

HIV Management  
Hepatitis Management

# THE NEW YORK COURSE

## **HIV and Aging: Optimizing Neurocognitive Function**

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# Disclosures

**Research funds were paid to UC San Diego on behalf of Dr. Letendre:**

- ▶ National Institutes of Health
- ▶ Gilead Sciences
- ▶ ViiV Healthcare

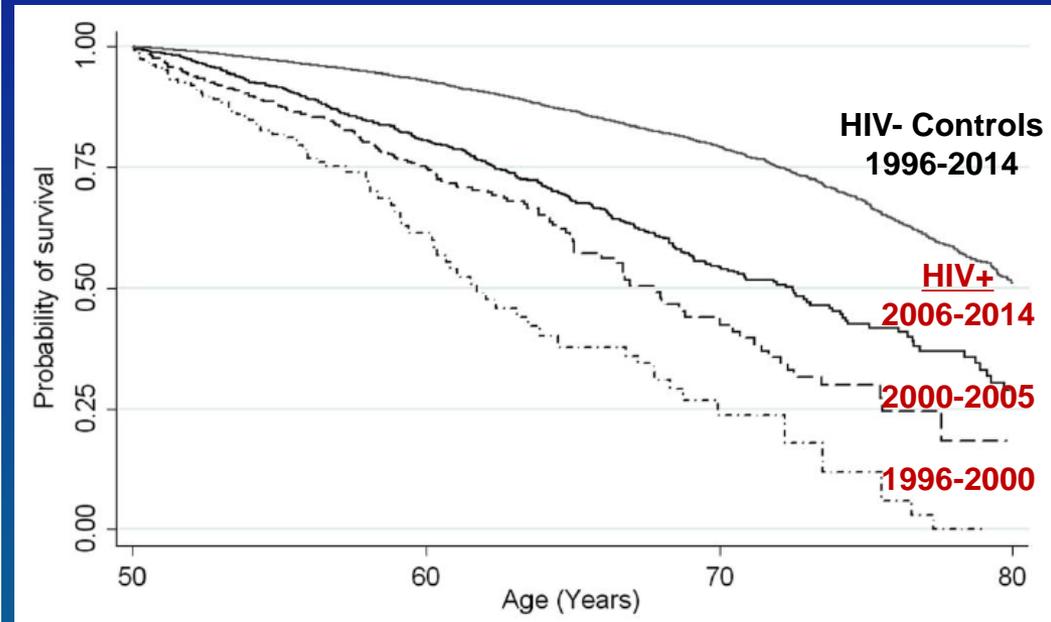
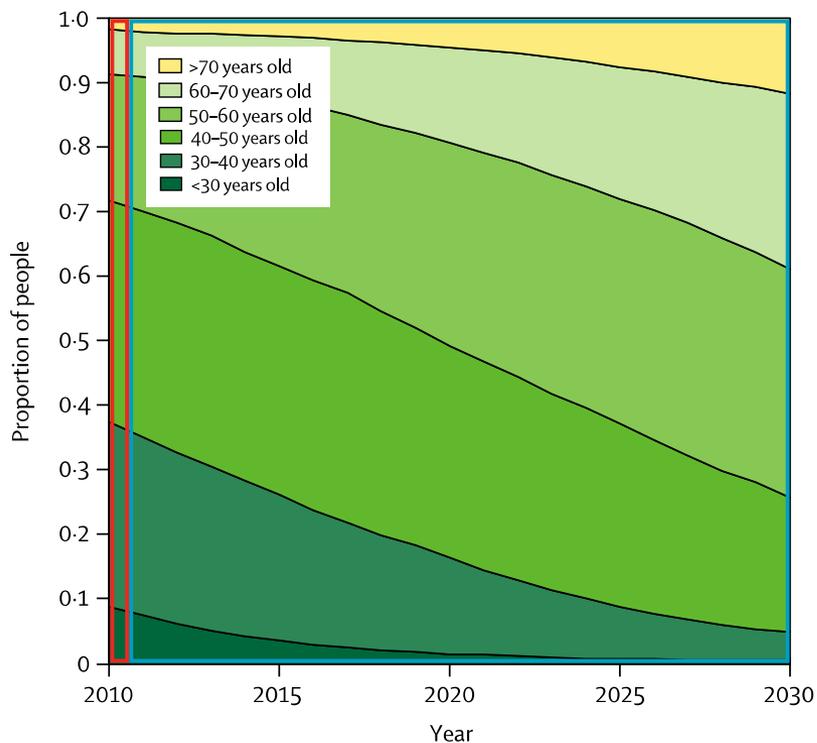
**Dr. Letendre was paid for an advisory board:**

- ▶ ViiV Healthcare

**Dr. Letendre was paid for a lecture:**

- ▶ Janssen

# HIV+ Adults Are Aging but Their Survival Has Not Yet Normalized



**~9 years shorter life expectancy even among those with no comorbidity**

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

*Legarth et al, JAIDS 2016, 71(2):213-8*

# Evidence of Premature Aging Has Been Found in Nearly Every Organ System

## ▶ **Nervous System**

- Cognitive Disorders
- Mood Disorders
- Sleep Disorders
- Neuropathy

## ▶ **Vascular System**

- Cardiovascular
- Cerebrovascular

## ▶ **Endocrine/Metabolic**

- Diabetes
- Hypogonadism

## ▶ **Immune System**

### ▶ **Liver**

- ↓ Drug Metabolism
- ↓ Synthetic Function

### ▶ **Kidney**

- Renal Insufficiency

### ▶ **Musculoskeletal**

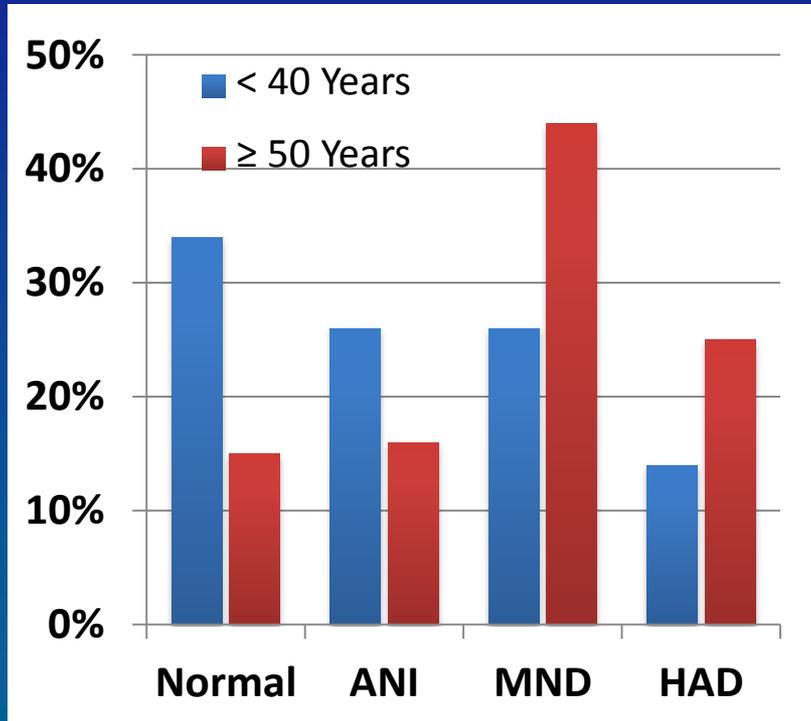
- Osteoporosis
- Frailty/Sarcopenia

### ▶ **Pulmonary System**

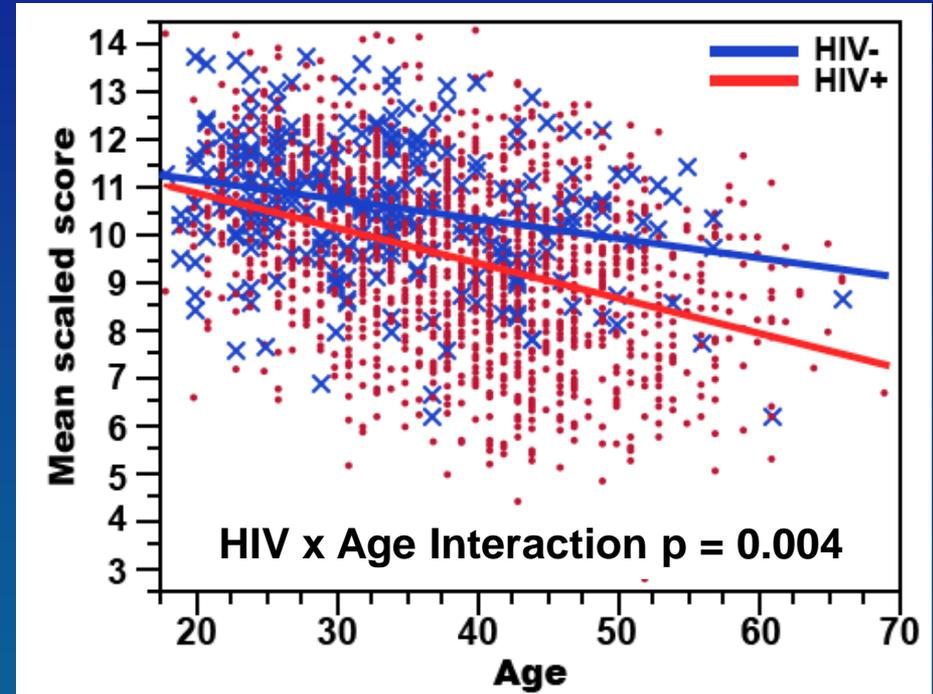
- Pulmonary Hypertension

*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 Accelerate Neurocognitive Decline



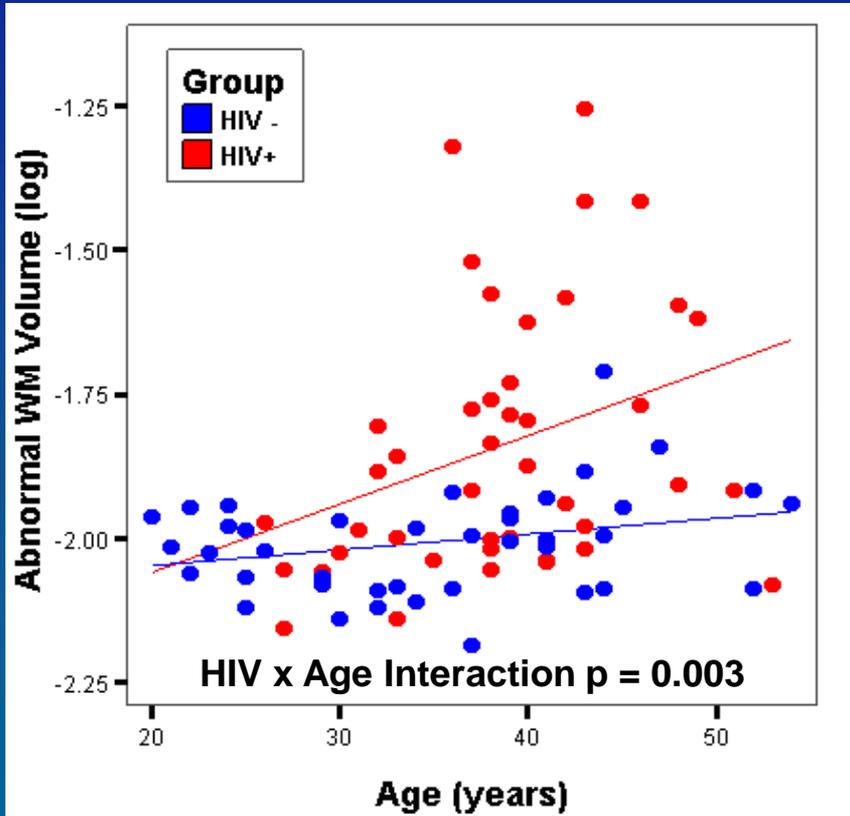
*Modified from Valcour et al, Neurology 2004;63:822–827*



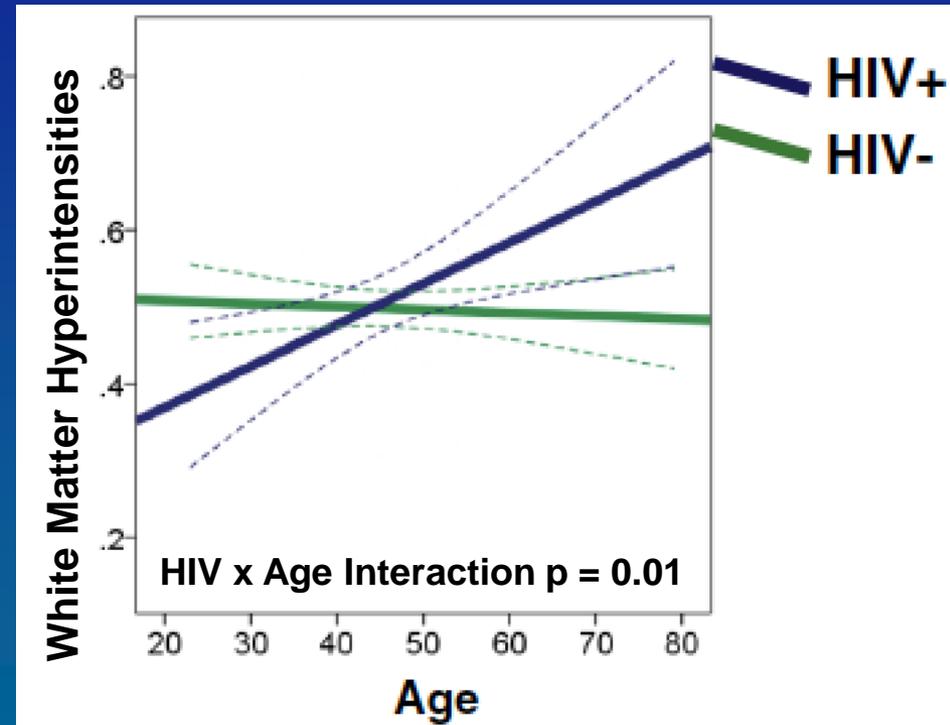
*Heaton et al, J Neurovirology, 2012, 18(Suppl 1): S46*

ANI = Asymptomatic Neurocognitive Impairment  
MND = Mild Neurocognitive Disorder  
HAD = HIV-Associated Dementia

# HIV May Accelerate White Matter Injury in the Brain

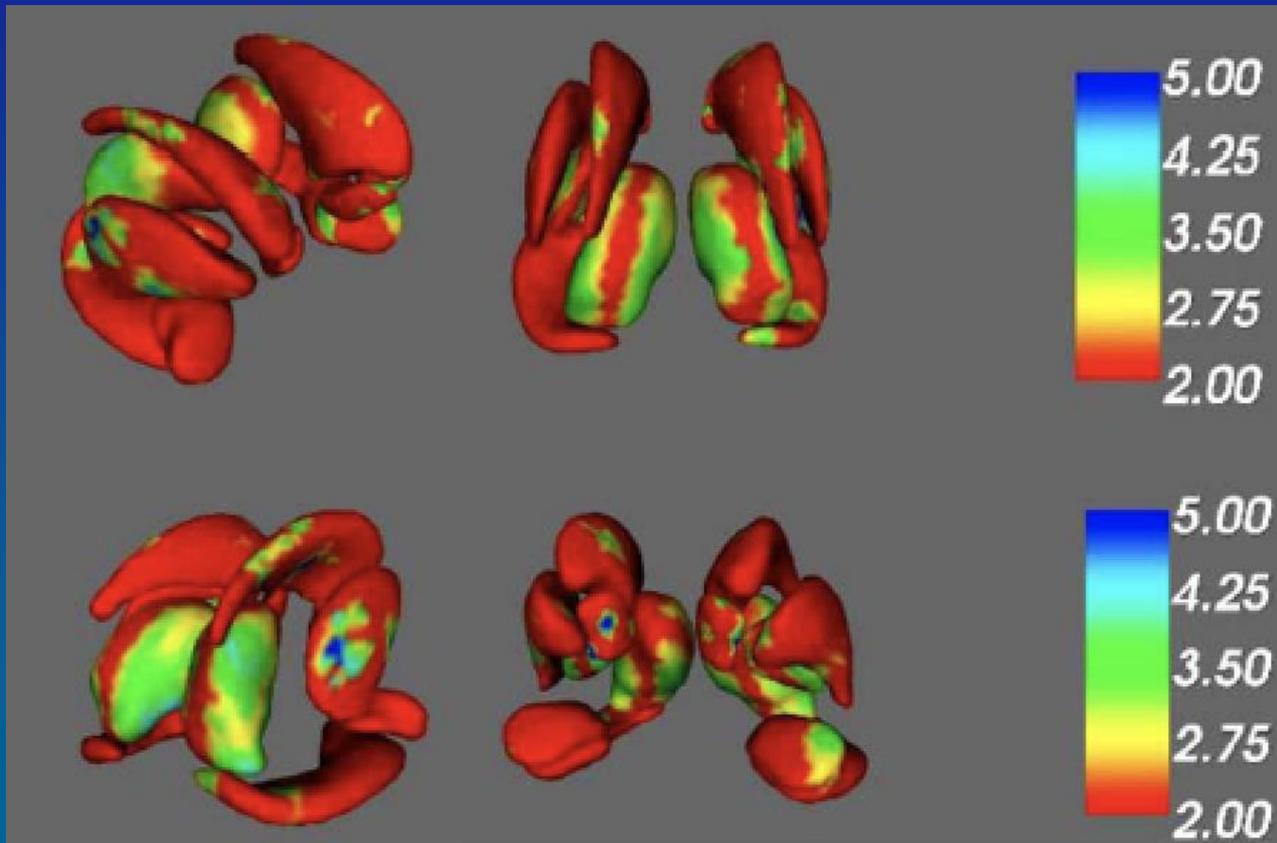


Unpublished CHARTER Data



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

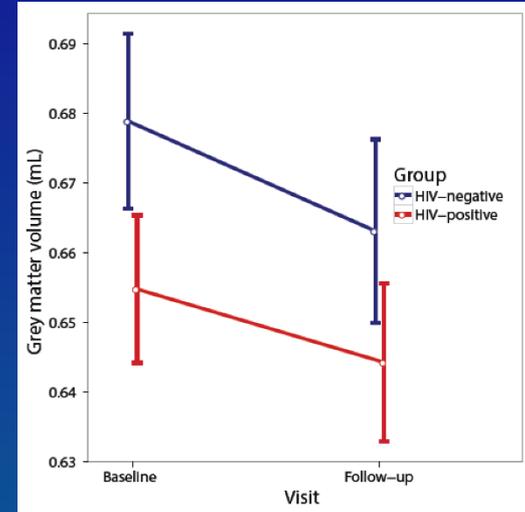
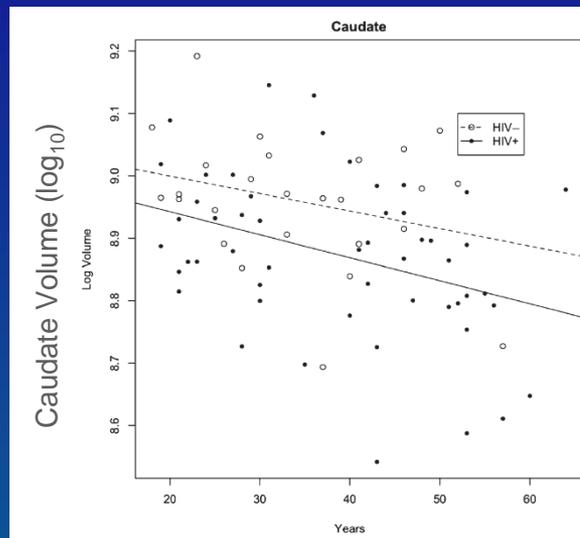
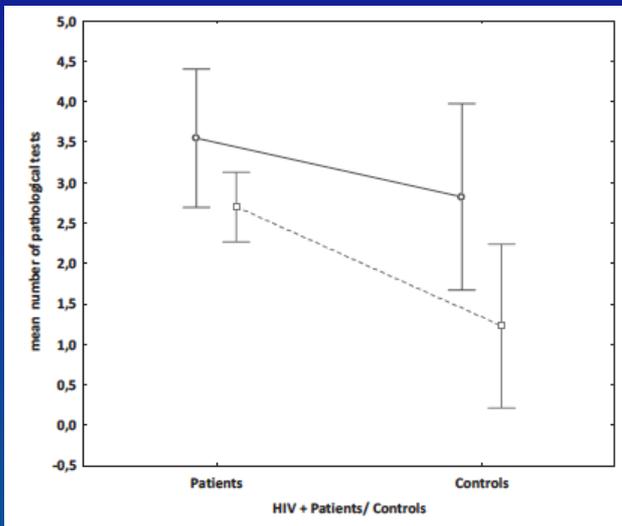
# HIV May Accelerate Subcortical Gray Matter Changes



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

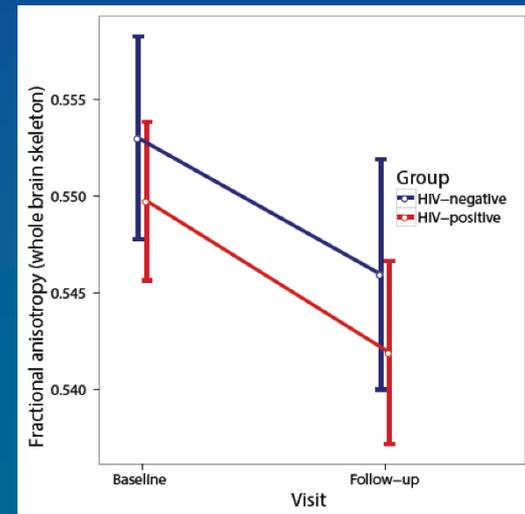
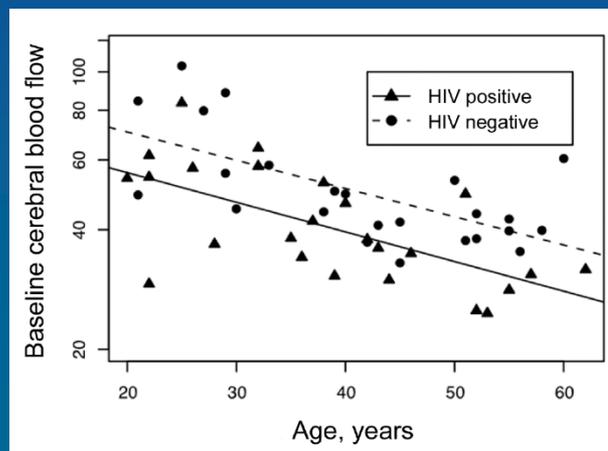
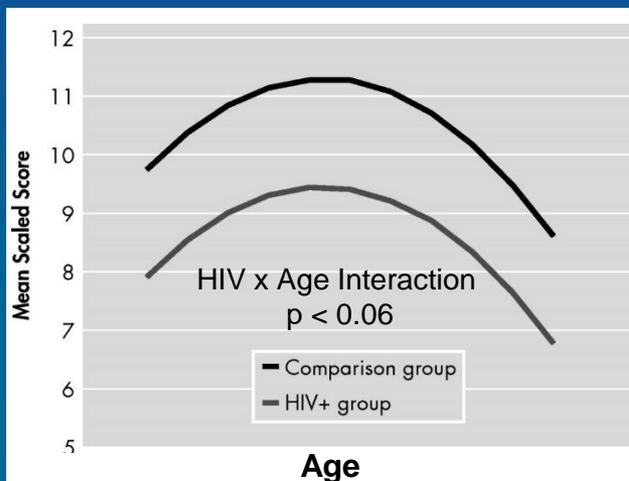
*Kuhn et al, Human Brain Mapping, 2016, DOI: 10.1002/hbm.23436*

# Some Studies Do Not Support Accelerated Brain Aging



Ciccarelli et al, JAGS 2012, 60:2048–2055

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

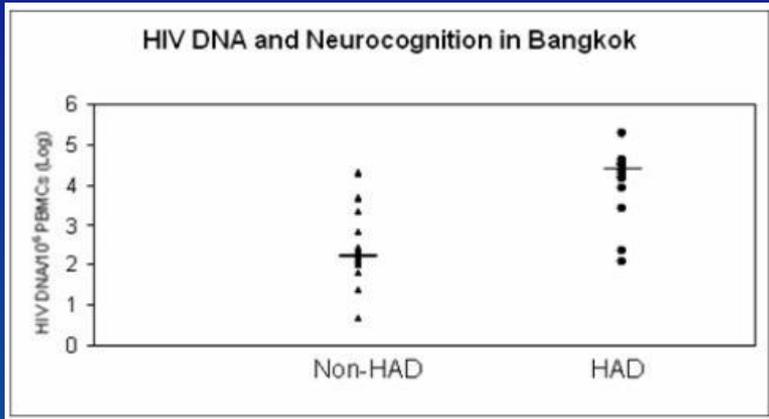


Cysique et al, J Neuropsych Clin Neurosci. 2011; 23(1): 83-9

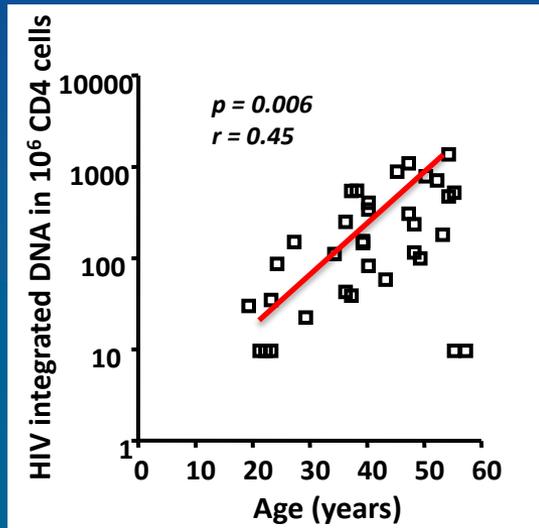
Ances et al, J Acquir Immune Defic Syndr 2012; 59: 469-77

Cole et al, CROI 2017 Abstract 359LB

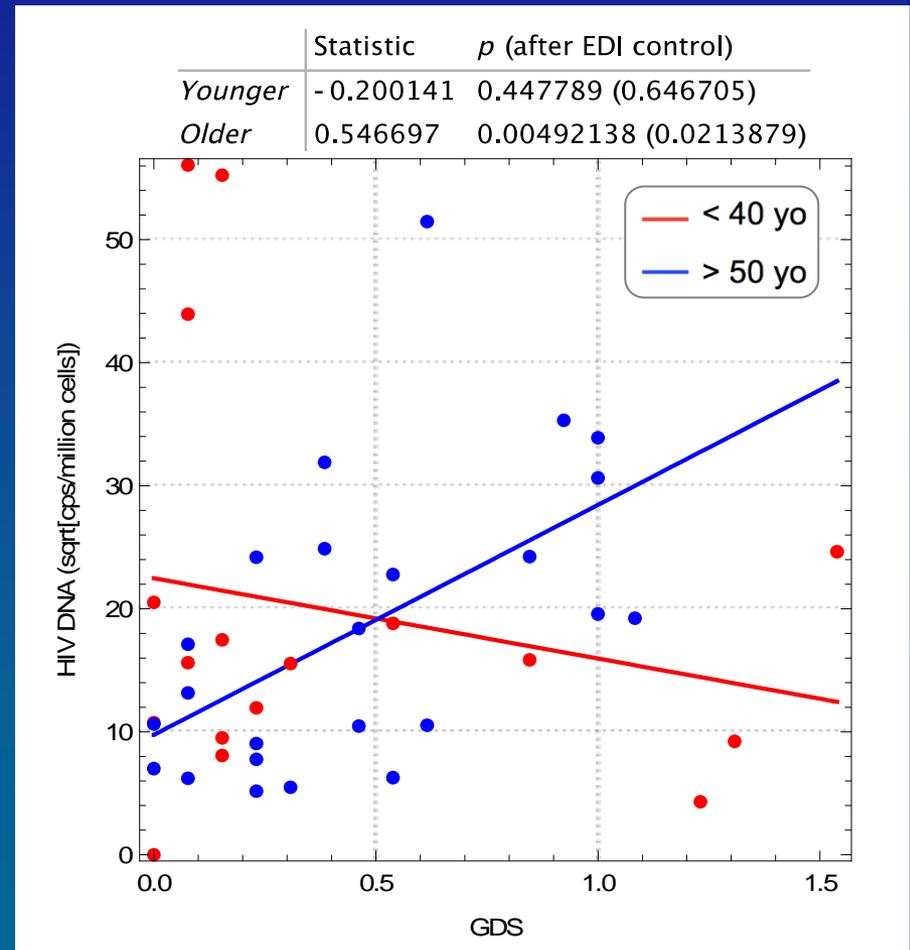
# Other Biomarkers May Be Better Indicators of Accelerated Aging



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

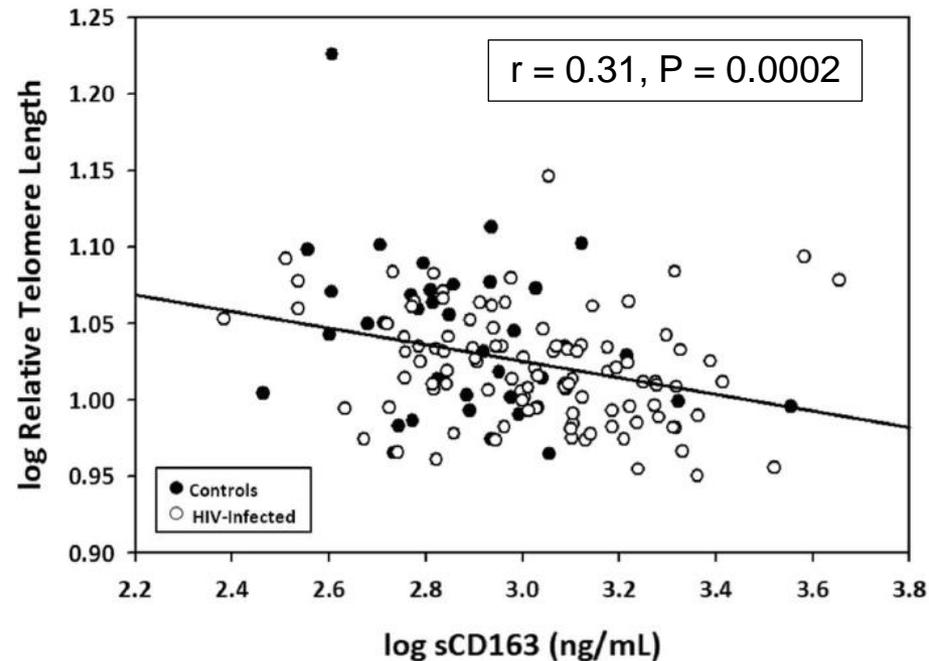
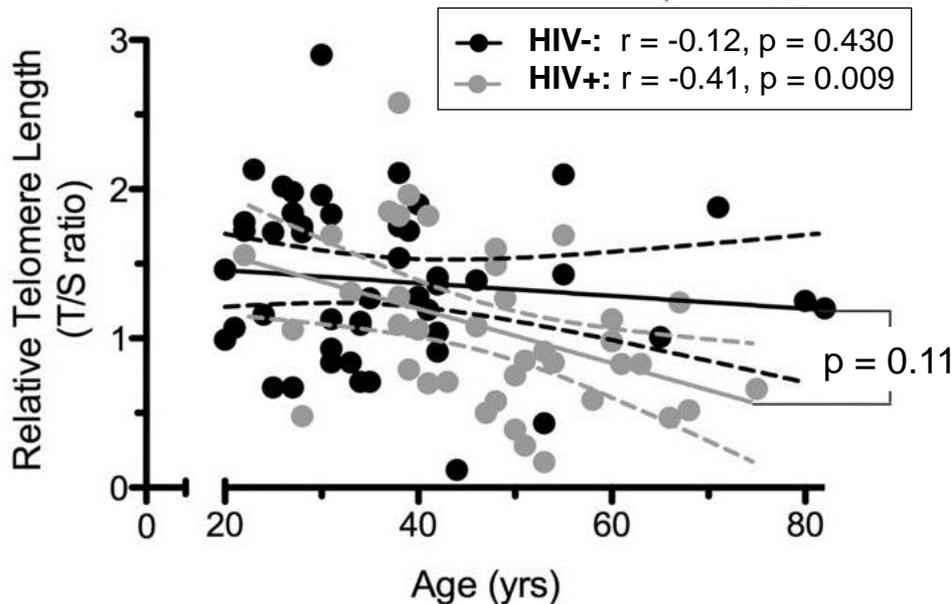


Boulassel, Routy et al. *J Clin Virol* 2012, 53: 29– 32  
Graph Courtesy Jean-Pierre Routy, McGill University



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

# HIV & Inflammation May Correlate with Shorter Telomere Length

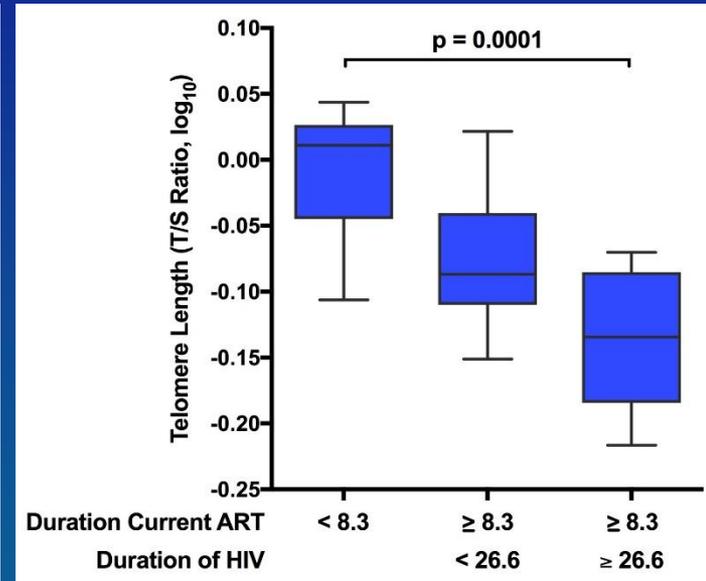
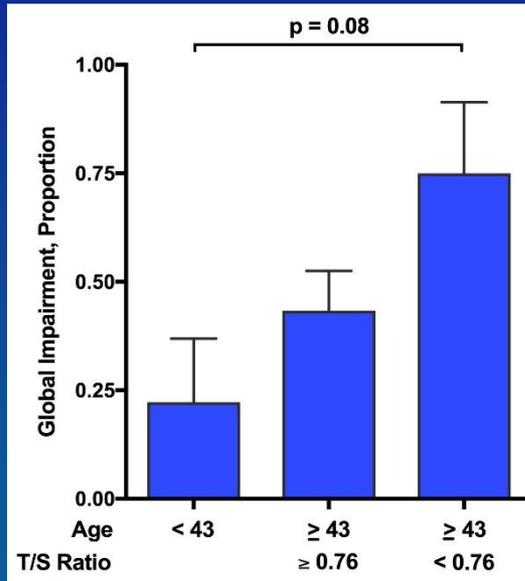
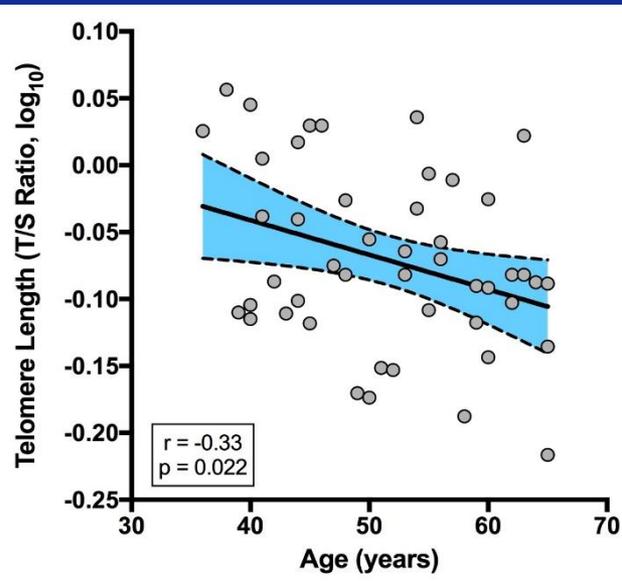


HIV x sCD163 Interaction:  $p = 0.12$

Leeansyah et al, JID 2013; 207:1157

Srinivasa et al, JAIDS 2014; 67: 414

# Shorter Telomeres and Worse Neurocognitive Performance



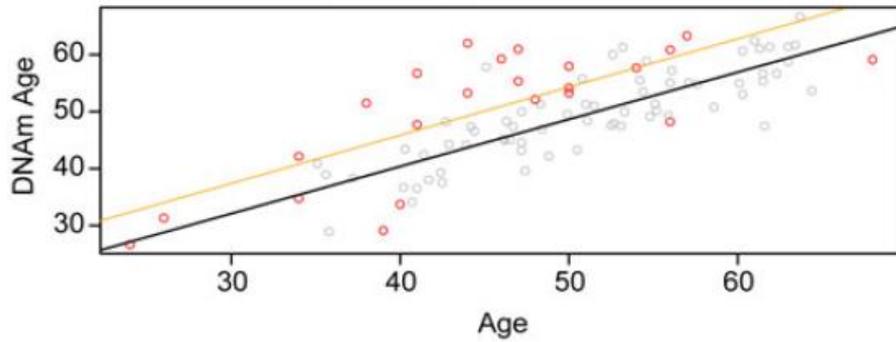
n = 47

Unpublished UCSD Data  
Copyright S. Letendre 2017

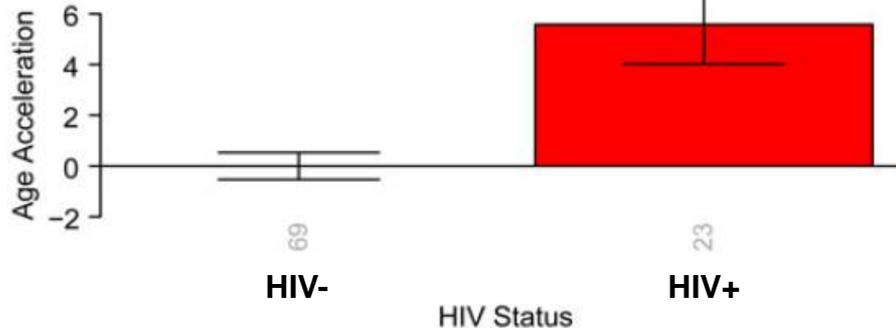
# Accelerated Aging in Brain by DNA Methylation "Epigenetic Clock"

Blood

Blood (data set 5) cor = 0.76, P = 1.6e-18

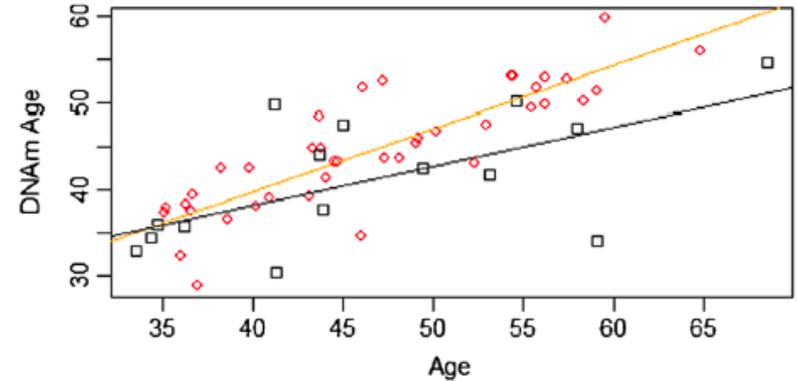


Blood (data set 5) P = .00036

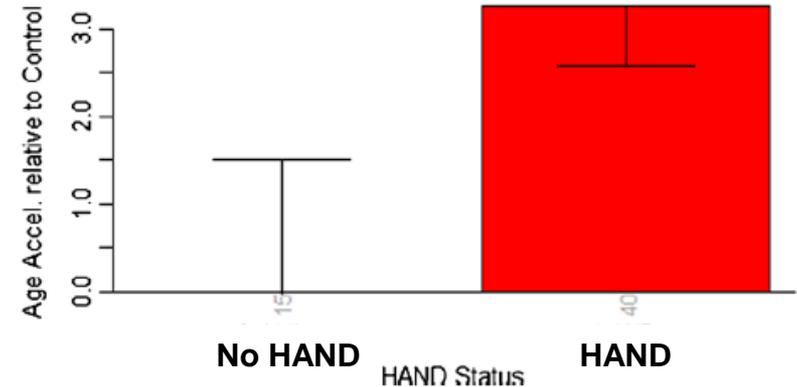


Brain

Age > 33 cor = 0.76, p = 1.7e-11

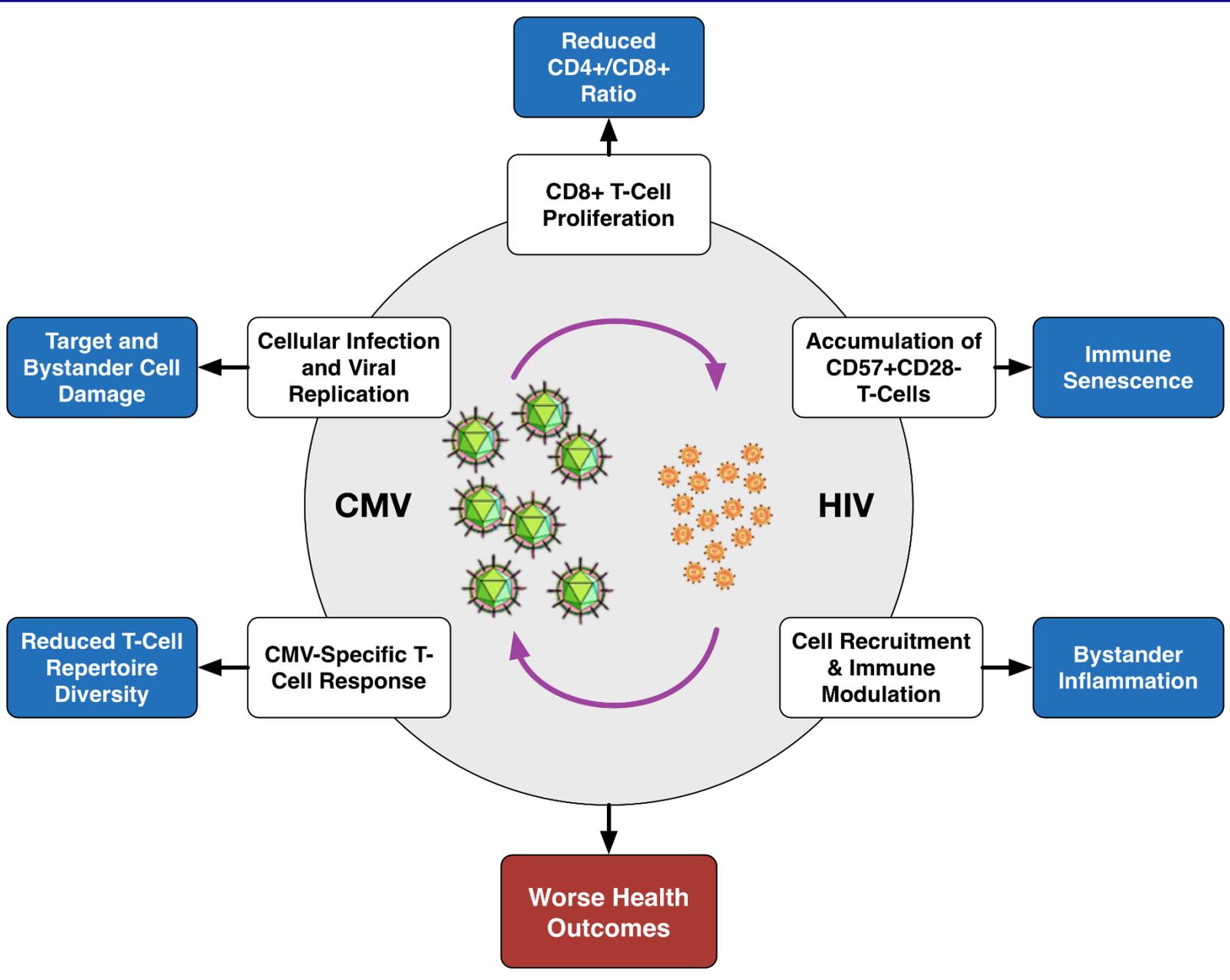


Age > 33 p = 0.027

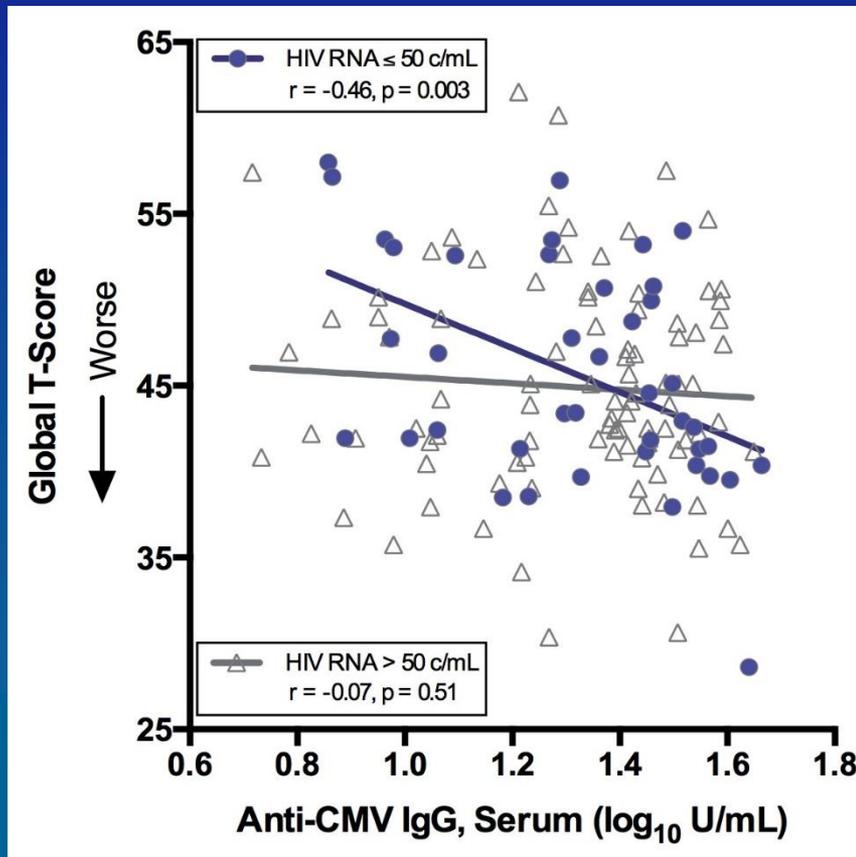


Horvath & Levine, *J Infect Dis*  
2015, 212:1563-73

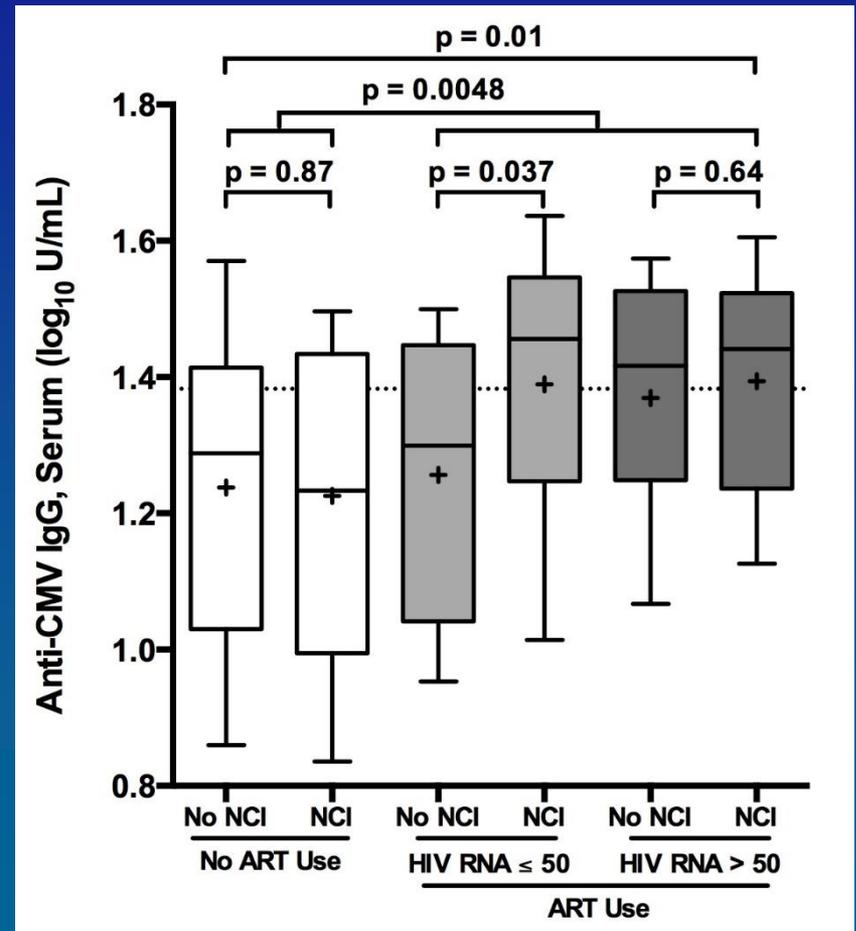
Levine et al, *J Neurovirol*  
2016; 22(3):366-75



# Higher Anti-CMV IgG Is Associated with Worse Cognitive Performance

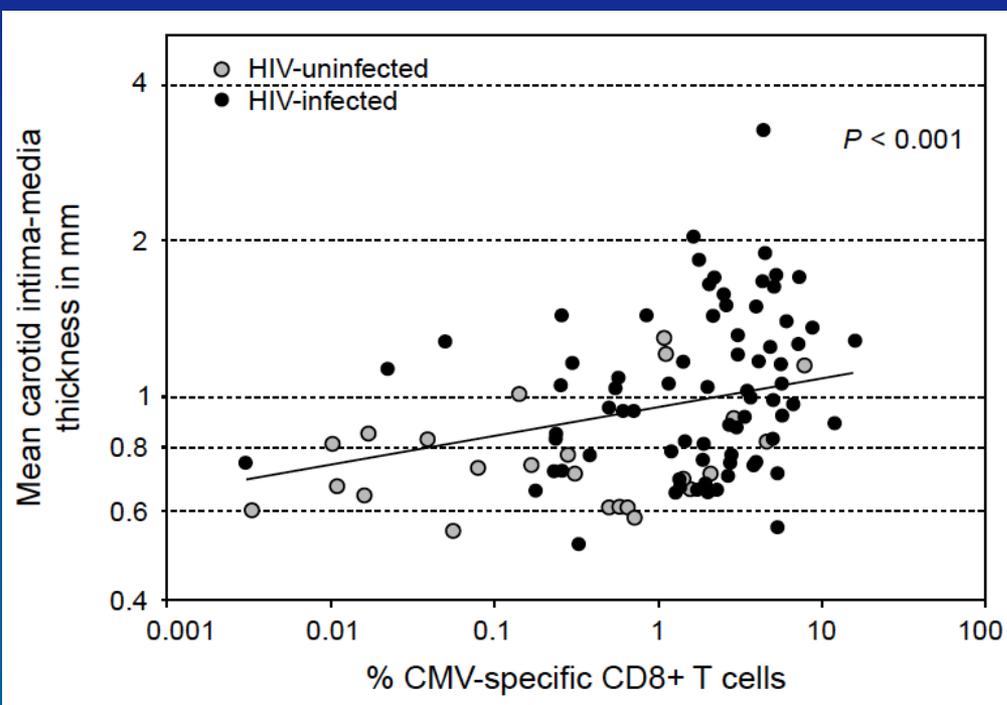


**Correlation for Entire Group:**  
 $r = -0.20$ ,  $p = 0.02$



# 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 HIV- adults
- ▶ 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*

# Vascular and Metabolic Disease Increase Risk for Cognitive Impairment

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

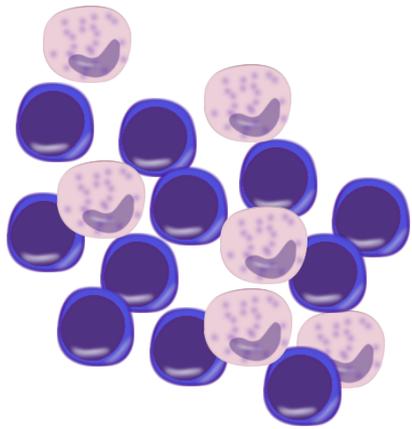
*Wright et al. Neurology 2010; 75: 864*

	Risk	OR	p
<b>Prior CVD</b>	Yes	6.2	0.01
<b>Total cholesterol</b>	Higher	1.1	0.06
<b>AIDS</b>	No	0.41	0.08
<b>Race</b>	Black	2.2	0.08

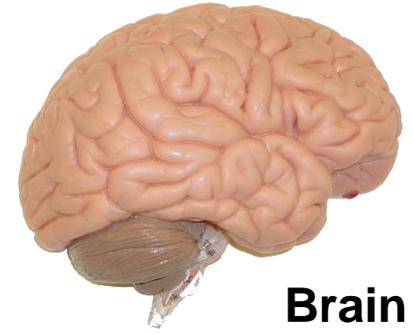
- 55 older HIV+ adults in the CHARTER study
- Diabetes and larger waist circumference were associated with NCI

*McCutchan et al. Neurology 2012. 78: 485*

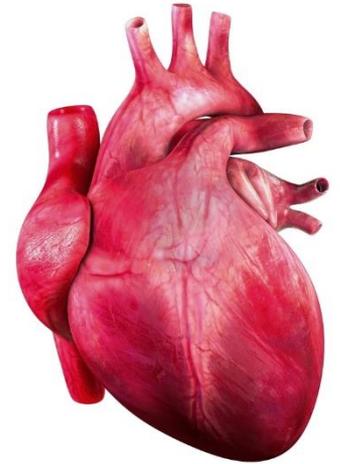
	Risk	OR	p
<b>AIDS</b>	Yes	49.6	0.01
<b>Diabetes</b>	Yes	17.6	0.07
<b>Waist circumference</b>	Larger	1.3	0.001
<b>Triglycerides</b>	Lower	0.32	0.09
<b>BMI</b>	Smaller	0.69	0.04



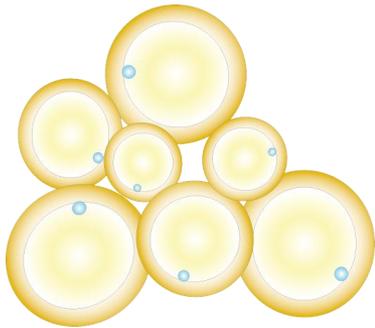
**Persistent  
Inflammation**



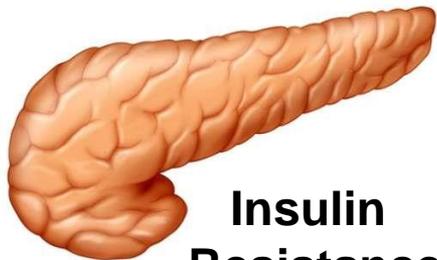
**Brain  
Disease**



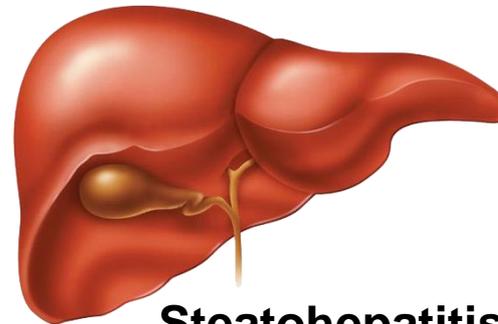
**Vascular  
Disease**



**Dyslipidemia  
Visceral Fat**



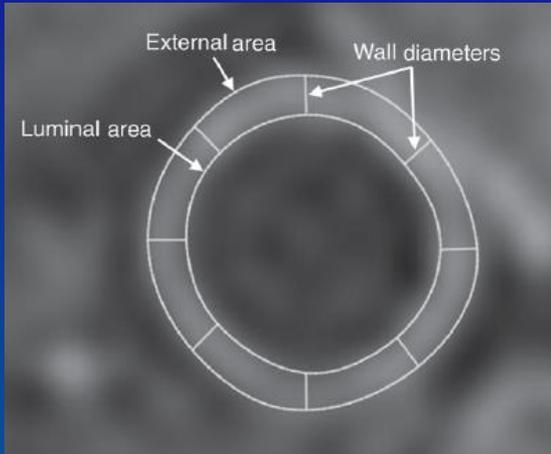
**Insulin  
Resistance**



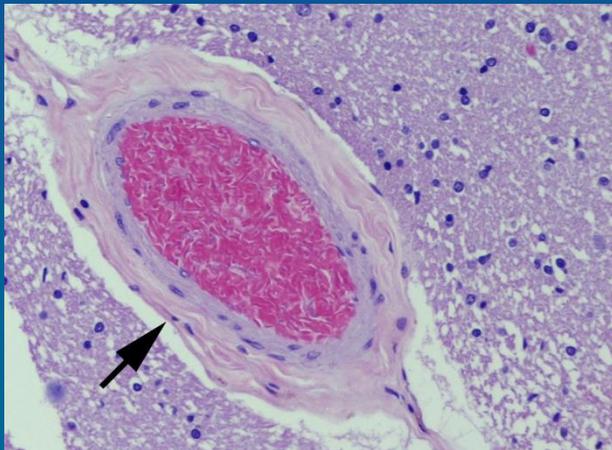
**Steatohepatitis  
Liver Fibrosis**

# ART Toxicity May Also Contribute

## Protease Inhibitors

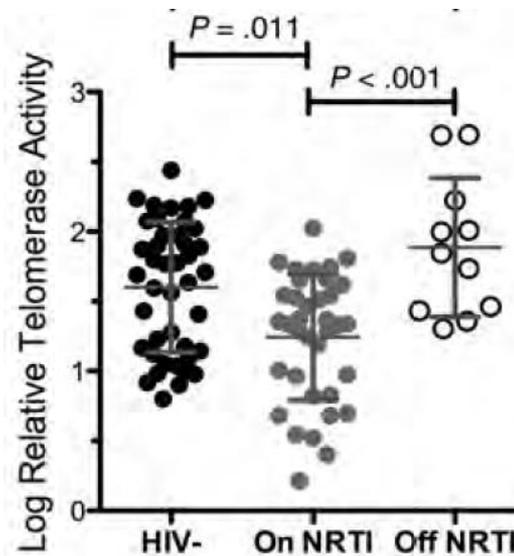


LaBounty et al, *HIV Medicine*  
2016, 17(7):516-23

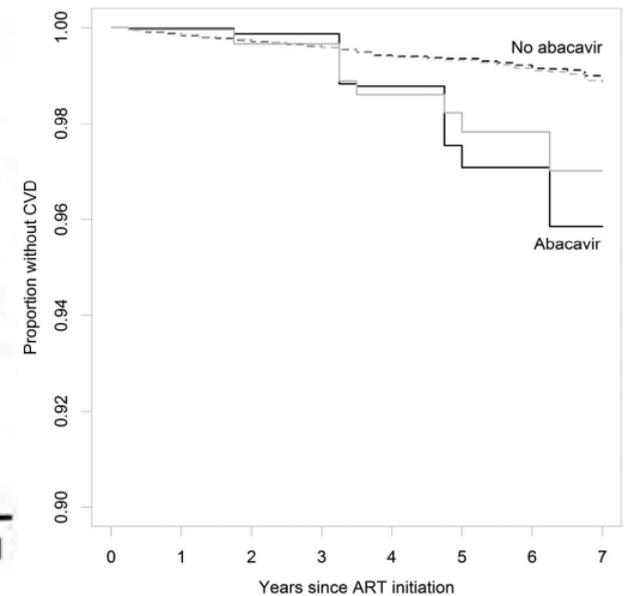


Soontornniyomkij et al, *AIDS*  
2014, 28:1297-1306

## NRTIs

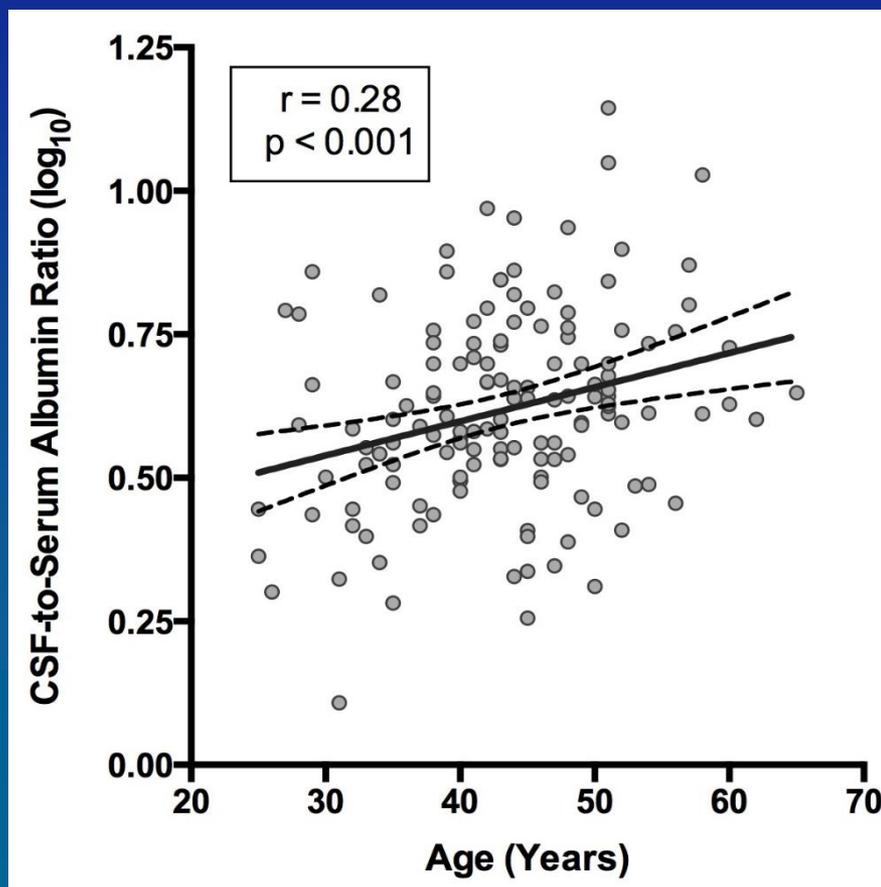


Leeansyah et al, *J Infect Dis*  
2013, 207:1157

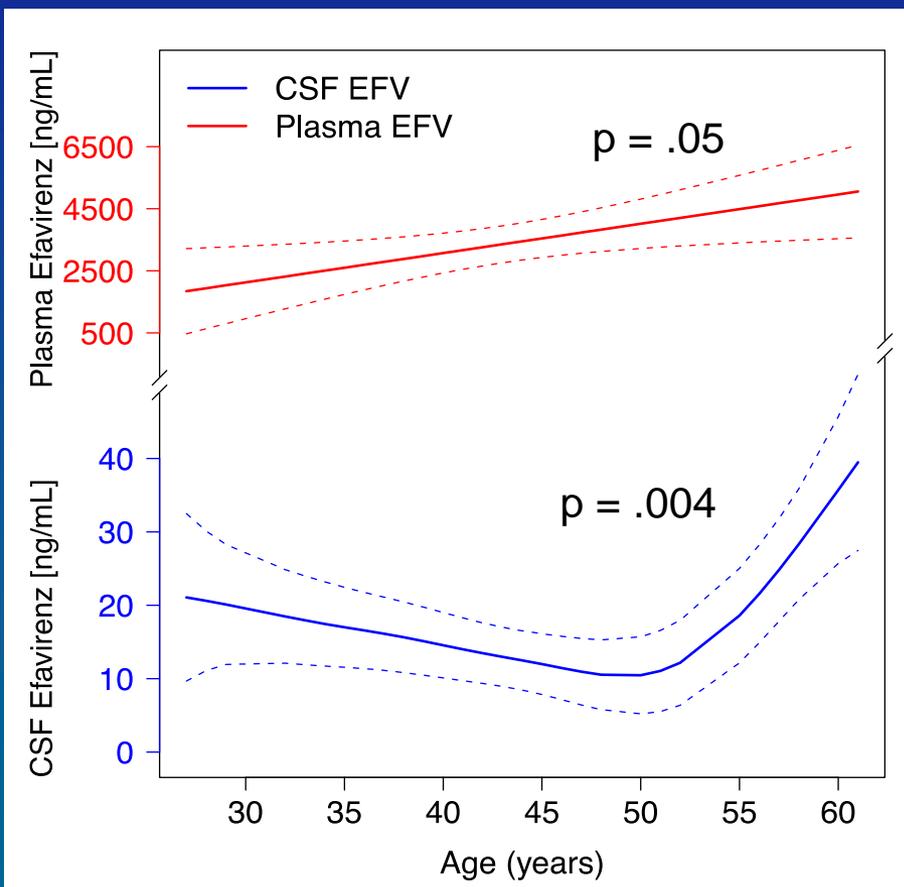


Marcus et al, *JAIDS*  
2016; 71:413-419

# Blood-Brain Barrier Permeability Increases with Age and May Alter Drug Distribution into the CNS

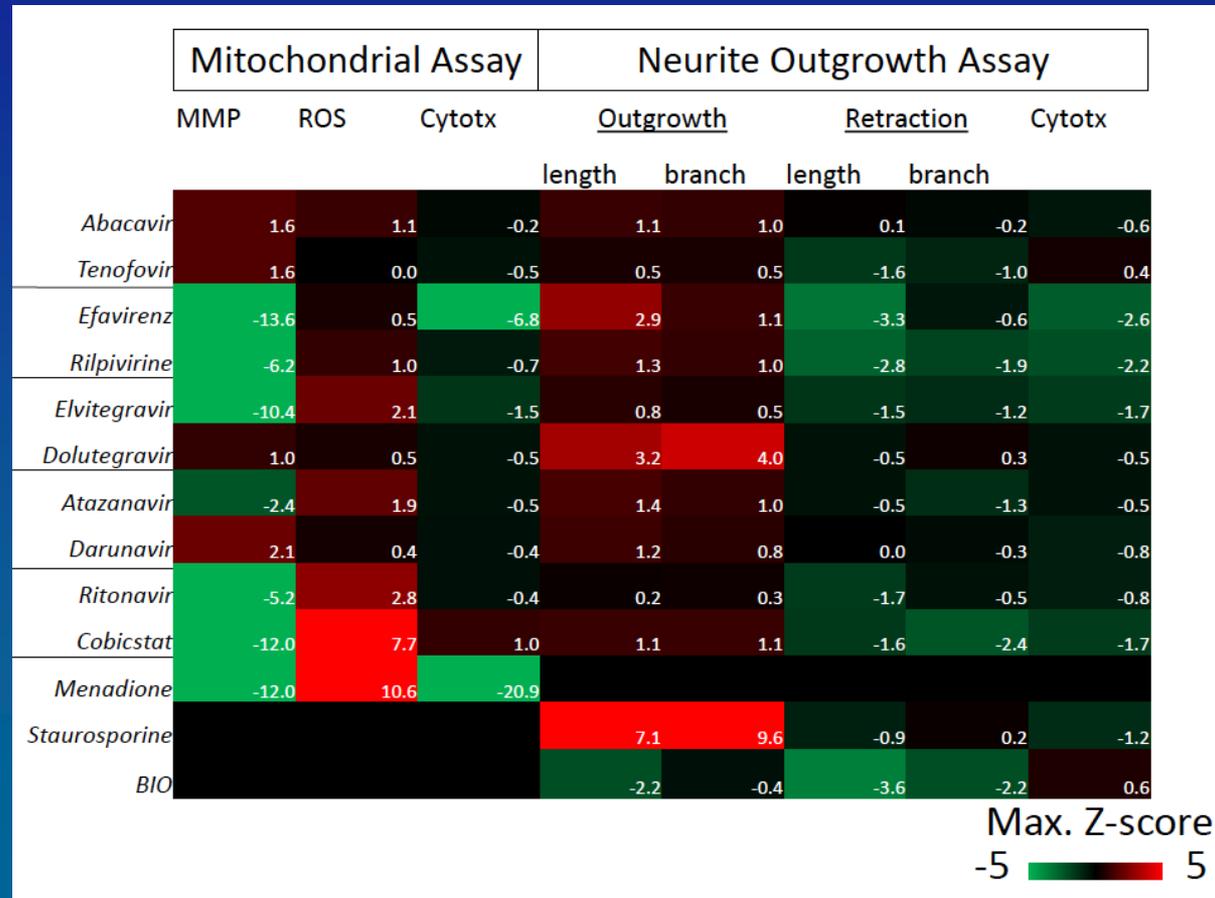
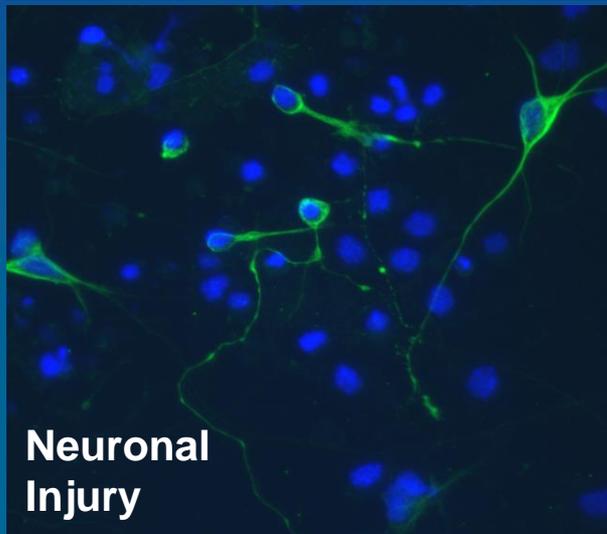
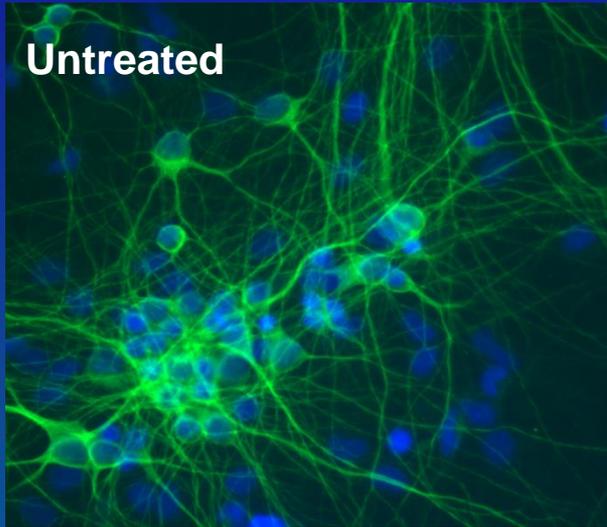


Letendre et al, 18<sup>th</sup> CROI, 2011, Abstract 408



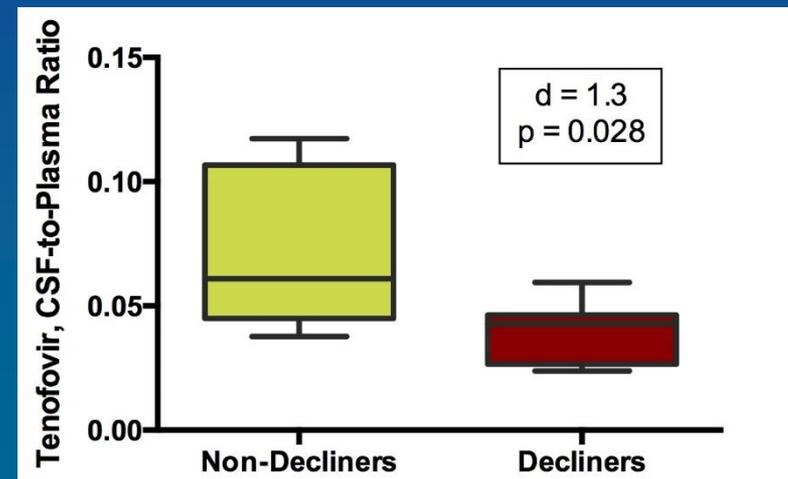
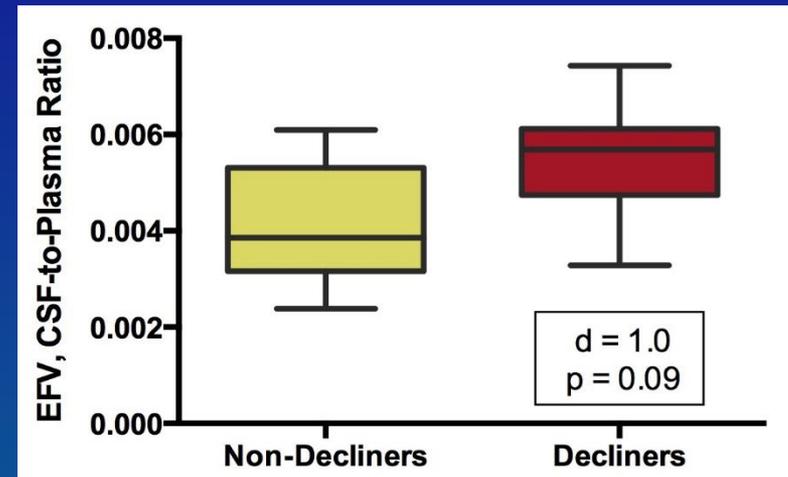
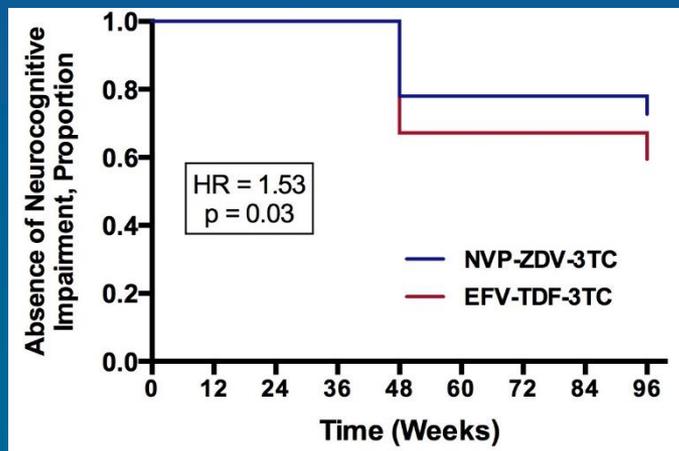
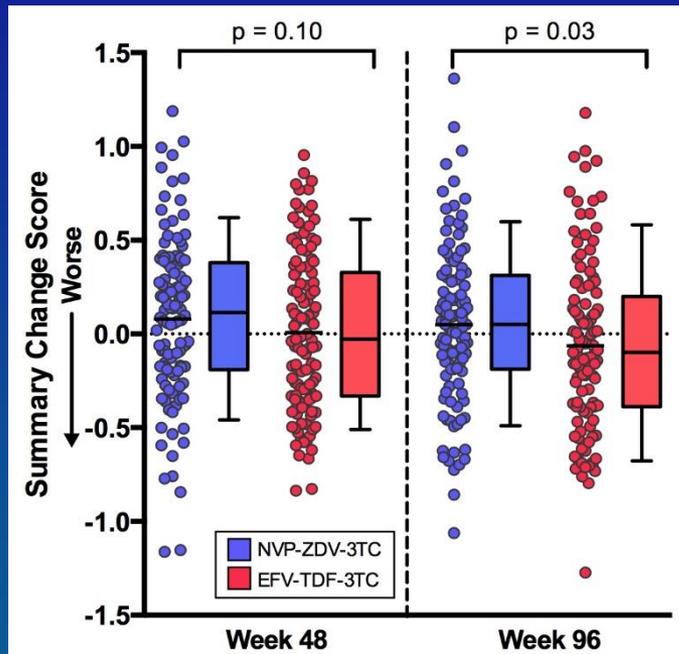
Croteau et al, 19<sup>th</sup> CROI, 2012, Abstract 592

# Higher Concentrations of ART Drugs Can Injure Neurons *in vitro*

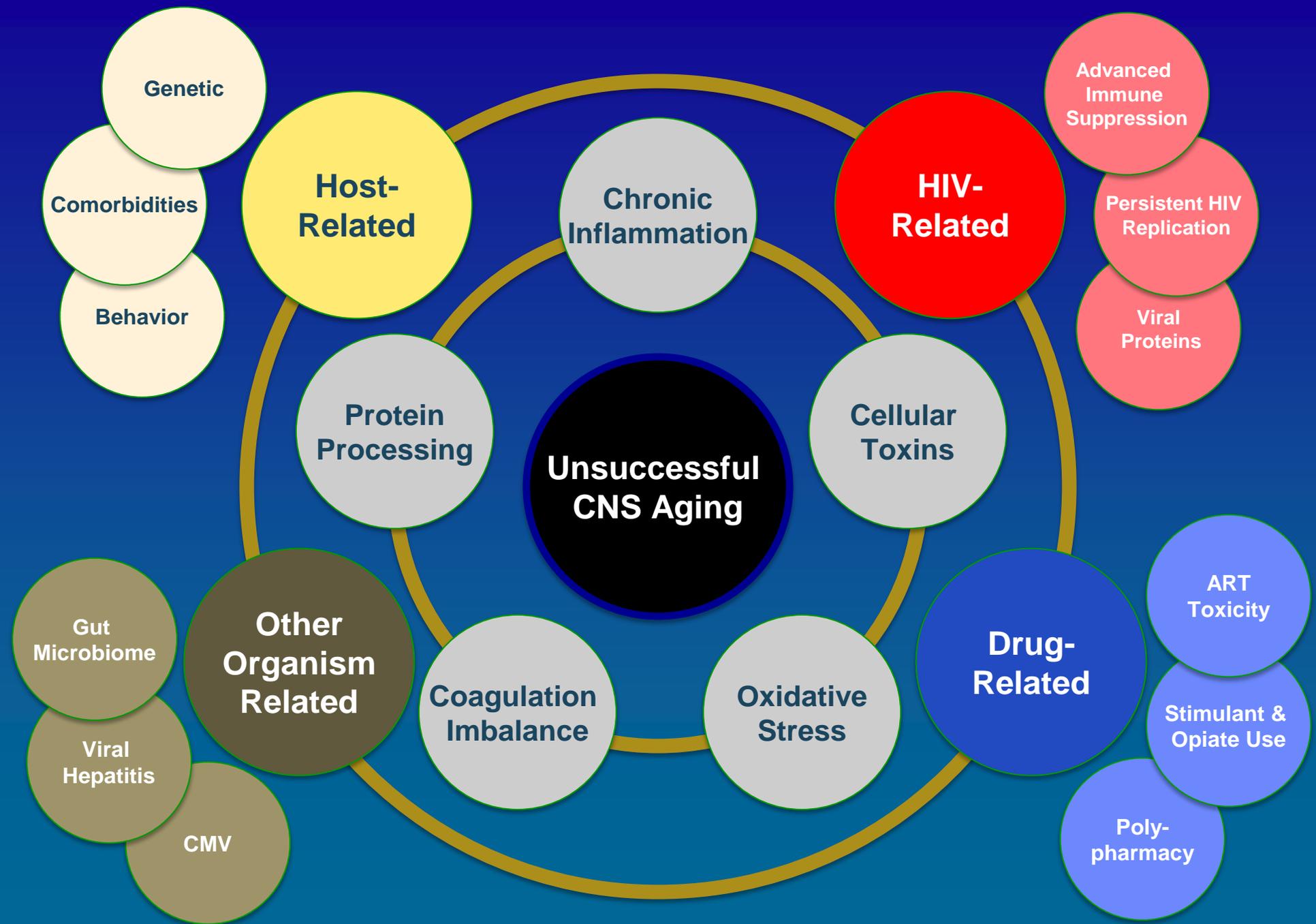


Hinckley et al, CROI 2016, Abstract 395

# Higher Efavirenz Distribution into the CNS Linked to Cognitive Decline



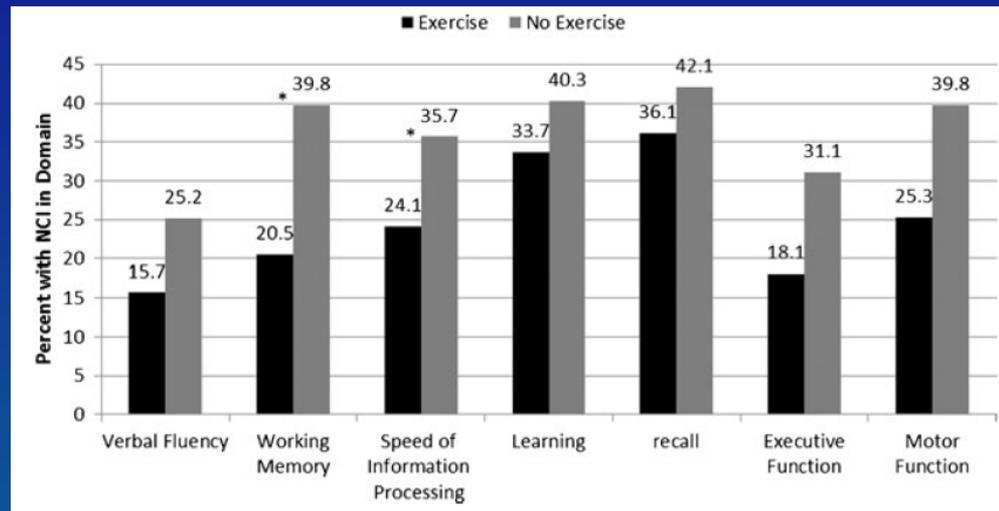
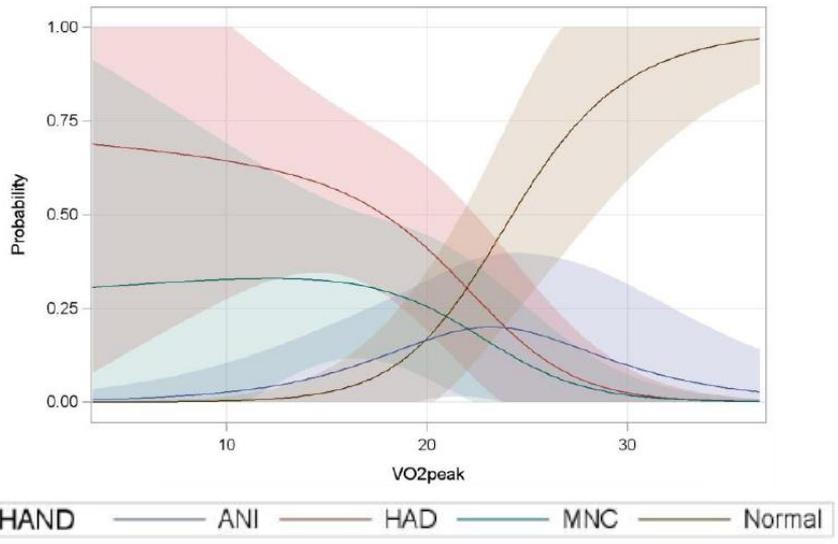
Zhang, et al, CROI 2015, Abstract 56  
Ma et al, CROI 2015, Abstract 444



# Optimizing Neurocognitive Performance in Aging Adults

- ▶ **Early initiation of ART**
  - Follow current treatment guidelines
  - Consider changing ART based on symptoms
- ▶ **Manage vascular/metabolic risk & disease**
  - Healthy diet, regular exercise, smoking cessation
  - Treat dyslipidemia and insulin resistance/diabetes
- ▶ **Treat coinfections (HCV, Syphilis, CMV)**
- ▶ **Treat mood, sleep, & substance use disorders**
- ▶ **Limit polypharmacy, drug-drug interactions**
- ▶ **Role of other interventions is unclear**
  - Antiinflammatories, neurotrophins/growth factors
  - Probiotics, hormone replacement
  - AChE inhibitors, NMDA-R antagonists

# Aerobic Fitness & Exercise Linked to Better Cognitive Performance

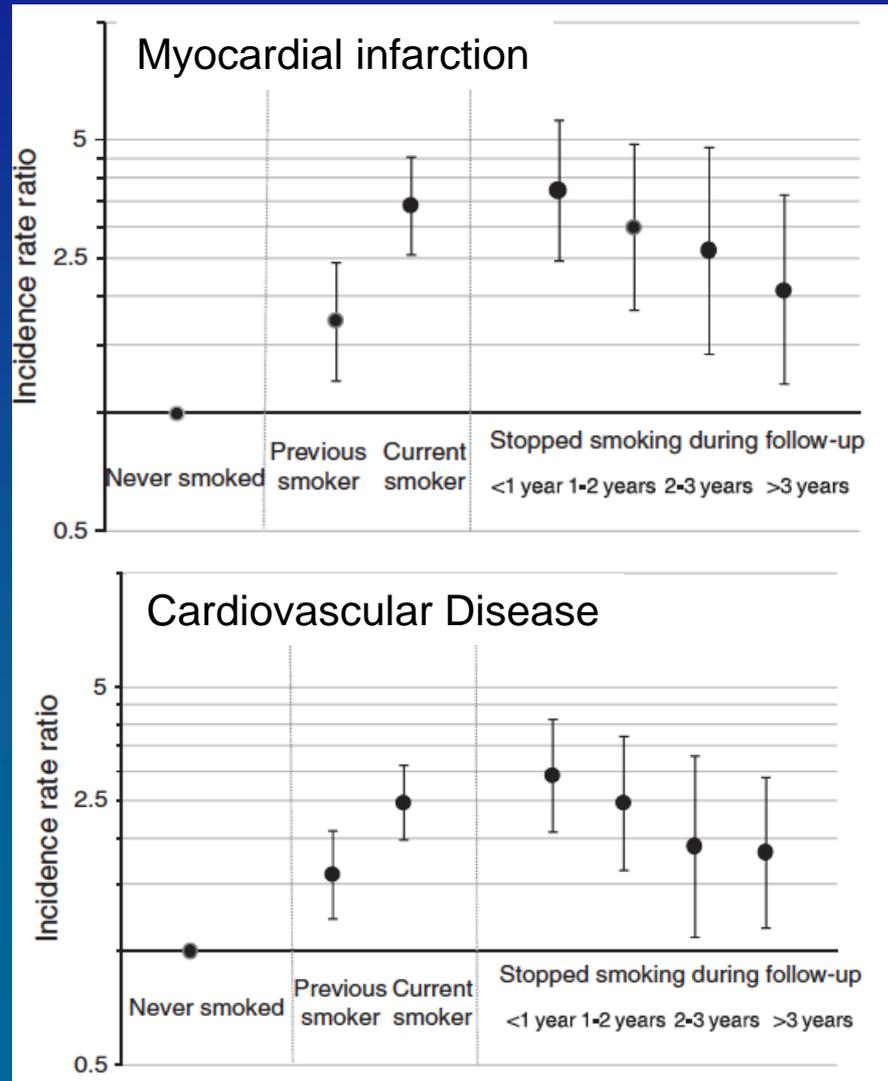


- Assessed 37 HIV+ adults older than 50 on a treadmill
- Peak VO<sub>2</sub> (oxygen consumption) related to verbal and visual memory, visual perception, and language
- **Lower peak VO<sub>2</sub> associated with more HAND** (p = 0.01)

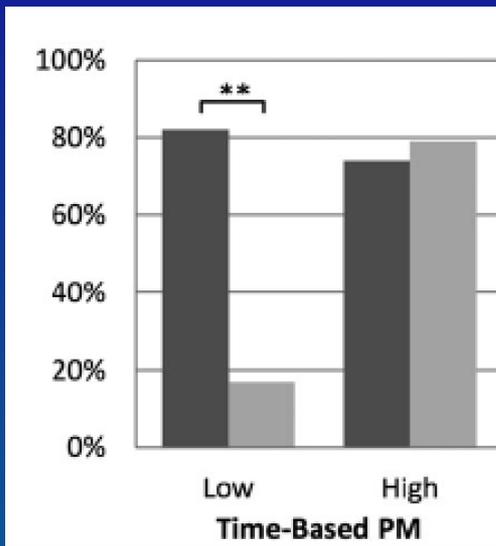
- ▶ 335 HIV+ adults with self-reported activity within 72 hours
- ▶ **Exercisers were less likely to have global neurocognitive impairment** (odds ratio = 0.38, p < 0.05)

# Smoking Cessation Reduces Risk of Cardiovascular Events

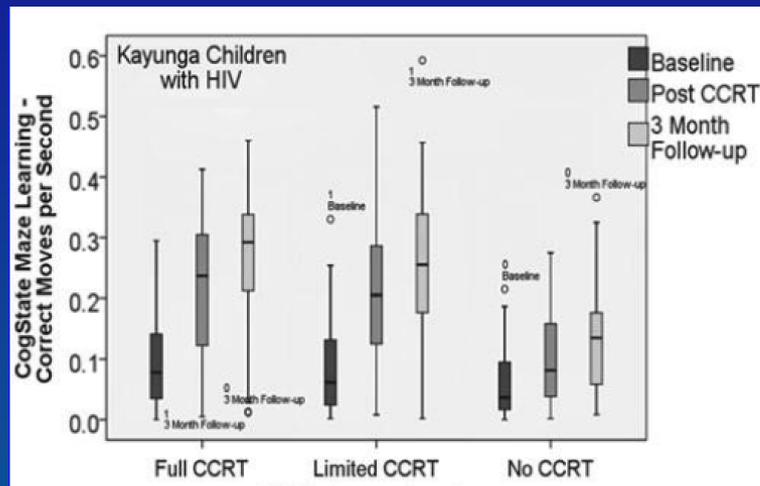
- ▶ More than 27,000 HIV+ adults had a total of 3,680 cardiovascular events or mortality
- ▶ Adjusted incidence rate ratio in patients who stopped smoking **decreased from 2.3 within the first year to 1.5 after >3 years** compared with those who never smoked



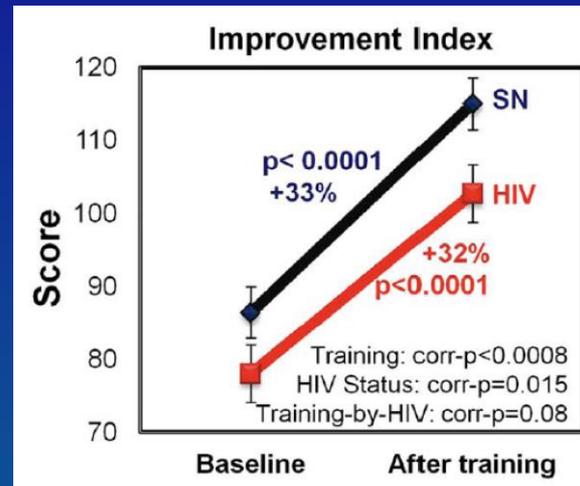
# Cognitive Training May Improve or Maintain Cognitive Abilities



Faytell et al, *Neuropsychol Rehabil.* 2015, 21:0-14

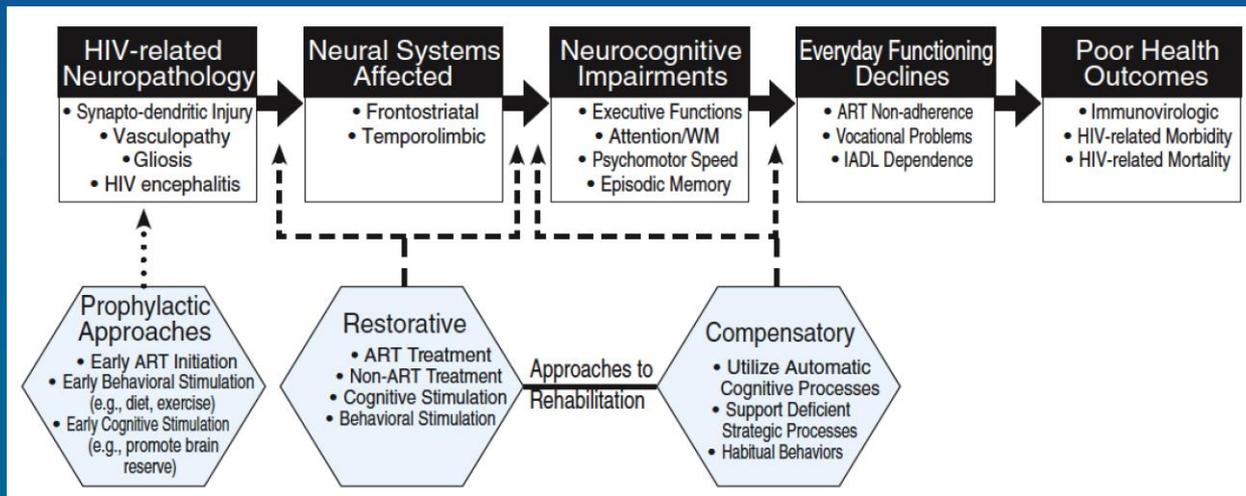


Boivin et al, *AIDS Res Hum Retrovir* 2016, 32(8): 743-55



Chang et al, *Ann Neurol* 2017;81:17-34

Weber et al, *Neuropsychol Rev* (2013) 23:81-98



# Newer NNRTIs Have Fewer CNS Side Effects Than Efavirenz

	RPV n=288	EFV n=255	p value
<b>Dizziness</b>	10.4%	27.8%	<0.001
<b>Abnormal dreams</b>	7.6%	13.7%	0.02
<b>Somnolence</b>	2.8%	6.3%	0.06
<b>Sleep disorder</b>	1.4%	3.9%	0.10
<b>Anxiety</b>	1.0%	3.1%	0.13
<b>Attention Disturbance</b>	0.7%	2.4%	0.16
<b>Depressive Disorder</b>	4.5%	2.7%	0.36

	DOR n=108	EFV n=108	p value
<b>Dizziness</b>	6.5%	25.9%	< 0.001
<b>Abnormal dreams</b>	5.6%	14.8%	0.04
<b>Headache</b>	2.8%	5.6%	0.50
<b>Nightmares</b>	5.6%	8.3%	0.59
<b>Sleep disorder</b>	4.6%	6.5%	0.77
<b>Insomnia</b>	6.5%	2.8%	0.33

*Behrens et al, AIDS Pat Care & STDs  
2014, 28(4): 168*

*Gatell et al, CROI 2016,  
Abstract 470*

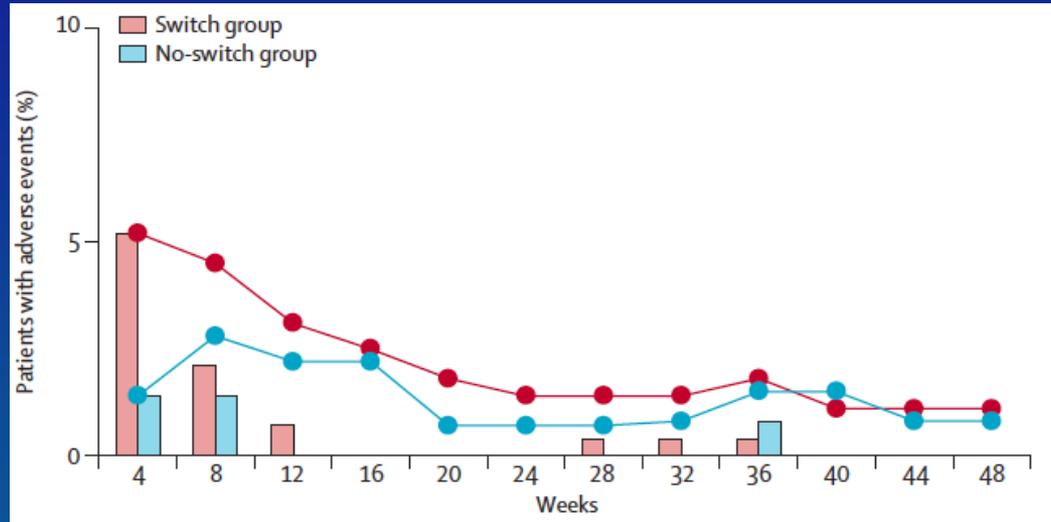
# Greater Than Expected Dolutegravir Intolerance in Holland

	Total (N=387)	ART-Naive (n=65)	ART-Experienced (n=322)
<b>Sleep Disturbance</b>	19 (4.9%)	5 (7.7%)	14 (4.3%)
<b>Gastrointestinal</b>	18 (4.6%)	4 (6.2%)	19 (5.9%)
<b>Neuropsychiatric</b>	12 (3.1%)	3 (4.6%)	9 (2.8%)
<b>Fatigue</b>	9 (2.3%)	1 (1.5%)	8 (2.5%)
<b>Headache</b>	8 (2.1%)	0 (0%)	8 (2.5%)
<b>Paresthesias</b>	6 (1.6%)	0 (0%)	6 (1.9%)
<b>Other</b>	6 (1.6%)	2 (3.1%)	4 (1.2%)

- Overall 62 of 387 (16%) discontinued dolutegravir
- 56 of 62 these (90.3%) discontinued due to adverse events
- These 56 had 78 adverse events:

**54 (69.2%) were nervous system-related**

# Headache Onset Usually within 12 Weeks and Then Typically Resolves



*Pozniak et al, Lancet Infectious Disease 2014; 14: 590–99*

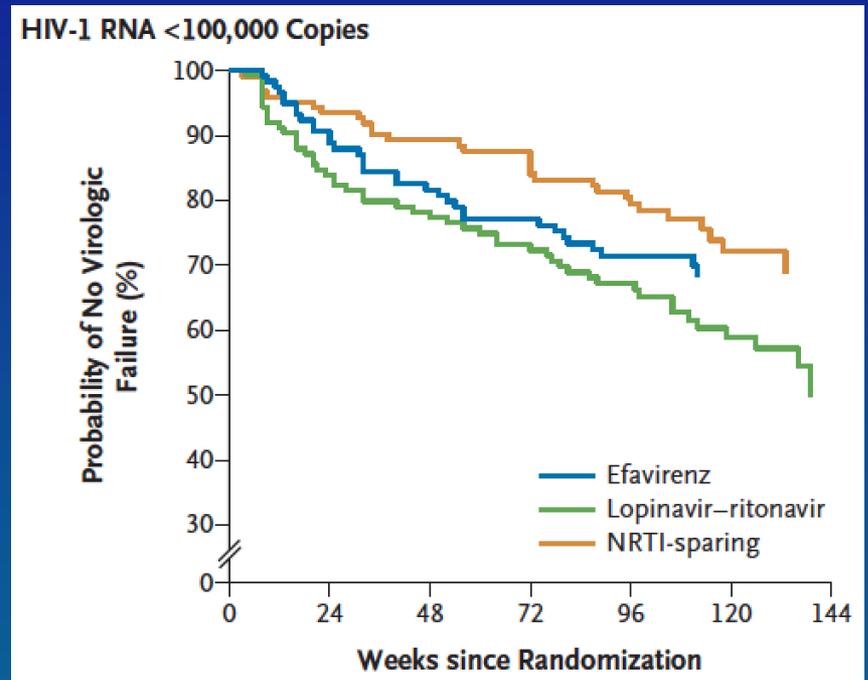
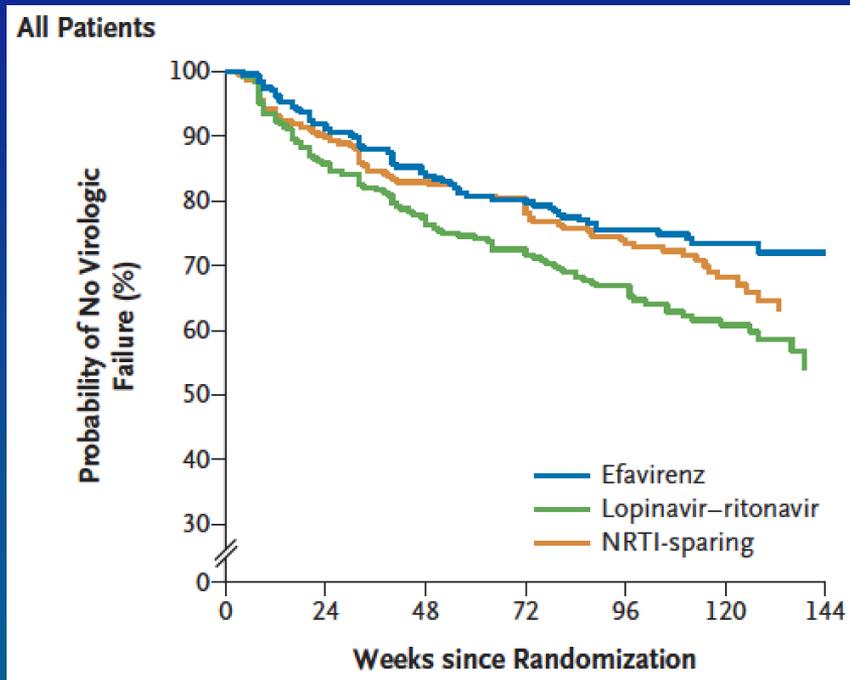
	Week 2	Week 16	Change (%)
<b>DTG Plasma, total*</b>	3360	3210	-4.5%
<b>DTG Plasma, unbound*</b>	17.1	23.9	+39.8%
<b>DTG CSF, total*</b>	18.2	13.2	-27.5%
<b>CSF–total plasma ratio, %</b>	0.516	0.412	-20.2%

\*ng/mL

All values are medians

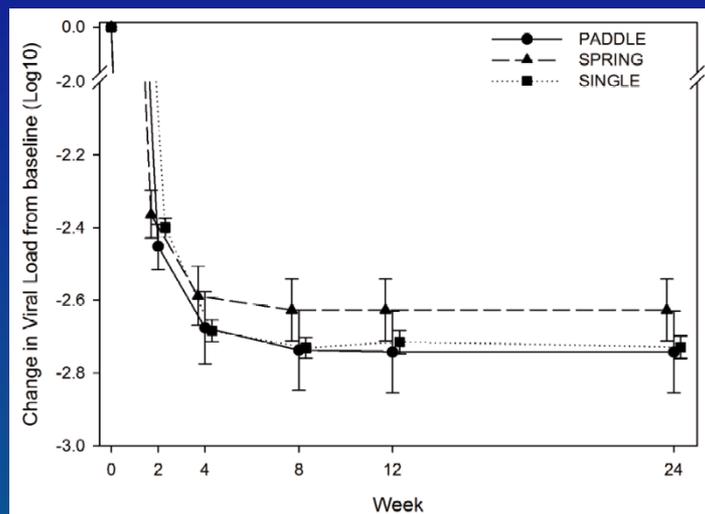
*Letendre et al, Clin Infect Dis 2014;59(7):1032–7*

# NRTI-Sparing ART May Be As Effective As Traditional ART



Regimen	Time to Virologic Failure	Time to Regimen Failure
Efavirenz vs. lopinavir-ritonavir	0.63 (0.45–0.87)	0.75 (0.57–0.98)
Efavirenz vs. NRTI-sparing therapy	0.86 (0.61–1.21)	0.93 (0.70–1.23)
Lopinavir-ritonavir vs. NRTI-sparing therapy	1.30 (0.95–1.77)	1.21 (0.93–1.56)

# Dual Therapy with Dolutegravir-Lamivudine May Be Effective



Sued et al, CROI 2016, Abstract 947

**Journal of Antimicrobial Chemotherapy**

Dolutegravir-based monotherapy or dual therapy maintained a high proportion of viral suppression even in highly experienced HIV-1-infected patients

Gubavu et al, JAC 2016; 71: 1046–1050

Virological control and metabolic improvement in HIV-infected, virologically suppressed patients switching to lamivudine/dolutegravir dual therapy

Borghetti et al, JAC 2016, doi:10.1093/jac/dkw147

AE	Adverse Events possible related to DTG	
	Grade I	Grade II
Somnolence	1	
Epigastric pain	1	
Headache	2	1
Diarrhea	1	
Nausea	2	

All AEs were reported at the first week of treatment

No grade 3-4 laboratory toxicities were reported through 24 weeks  
No SAEs reported

Figuroa et al, EACS 2015, Abstract LBPS4/1

# Summary and Conclusions

- ▶ **HIV appears to accelerate aging of the CNS**
  - May be due to prior injury
- ▶ **Neurocognitive impairment in older HIV+ adults has multiple contributors**
  - Managing metabolic and vascular disease may benefit the CNS
  - Exercise and cognitive training may also be valuable
- ▶ **Optimal ART regimens in older adults are being investigated**
  - Switching or simplification may be viable options

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### Industry

- Gilead Sciences
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<http://www.virology-education.com/event/upcoming/8th-hiv-aging-workshop-2017/>

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