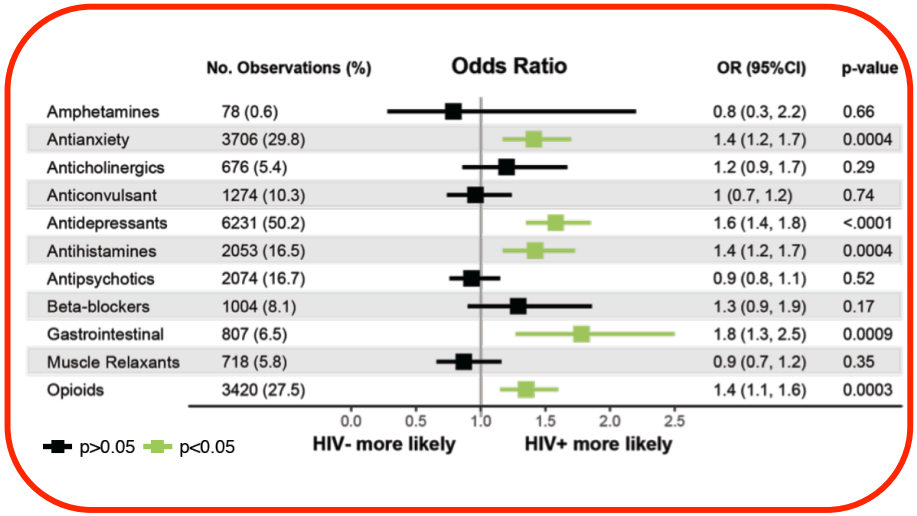


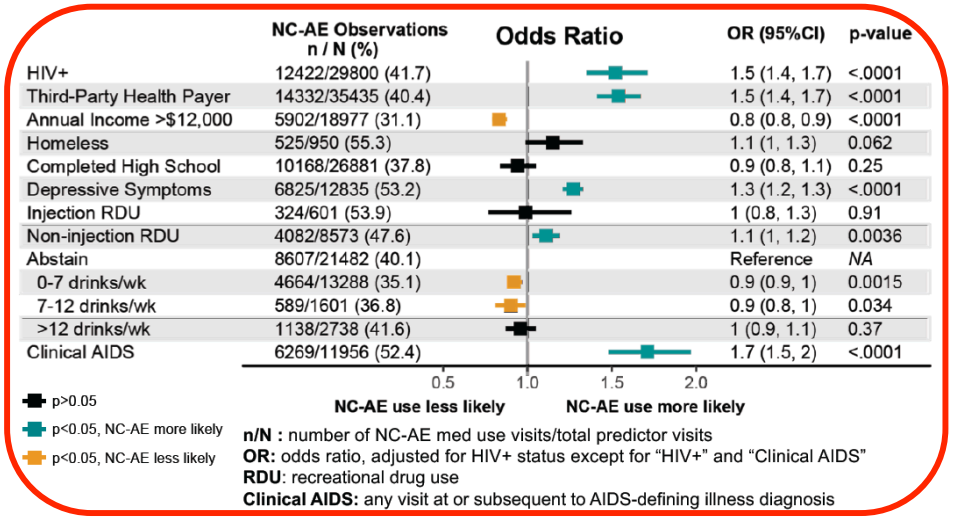
	Learning	Executive Function	Working Memory	Recall	Processing Speed	Motor Function	Verbal Fluency
Anxiolytics	**	**	**	**	**	-	*
Antipsychotics	**	**	**	**	-	*	**
Opioids	**	**	**	*	**	*	-
Antimicrobials	**	**	-	**	*	-	-

** (Red): p < 0.01, * (Yellow): p < 0.05, - (Green): p > 0.10, statistical significance

Ma, et al CROI 2019, Abstract 437

Women with HIV are More Likely to Use Other Medications Associated with NP-AEs





n/N : number of NC-AE med use visits/total predictor visits
OR: odds ratio, adjusted for HIV+ status except for "HIV+" and "Clinical AIDS"
RDU: recreational drug use
Clinical AIDS: any visit at or subsequent to AIDS-defining illness diagnosis

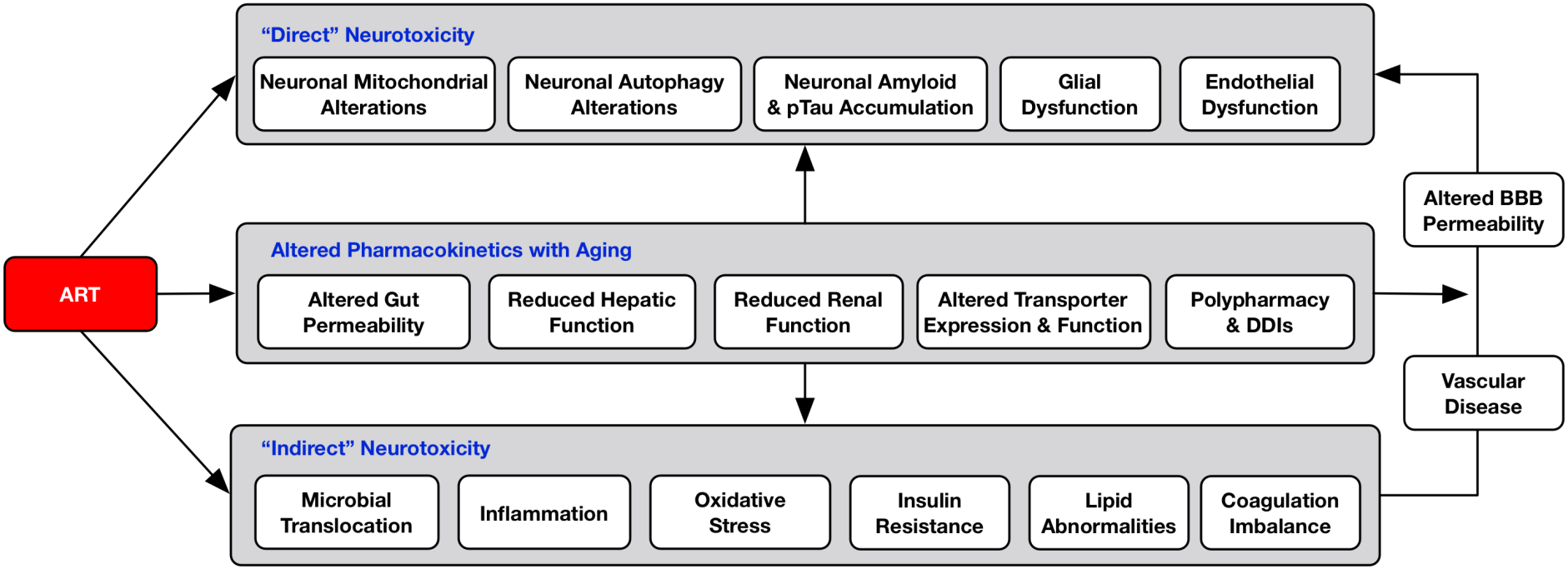
NP-AE Drug Use and ART

Outcome	OR (95% CI)	p-value
cART use	1.46 (1.35-1.57)	<0.0001
cART adherence	1.03 (0.95-1.12)	0.45
Undectable viral load	1.12 (1.05-1.19)	0.0008

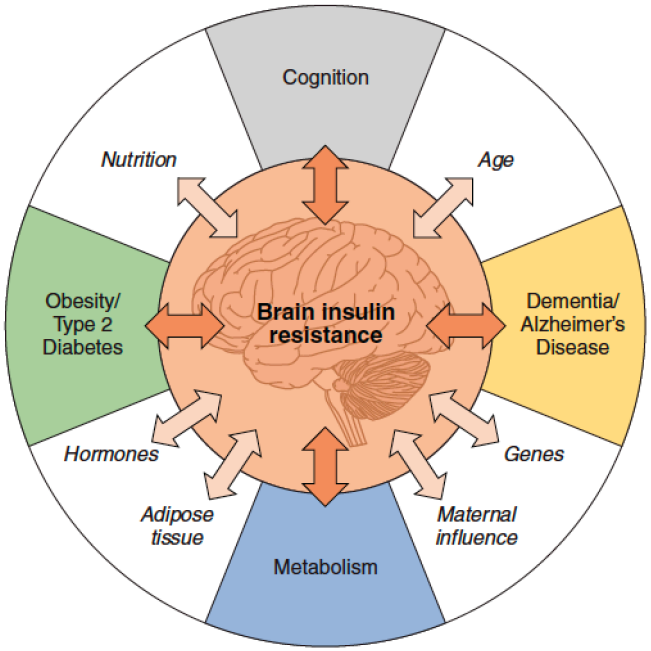
CROI
Conference on Retroviruses and Opportunistic Infections

Radtke, et al. CROI 2018, Abstract 401

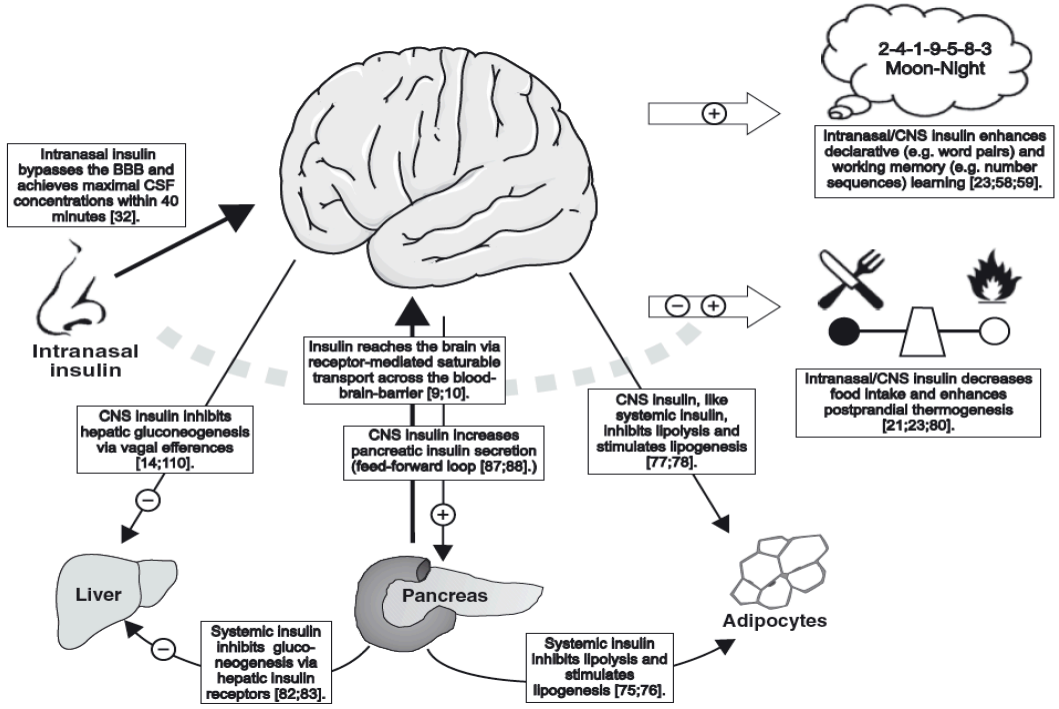
Multiple Mechanisms May Contribute to Neurotoxicity of Drugs with Aging



Brain Insulin Resistance Worsens with Age

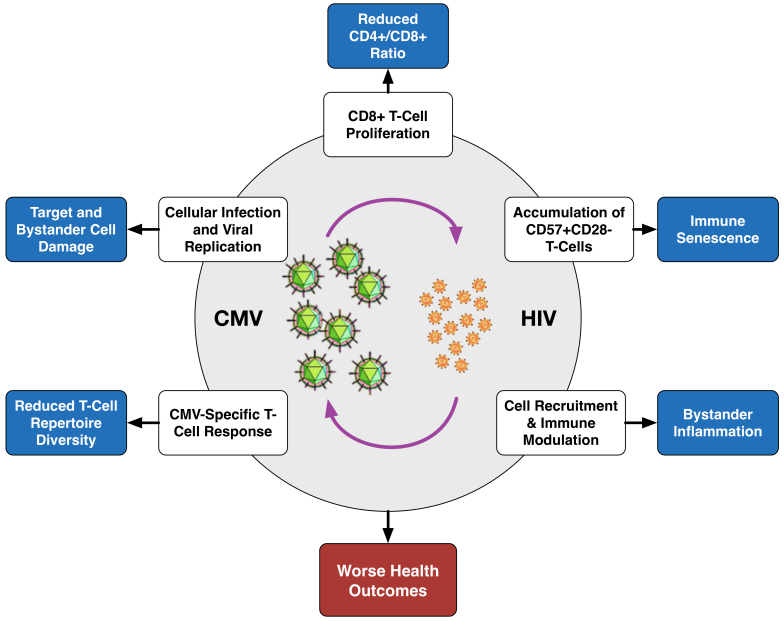


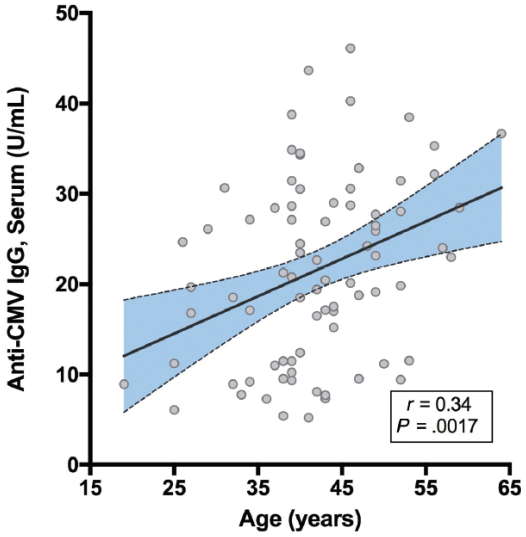
Kullmann et al, Physiol Rev 2016, 96: 1169–1209

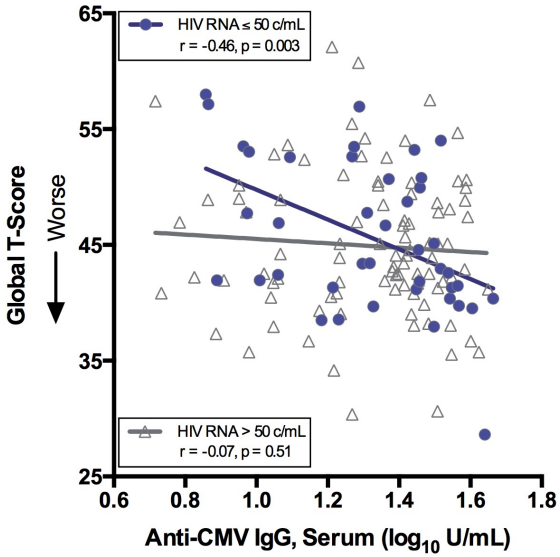


Ott et al, Diabetes, Obesity and Metabolism 2012, 14: 214–221

CMV is Associated with Worse Neurocognitive Performance

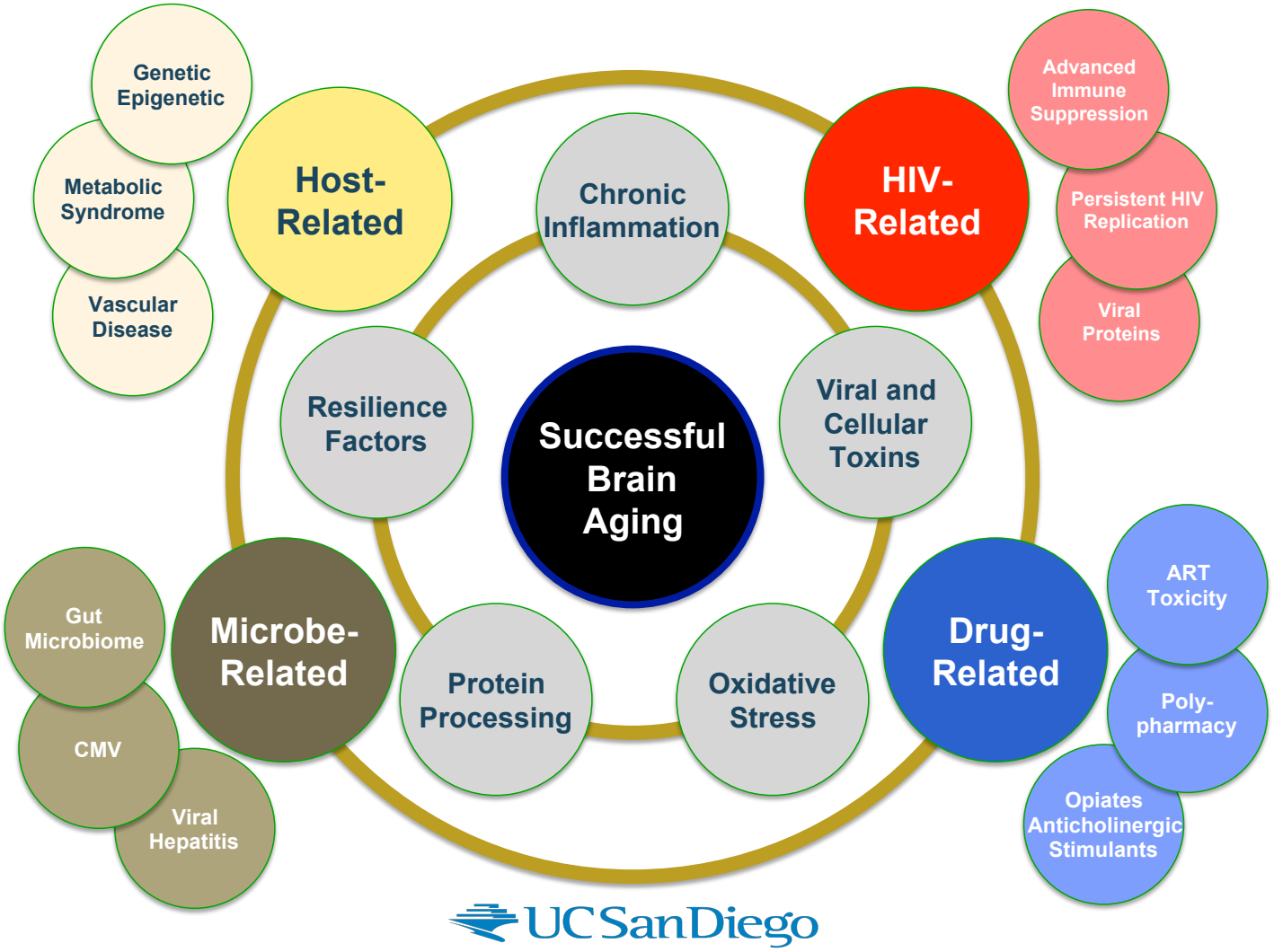






Gianella & Letendre, J Infect Dis 2016

Letendre, et al, Clin Infect Dis. 2018;67(5):770-777


Genetic Epigenetic
Metabolic Syndrome
Vascular Disease
Host-Related
Chronic Inflammation
HIV-Related
Advanced Immune Suppression
Persistent HIV Replication
Viral Proteins
Resilience Factors
Successful Brain Aging
Viral and Cellular Toxins
Gut Microbiome
CMV
Viral Hepatitis
Microbe-Related
Protein Processing
Oxidative Stress
Drug-Related
ART Toxicity
Poly-pharmacy
Opiates Anticholinergic Stimulants
UC San Diego

Possible Interventions for Premature Brain Aging

- Modify Medications
- "Lifestyle" modification
  - Exercise
  - Weight loss
  - Smoking Cessation
  - Moderate Alcohol Use
- Microbial-focused
  - Microbiome Alteration
  - Letermovir (CMV)
- Anti-inflammatory
  - Corticosteroids
- Psychiatric
  - Antidepressants
- Metabolic-focused
  - Pitavastatin
  - Metformin
  - Tesamorelin
  - Intranasal insulin
- Neuroprotective
  - Intranasal IGF-1
  - Cannabidiol
- Senotherapeutics
  - Dasatinib + quercetin
  - Bcl2 family inhibitors
  - FOXO4 peptide

Graphic courtesy of Peter Hunt, UCSF (and ulead.org)

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NIH

- …Mental Health
- …Drug Abuse
- …Aging
- …Allergy and Infectious Diseases

Trainees

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- Qing Ma (Buffalo)
- Bert Anderson (Emory)
- Kemi Okwuegbuna
- Josue Perez Santiago
- Micol Ferrara


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