

# NeuroAIDS in the modern treatment era

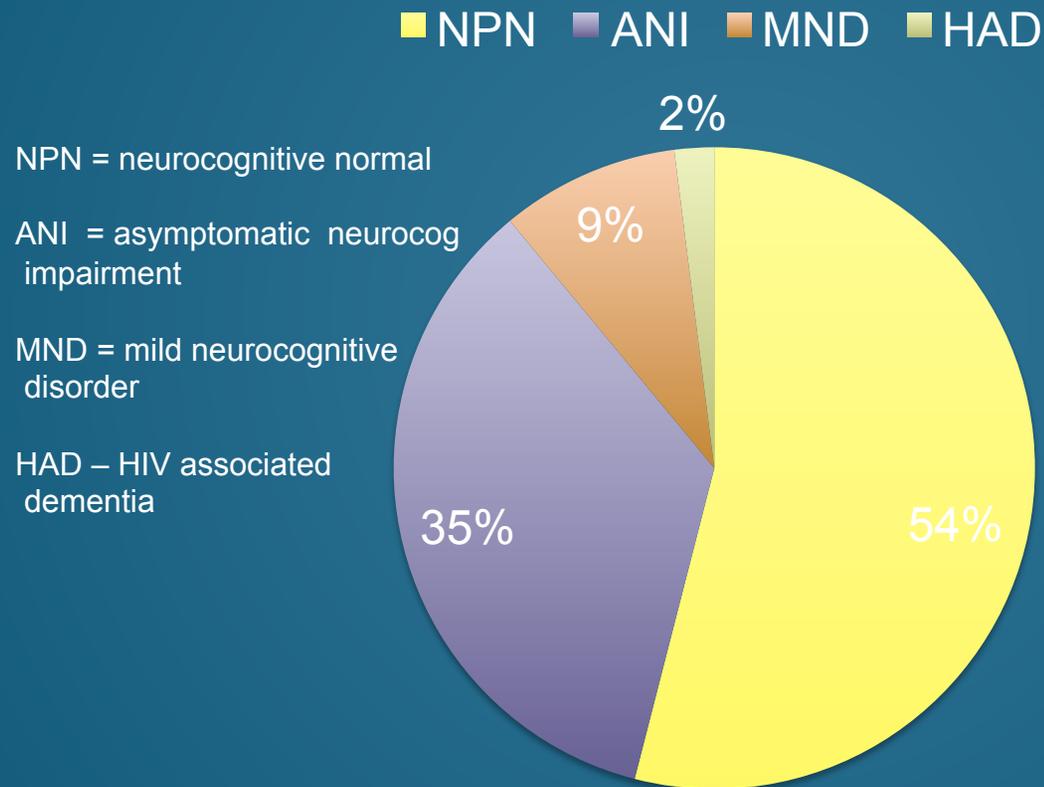
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NIH – RFBR Collaborative Research Partnership  
St Petersburg, Russian Federation, 14 April 2016

# HIV brain disease in the modern treatment era

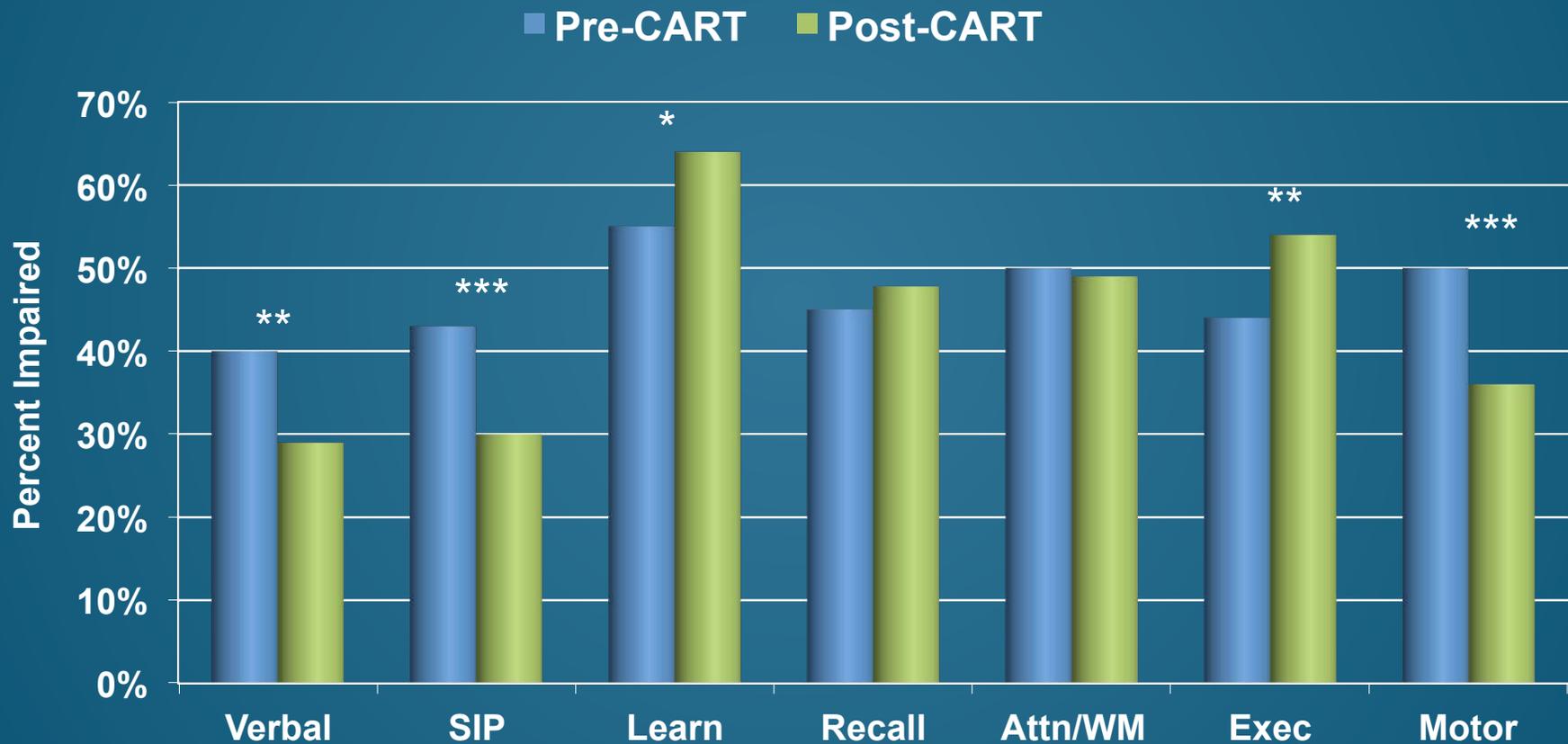
- Although modern ARV treatment has markedly reduced brain disease from opportunistic infections, **HIV associated neurocognitive disorders (HAND)** remain prevalent, affecting about 40% of HIV+
- HAND still occurs in successfully treated [plasma HIV undetectable] individuals
- As HIV+ people survive longer, there may be increasing “brain burden” due to chronic inflammation which may amplify effects of
  - » Age related metabolic, vascular, and neurodegenerative processes
  - » Comorbidities, eg drug abuse, head injury, HCV, other coinfections
- HAND affects critical behaviors that are of public health concern
  - » Medication adherence [transmission risk; resistance]
  - » Risk behavior [transmission risk; superinfection]
  - » Everyday functions, eg., driving [risk to self and others]
  - » Reduced work efficiency; more unemployment [loss of productivity; personal and societal economic impact]

# Prevalence of Specific HAND Diagnoses in CHARTER (N=1555 HIV+):



*Heaton et al., Neurology 2010, 75(23): 2087-96*

# Neurocognitive Impairment by Domain in HIV+ from Pre-CART and Post-CART Eras

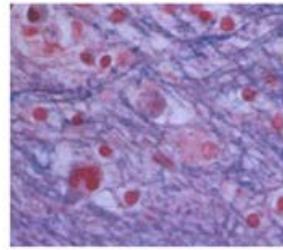
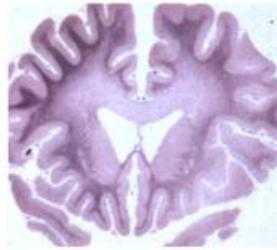


\*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$   
 SIP= speed of information processing

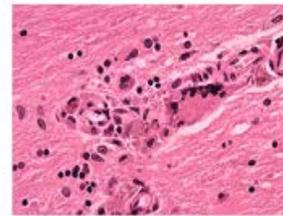
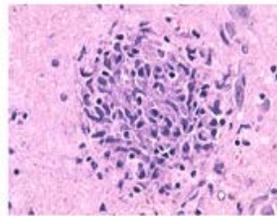
Heaton, et al, (2011) *Journal of Neurovirology*, 17(1), 3-16.

# Neuropathology of HIV in the pre-HAART era

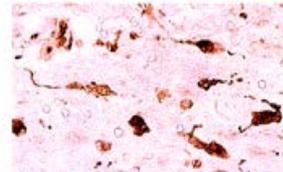
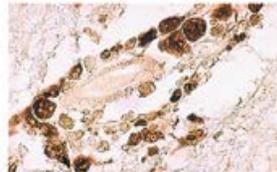
## HIV Encephalitis



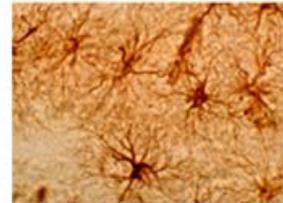
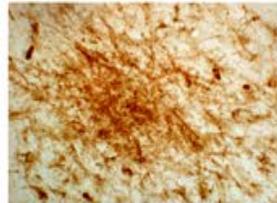
*Atrophy  
white matter  
pallor*



*Microglial  
Nodules  
MNGC's*

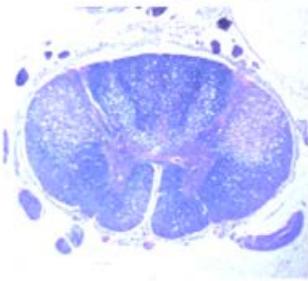


*HIV p24*

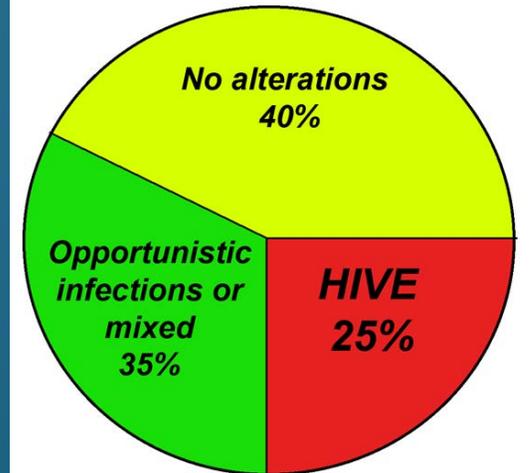
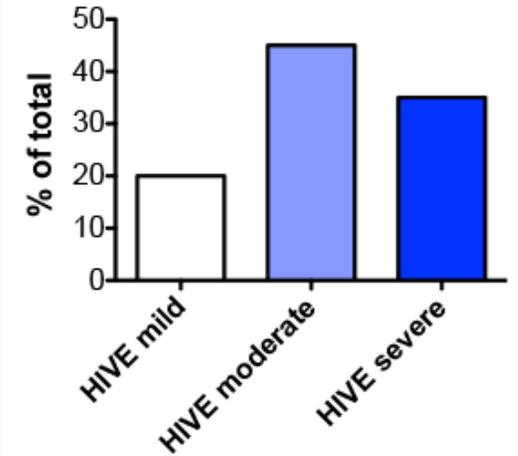


*Microgliosis  
Astrogliosis*

## Vacuolar myelopathy

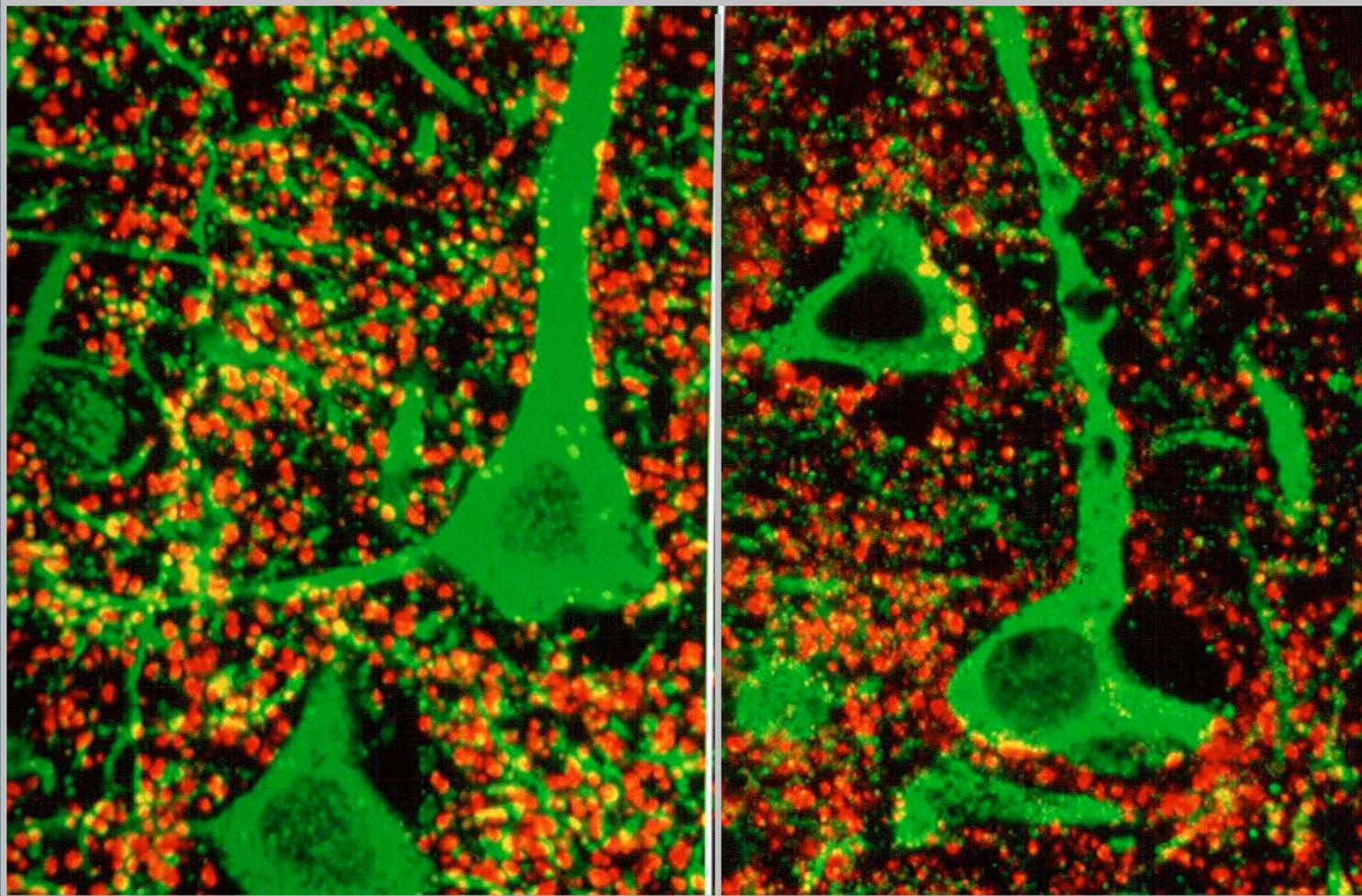


Severity of HIV in the Pre-HAART era



Courtesy Eliezer Masliah, UCSD HNRP

# Loss of synapses and dendrites in HIV+



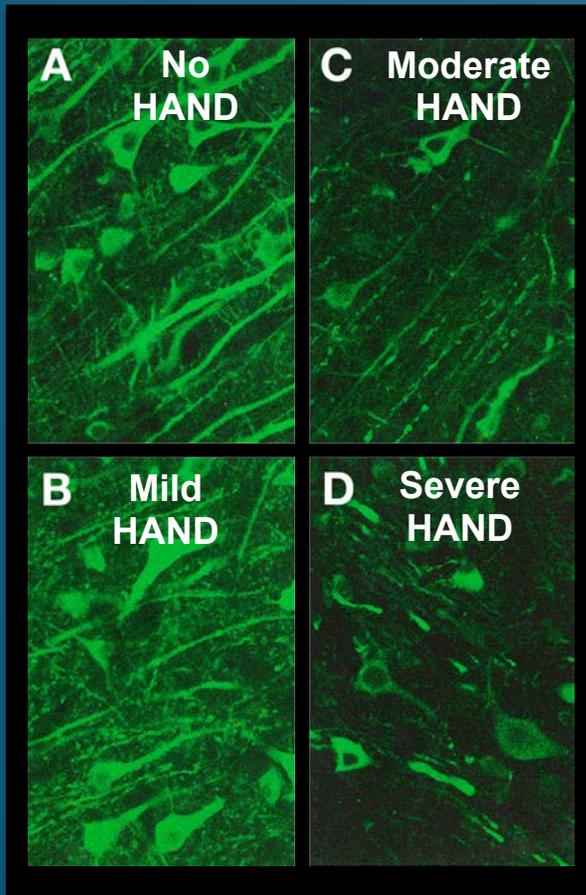
HIV-

HIV+

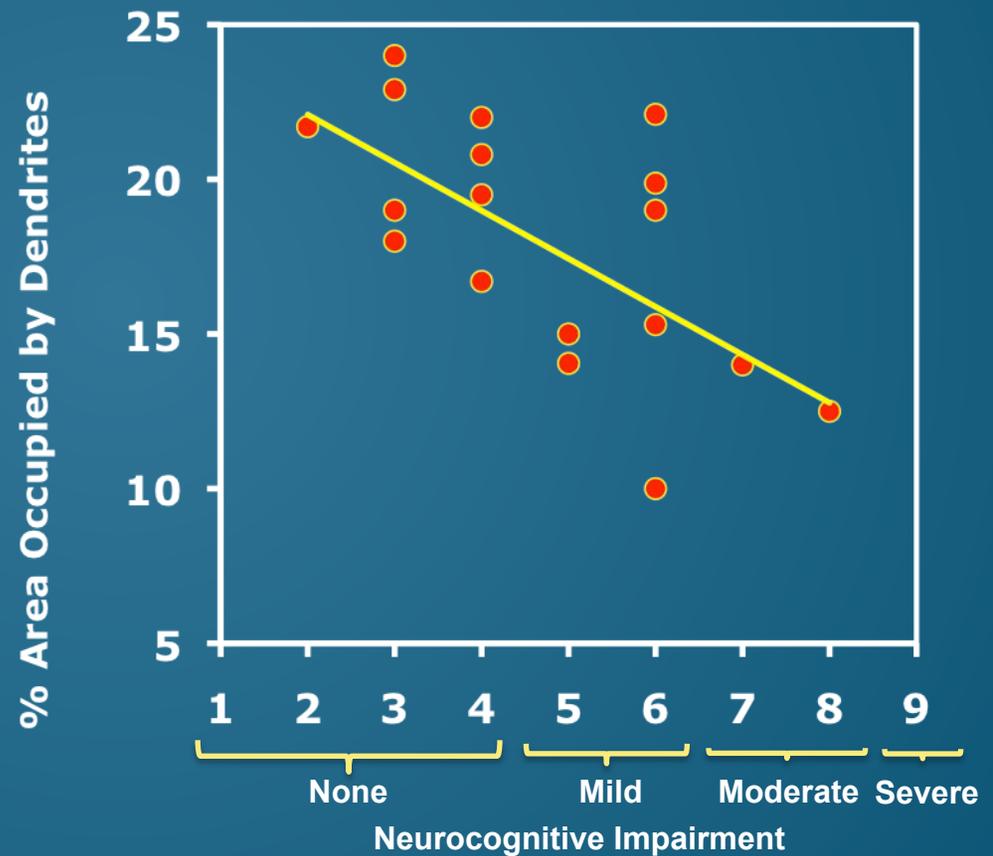
Courtesy Eliezer Masliah  
UCSD HNRP

# Injury to synapses and dendrites may form a basis of HIV neurocognitive impairment

Progressive Dendritic Loss from No HAND (A) to Severe HAND (D)

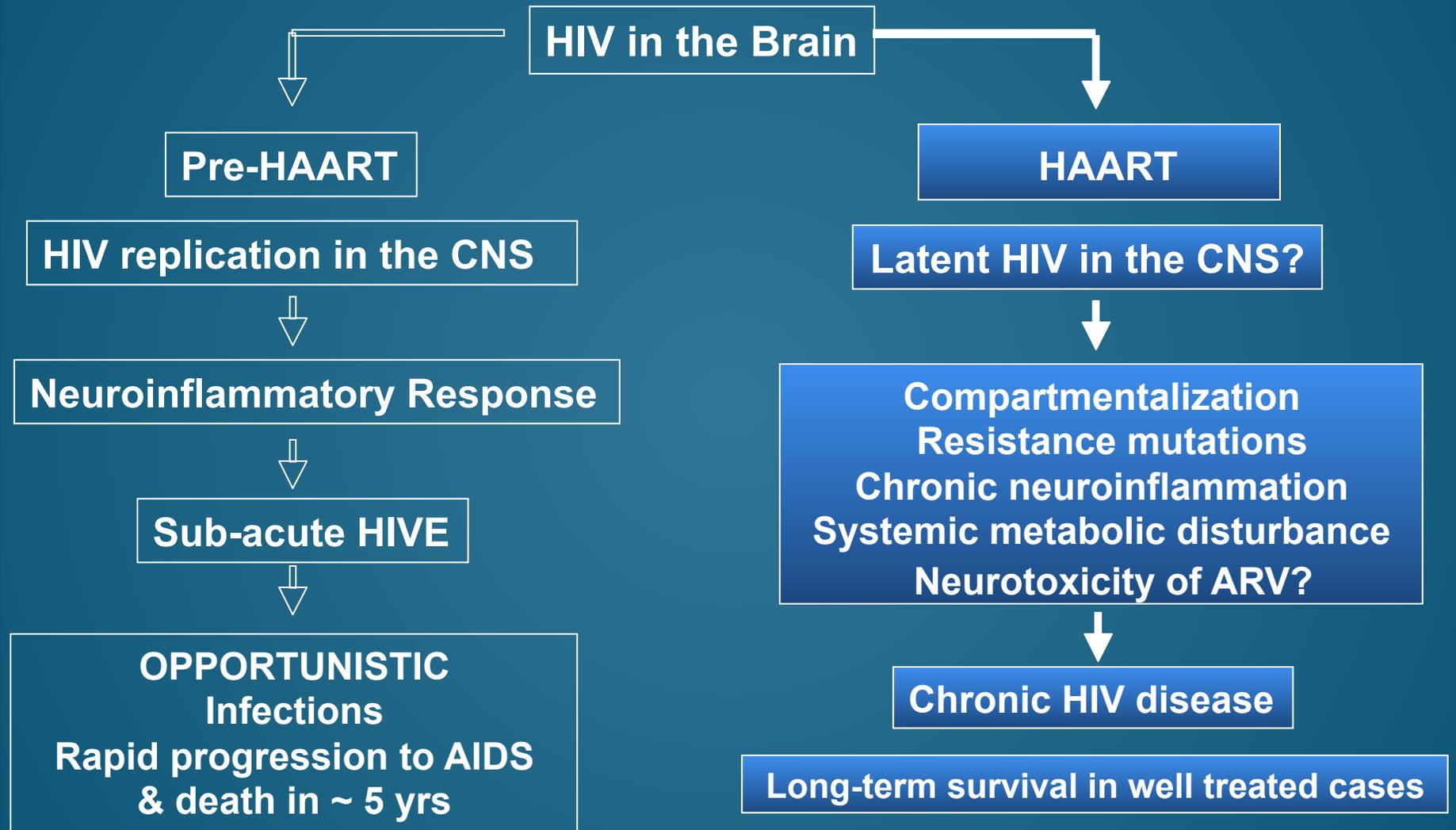


Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss



Masliah, et al. *Ann Neurol.* 1997, 42(6): 963-72

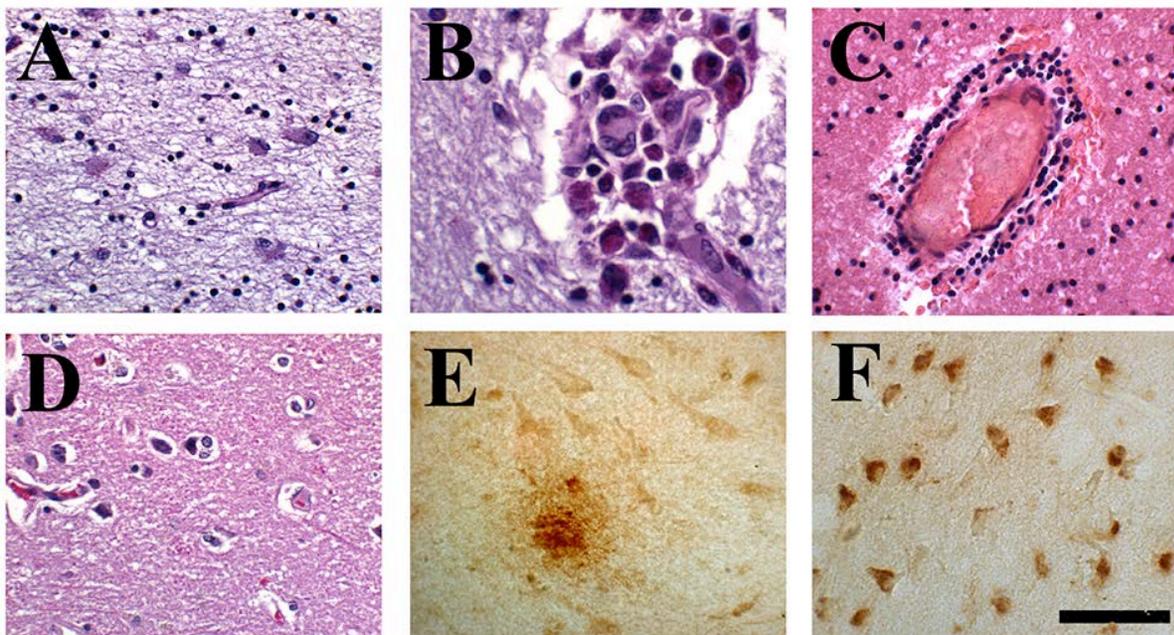
# HIV: from subacute to chronic disease



Courtesy Eliezer Masliah, HNRP UCSD

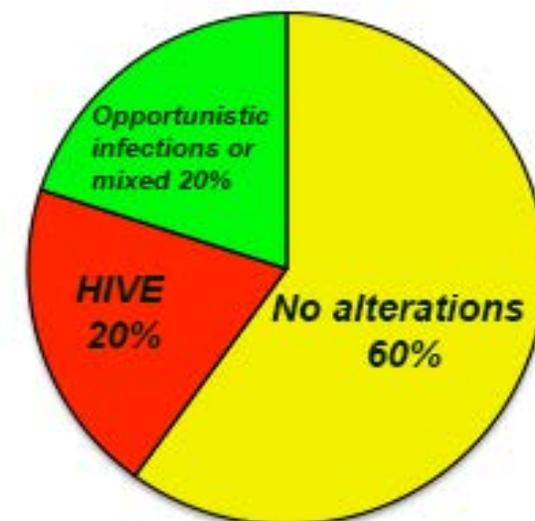
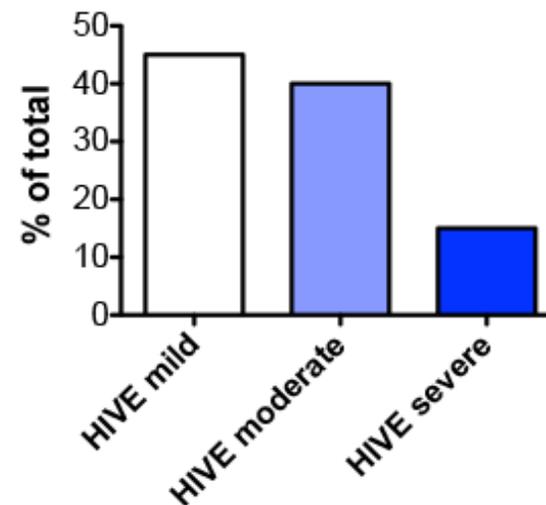
Co-morbidities: *Aging, Drugs, HCV*

# Neuropathology of HIV in the HAART era



(A) Severe white matter injury with astrogliosis (LFB). (B) Vascular infiltration in the white matter by macrophages (PAS). (C) Lymphocytic perivascular infiltration (H&E). (D) 'Burnt-out' form with neuronal atrophy (H&E). (E) Plaque-like lesions (anti-A $\beta$ , 4G8). (F) Intra-neuronal A $\beta$  (anti-A $\beta$ , 4G8). Scale bar 35  $\mu$ m.

Severity of HIV in the HAART era



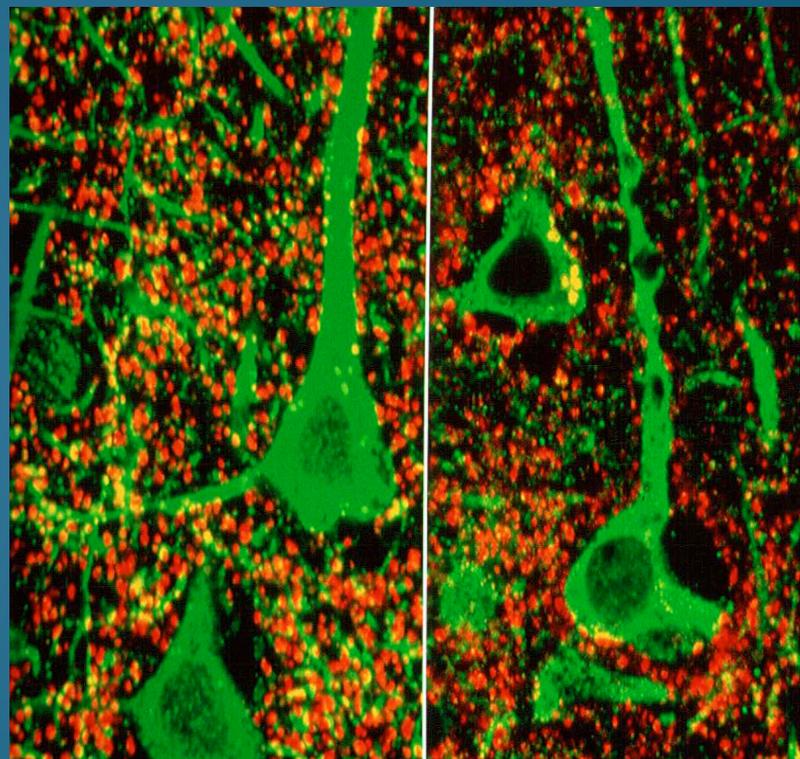
Courtesy Eliezer Masliah, HNRP UCSD

# What factors are associated with HAND?

- **Viral factors**
  - » Clade? Probably not
  - » Higher molecular viral diversity in circulating HIV?
  - » Shift in viral tropism, eg., to dual tropism? Maybe
  - » Specific neurotropic/neuropathogenic variants? Unclear
  - » ARV resistance?
  - » Viral molecules, eg., Tat; gp120: contribute to abnormal intracellular signaling, protein mismanagement, and dendritic injury
- **Host vulnerability**
  - » Unknown if specific host genetic factors confer neuro-vulnerability. Possibly APO E4
  - » Co-morbidities may amplify HIV effects: substance abuse; HCV; head injuries; aging; metabolic syndrome
- **Treatment factors**
  - » Treatment not begun early enough to prevent lasting brain injury?
  - » Ineffective: not sustained suppression, particularly in CNS; persisting viral reservoirs?
  - » Neurotoxicity of ARV?

# Productive and latent forms of HIV in the brain can release viral proteins that

- activate apoptotic pathways
- dysregulate calcium homeostasis
- promote oxidative stress
- **alter cell cycle signaling pathways such as CDK5, leading to protein phosphorylation and misfolding**
- interfere with clearance pathways such as autophagy, leading to abnormal protein aggregation

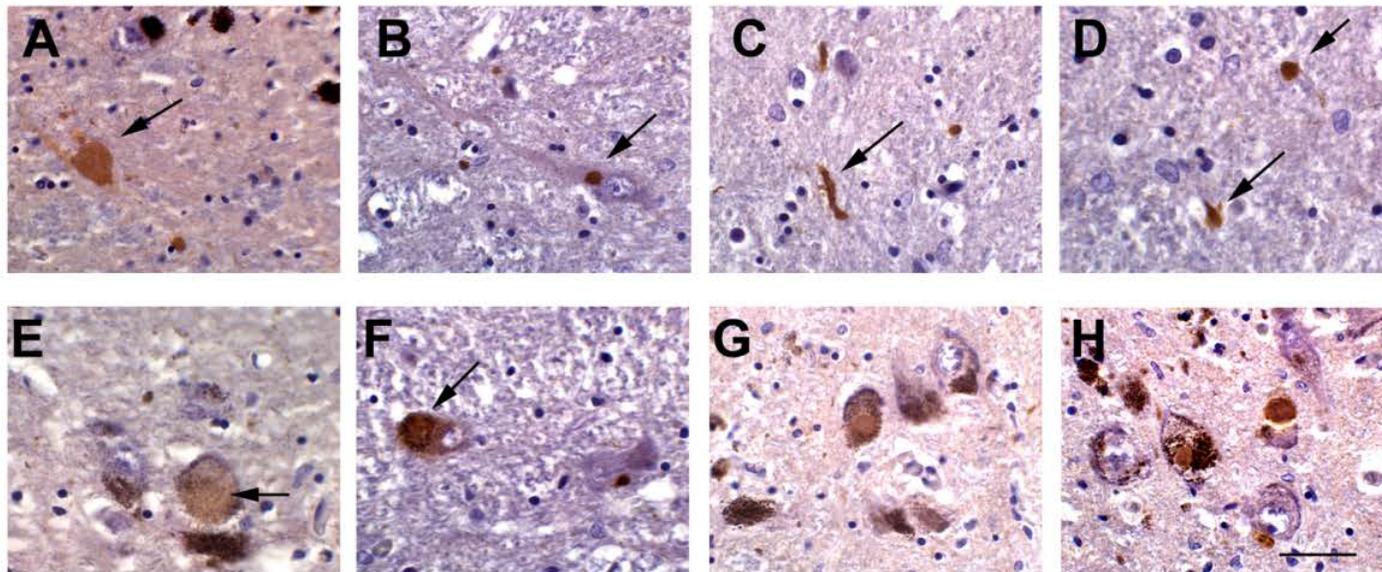


These processes converge on a final common pathway leading to synaptodendritic injury

Courtesy Eliezer Masliah  
UCSD HNRP

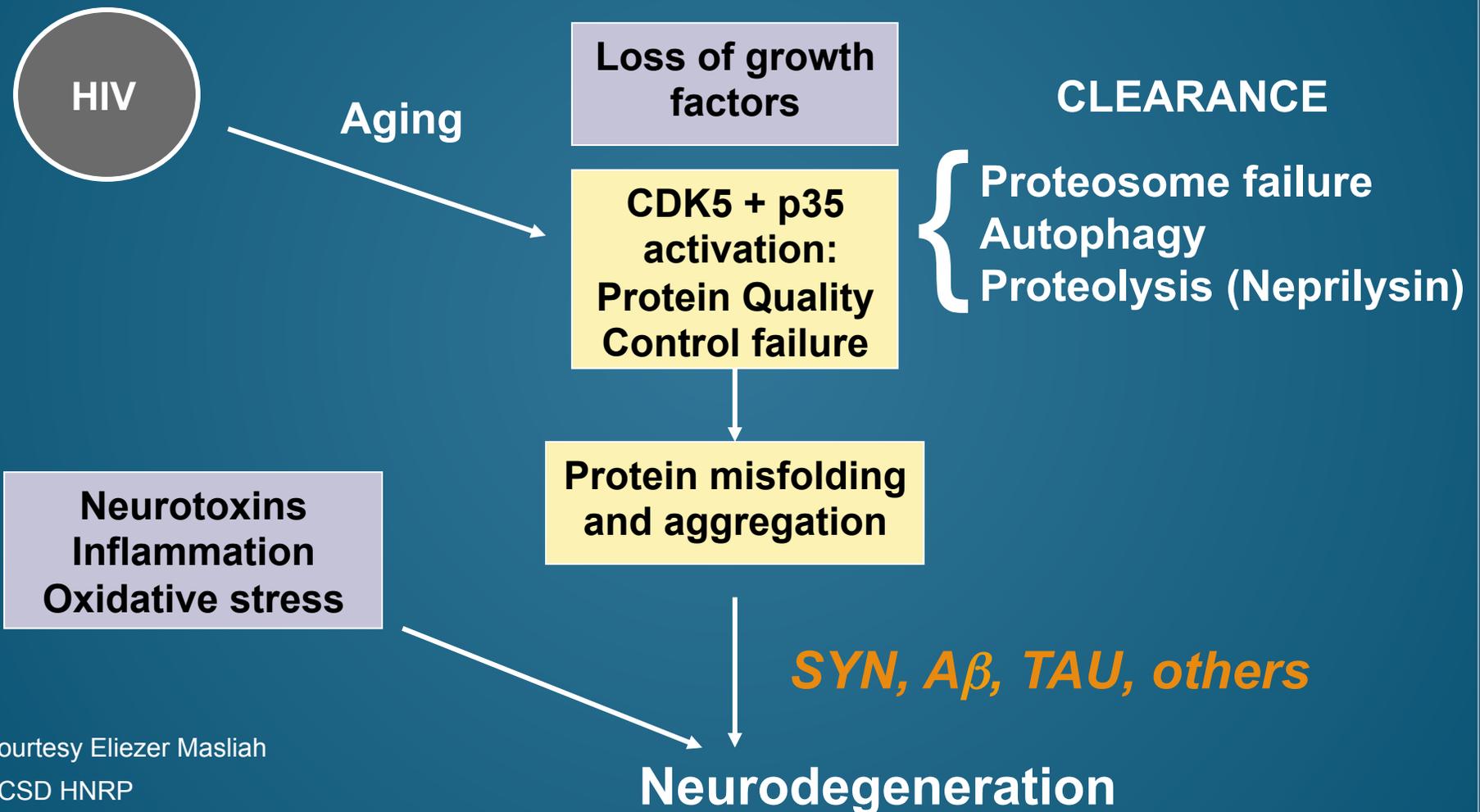
## Increased neuritic alpha synuclein expression in brains of 55-65 year olds; accelerated age related “protein mismanagement” in brains of HIV+?

- Neuritic  $\alpha$ -synuclein expression (arrows) was found in 16% of the substantia nigra studied (12/73)



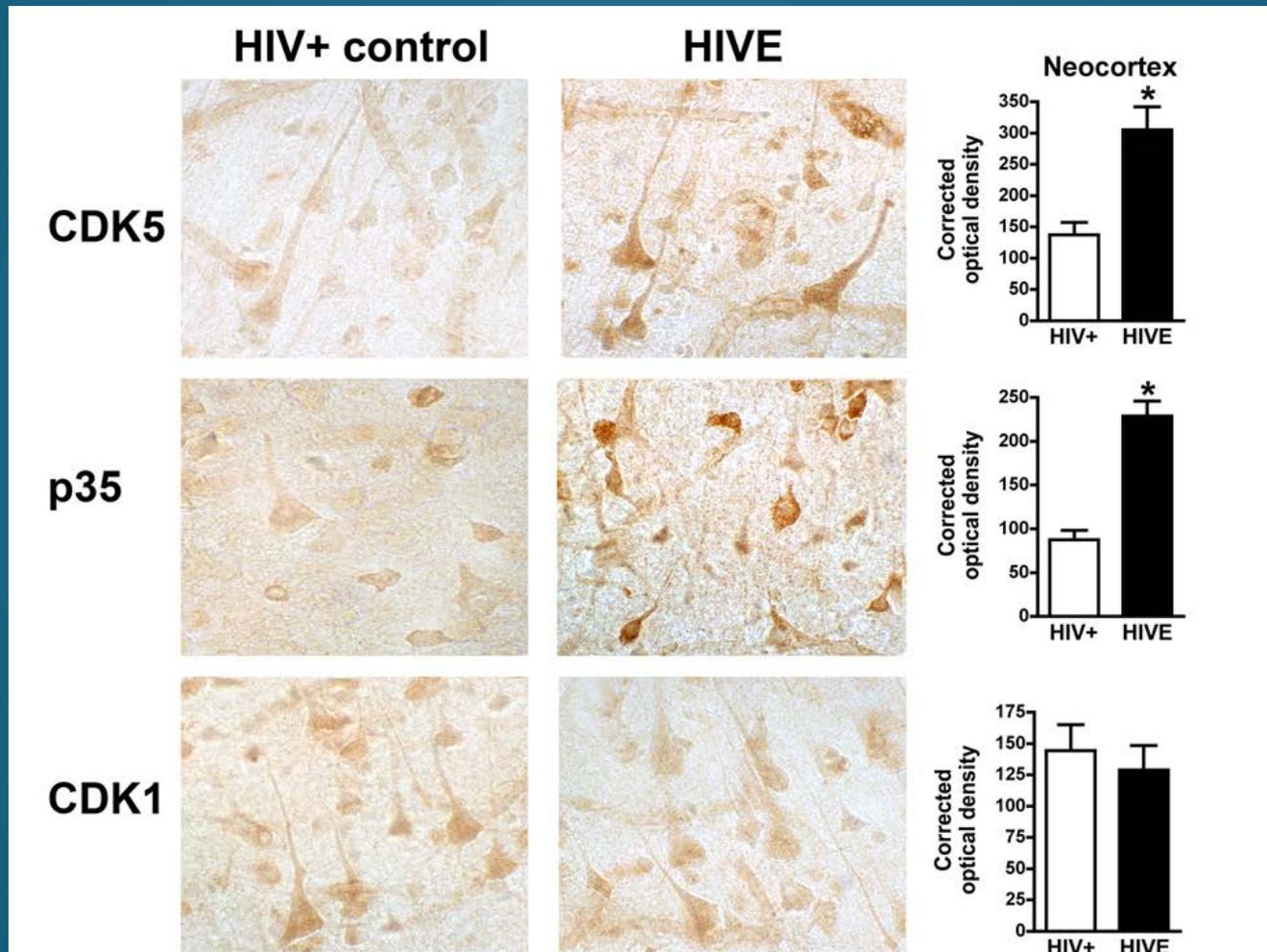
*Khanlou et al., J Neurovirol; 2009;15(2):131-138*

# Mechanisms of neurodegeneration: Cyclin Dependent Kinase 5 (CDK5) activation and abnormal phosphorylation



Courtesy Eliezer Masliah  
UCSD HNRP

# Specific increase in CDK5 and activator p35 expression in human brains with HIVE



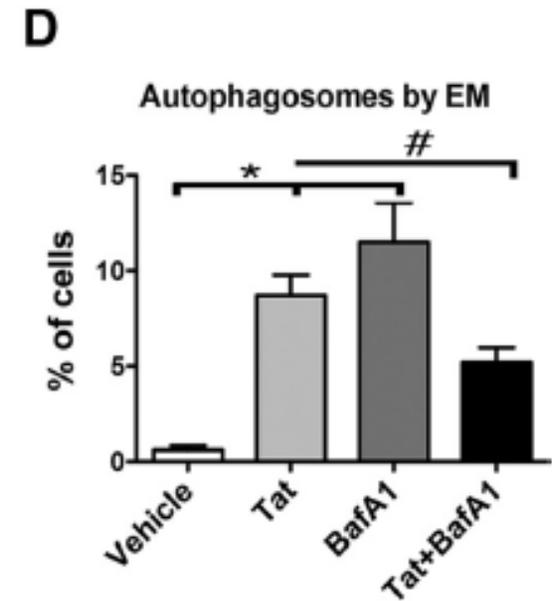
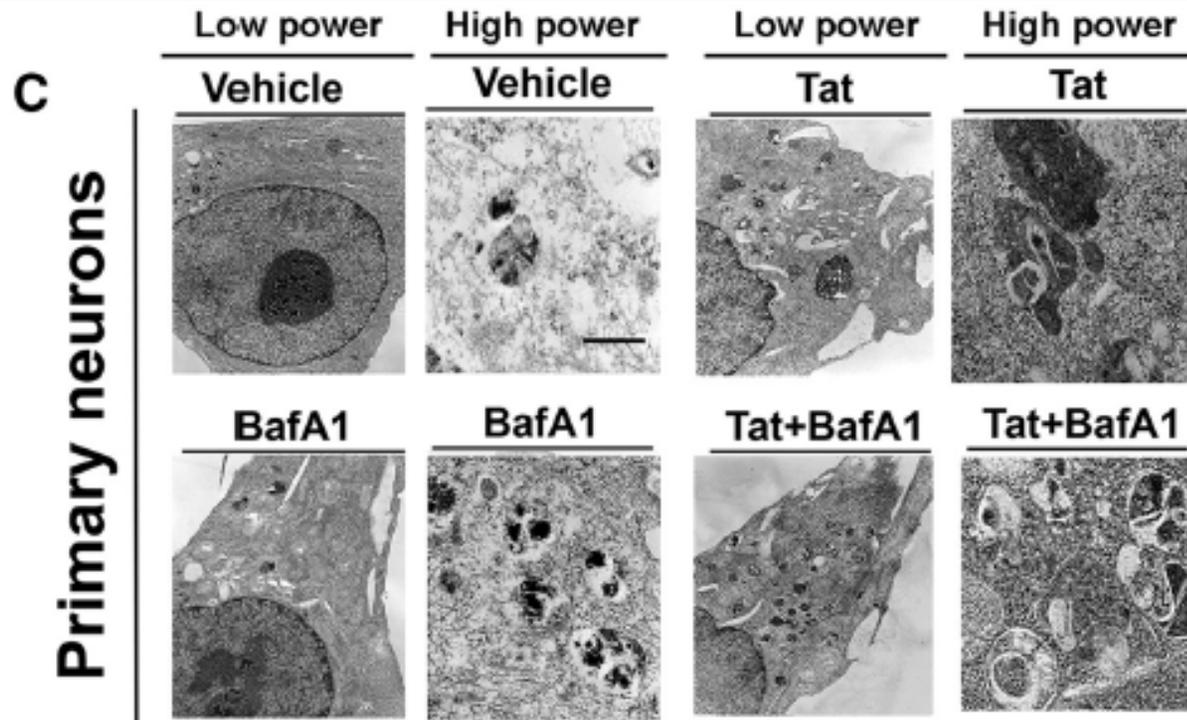
Patrick et al Am J Pathol; Crews et al CDD 2012, 2013

# Productive and latent forms of HIV in the brain can release viral proteins that

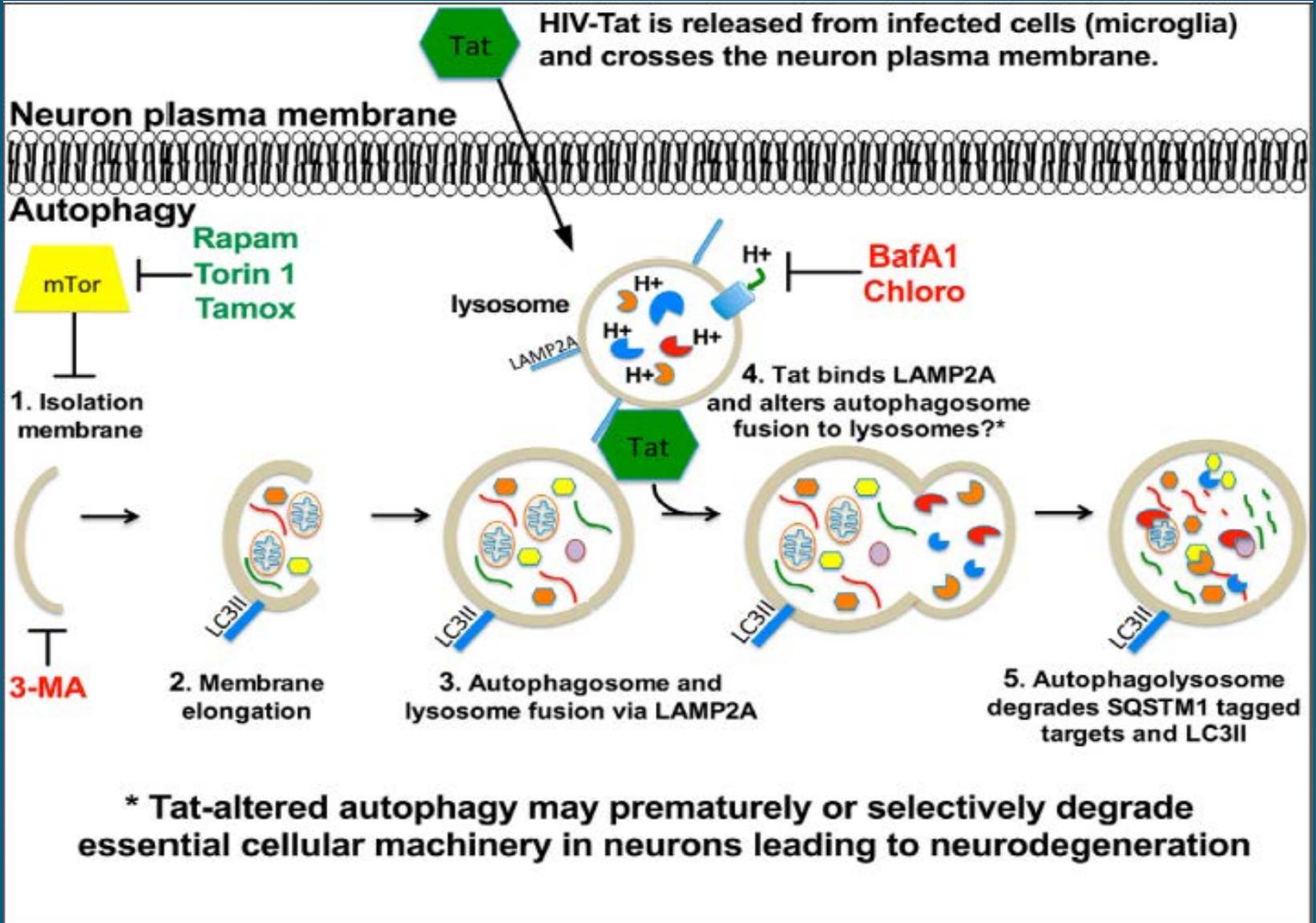
- activate apoptotic pathways
- dysregulate calcium homeostasis
- promote oxidative stress
- alter cell cycle signaling pathways such as CDK5, leading to protein phosphorylation and misfolding
- **interfere with clearance pathways such as autophagy, leading to abnormal protein aggregation or premature degradation of essential proteins**

Thereby contributing to synaptodendritic injury

# Abnormal accumulation of autophagosomes in Tat treated mouse neuronal cells



Fields (2015) *J Neurosci*, 35(5):1921-38



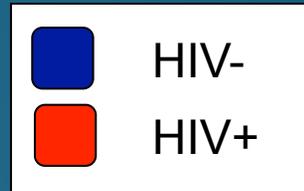
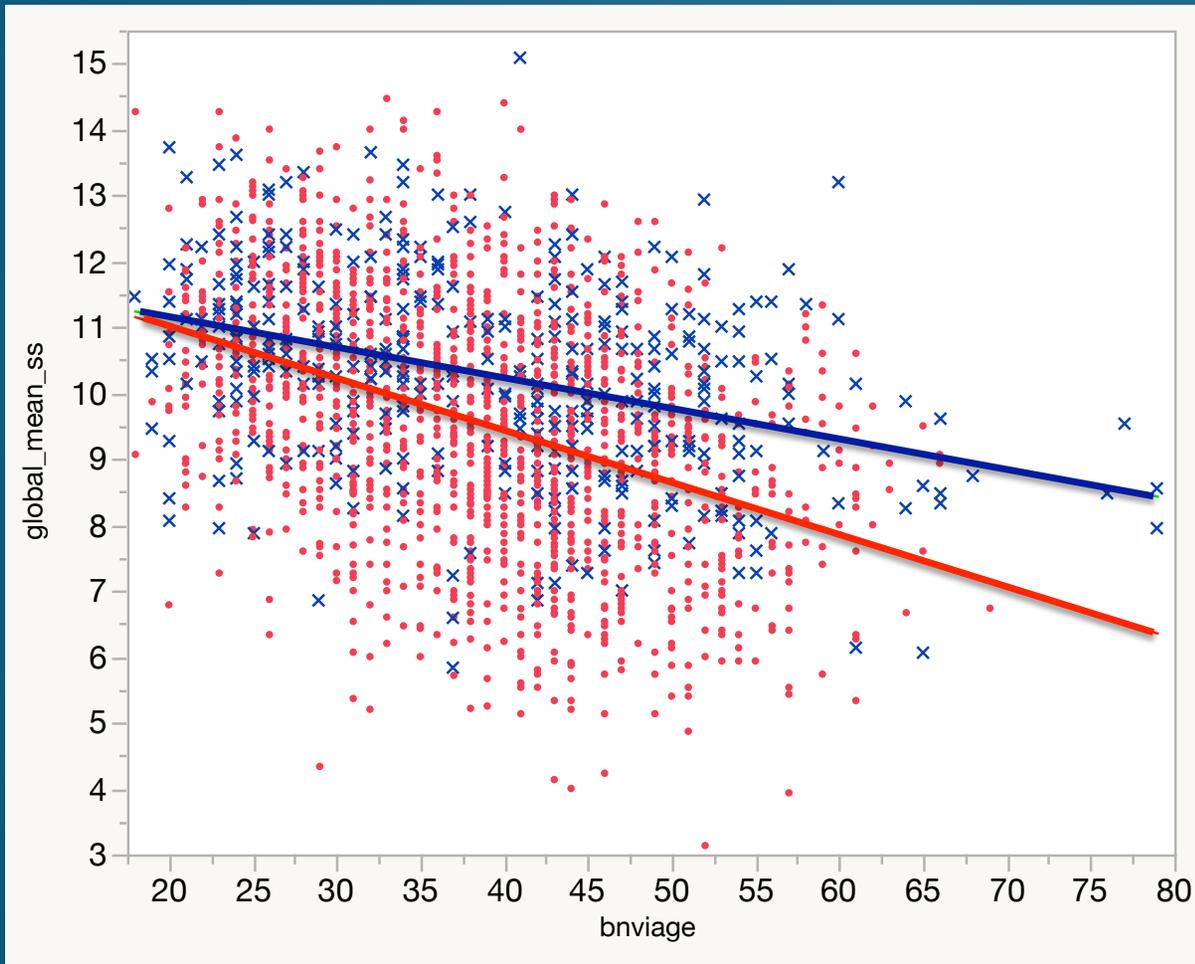
*How Tat may interfere with neuronal autophagy. From Fields (2015) J Neurosci, 35(5):1921-38*

# Persistence of Neurocognitive Complications may be driven partly by comorbid factors

- Aging
- Metabolic Syndrome
- Drug and Alcohol Abuse
- Coinfections eg., Hepatitis C, CMV, toxoplasma, TB, etc
- Neurotoxicity of treatments
- History of Neurologic Insults, eg., head injury, that may increase vulnerability to neuroAIDS

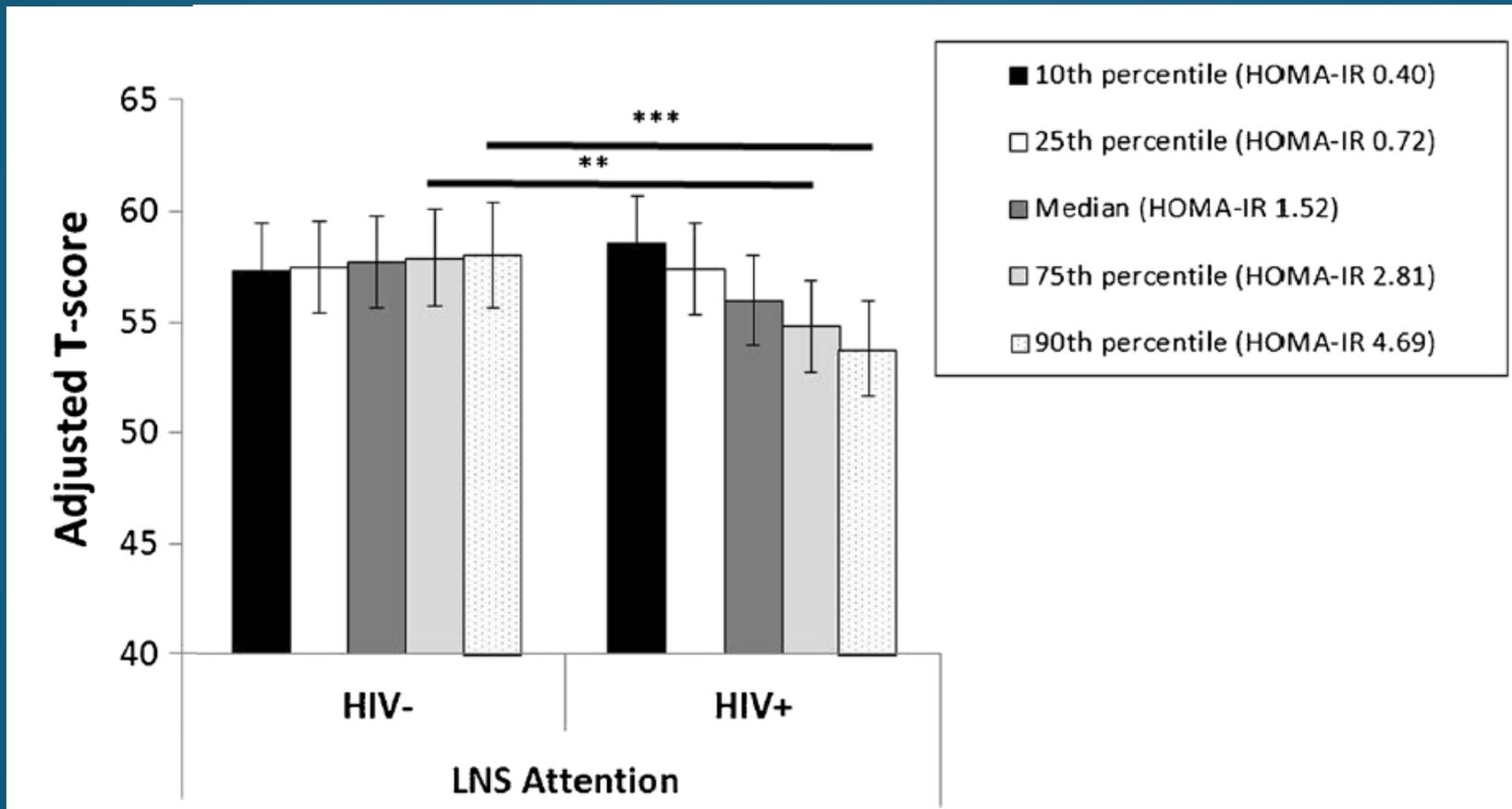
# Neurocognitive performance declines faster with age in HIV+ compared to HIV-

Data from UCSD HIV Neurobehavioral Research Program



Age Effect:  $p < .0001$   
HIV Effect:  $p < .0001$   
Interaction:  $p < .0001$

## Example of HIV and medical morbidity interaction on cognitive performance: attentional function worsens with greater insulin resistance in HIV+ but not HIV-



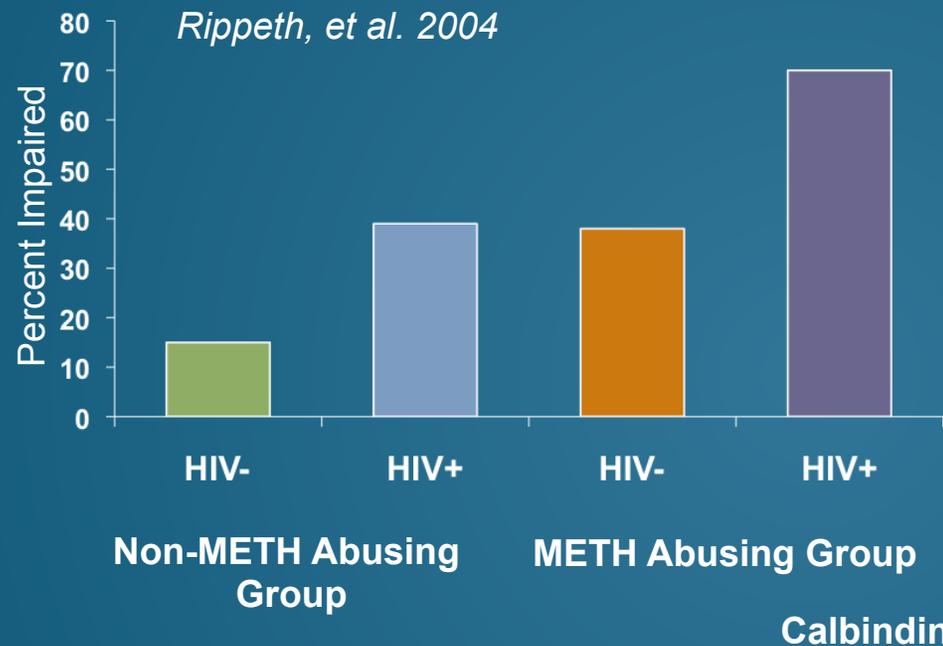
The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function

Valcour (2015) *J Neurovirol*, 21:415-421

# Do drugs of abuse cause brain damage? Do these drugs potentiate neuroAIDS?

Drug	Evidence for Brain damage? Neurocognitive Impairment (NCI)?	HIV X drug?
Alcohol	Well documented in long term alcoholics	maybe
Methamphetamine	Well documented in extensive users	yes
Cocaine	Data are mixed. Animal and imaging data on potential damage not consistently supported by neurocognitive reports	uncertain
Heroin/opioids	Numerous reports with contradictory findings; Some human neuropath and preclinical work suggests neural injury. No systematic evidence for neurocognitive impairment	unknown
Sedative/hypnotics	NCI in chronic heavy users	unknown
Hallucinogens	Data too fragmentary	unknown
Cannabis	Mixed neuroimaging findings; meta-analyses of studies on adults report weak to null effect on neurocognition in those who are not using at time of testing	no effect or possibly protective?

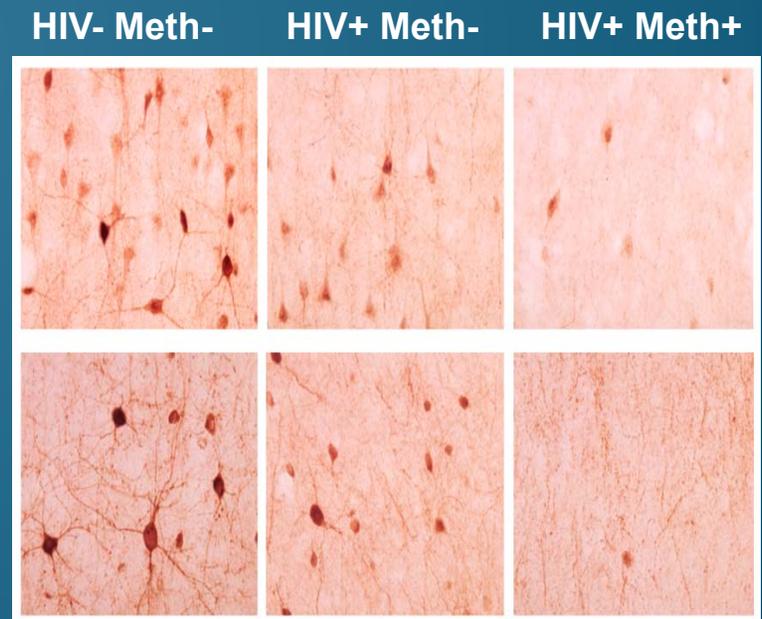
# HIV and METH enhance each other's neurotoxicity



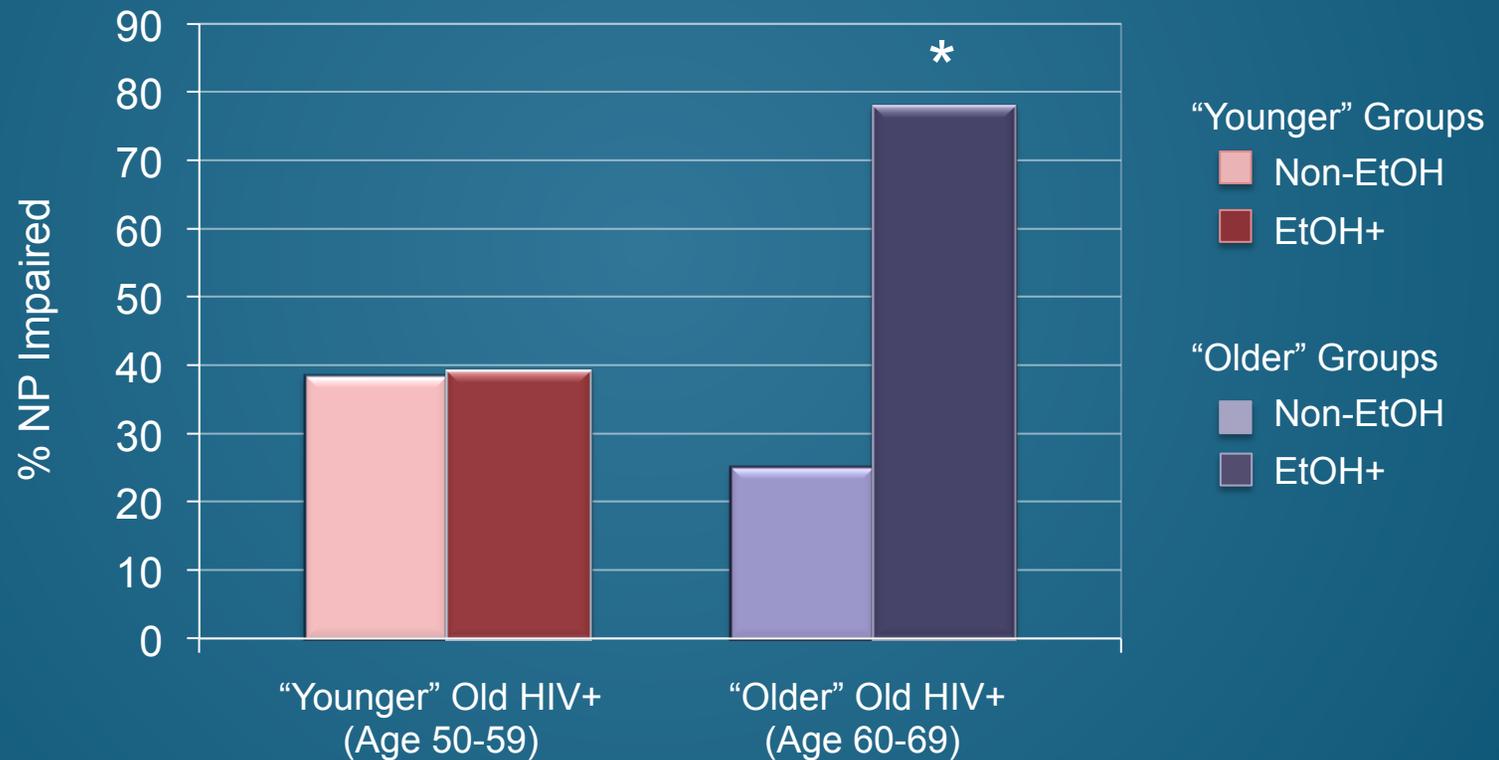
- Marked reduction in interneurons in HIV+ METH+

- Increased rates of neurocognitive impairment in HIV+ METH+

Parvalbumin



# Comorbidities can amplify each other: Alcohol abuse is Associated with Poorer Neurocognitive Functioning in Older but not Younger HIV+



Gongvatana et al., in prep, TMARC

\* $p < 0.01$

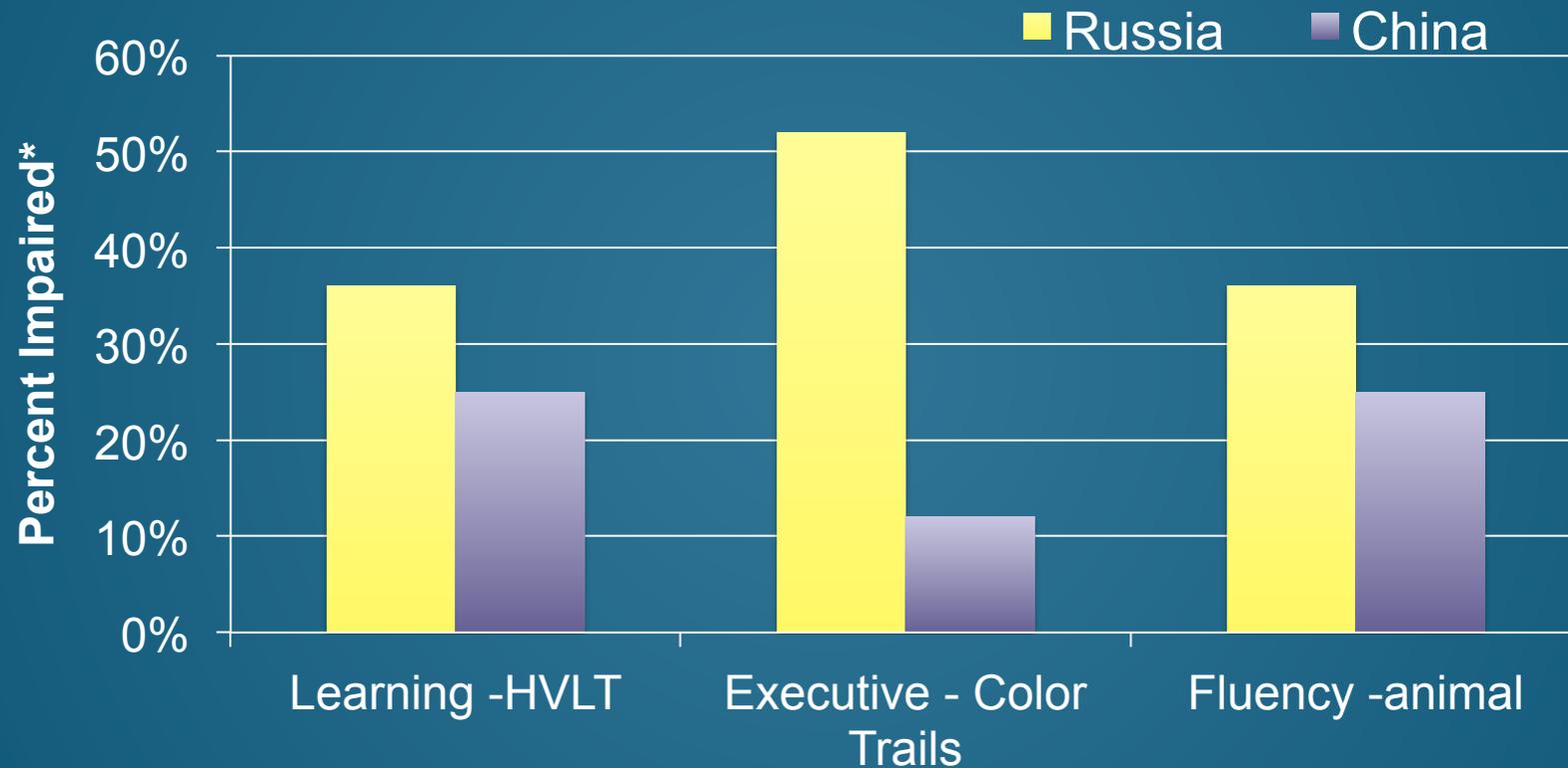
# Opioid using HIV+ in Russia and China

	Russia HIV+/Opioid+	China HIV+/Opioid+
n	30	204
Age (years)	34.6 (3.2)	33.7 (4.4)
Education (years)	10.6 (1.8)	9.5 (1.9)
% Male	100%	66%
CD4	265 [134-386]	464 [345-692]
HIV RNA (log <sub>10</sub> )	4.5 [4.3-4.7]	3.9 [1.7-4.5]
% Impaired based on 3 domains	40%	25%

Russia data based on 30 cases examined in “Russia R21” collaboration between Pavlov and UCSD TMARC (I. Grant, E. Krupitsky et al.). China data from 204 cases in China CDC-HNRP collaboration (S. Letendre, R. Heaton, F. Zhang et al.)

# Rates of neurocognitive impairment are elevated in HIV+ opioid addicts in Russian sample

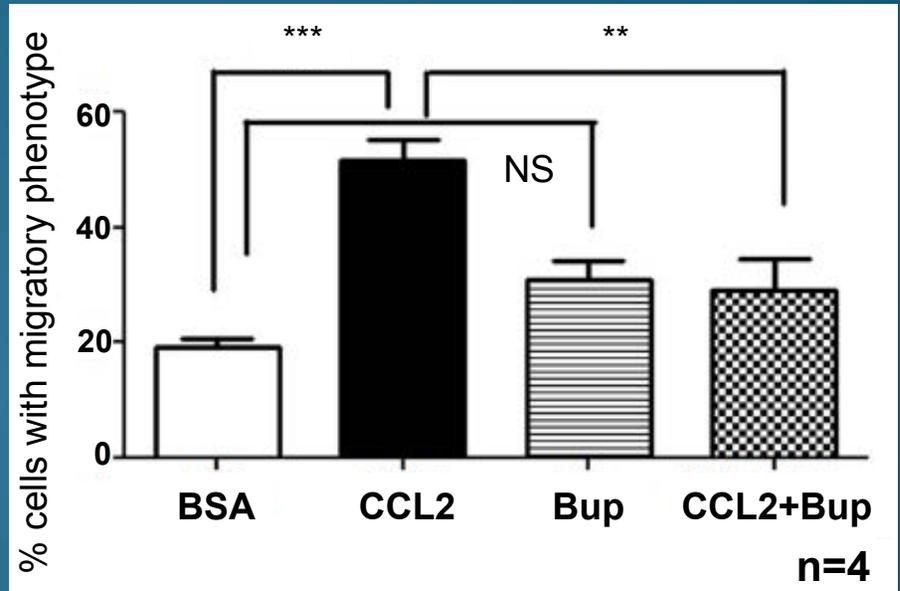
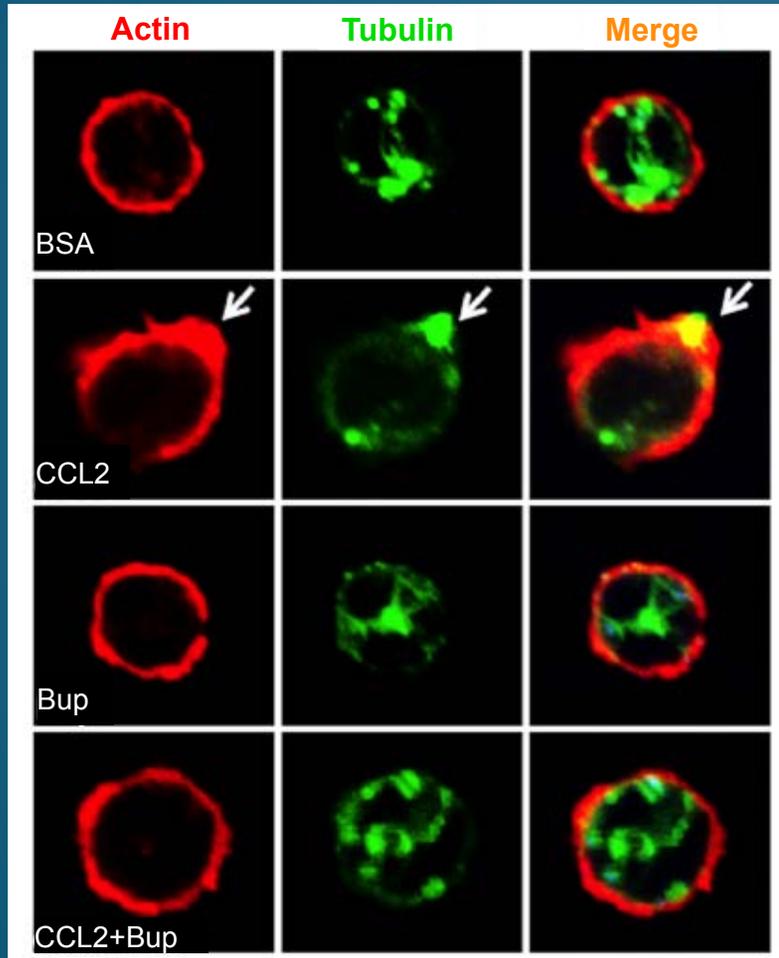
## Are lower rates in China due to concurrent methadone treatment?



Russia data based on 30 cases examined in “Russia R21” collaboration between Pavlov and UCSD TMARC (I. Grant, E. Krupitsky et al.). China data from 204 cases in China CDC-HNRP collaboration (S. Letendre, R. Heaton, F. Zhang et al.)

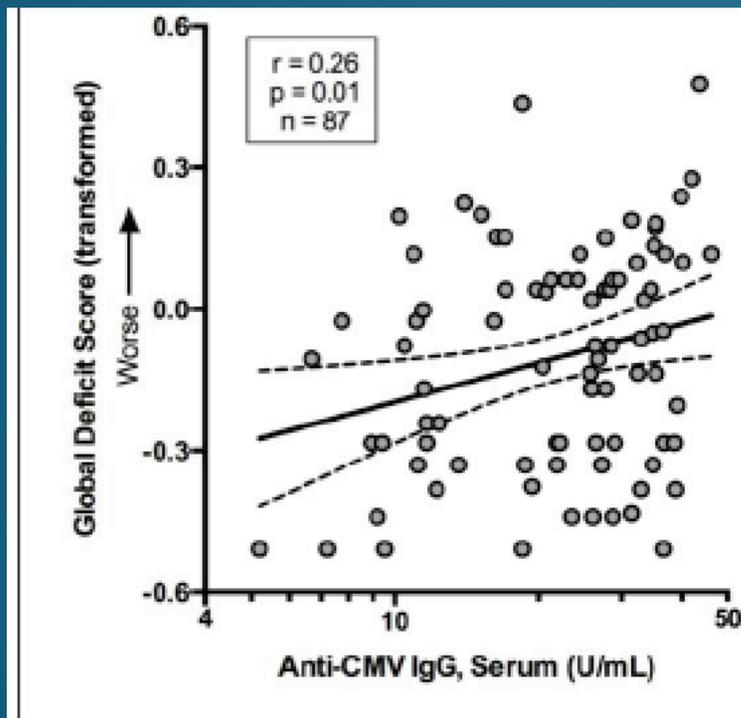
\*Uses US normative corrections

# Opioid partial/full agonists may inhibit chemokine CCL2-MCP1 induced monocyte migration possible neuroprotective effect in HIV infection?

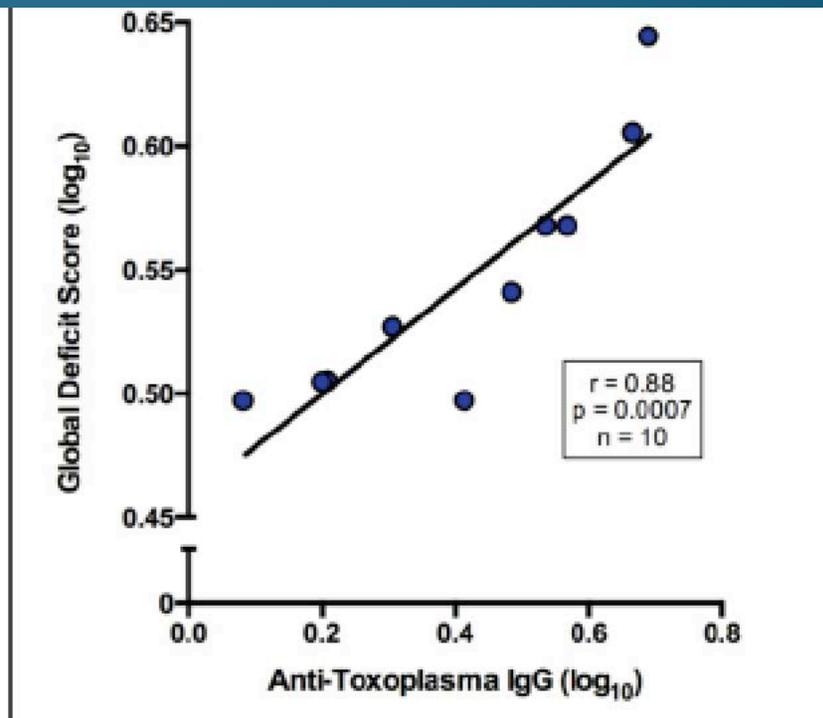


Cavallo et al., *J Immunol*;  
2015; 194(7): 3246-3258

## Comorbidities that may influence HAND: possible effects of latent CMV and toxoplasmosis



**5A:** Higher CMV IgG levels were associated with worse GDS values.



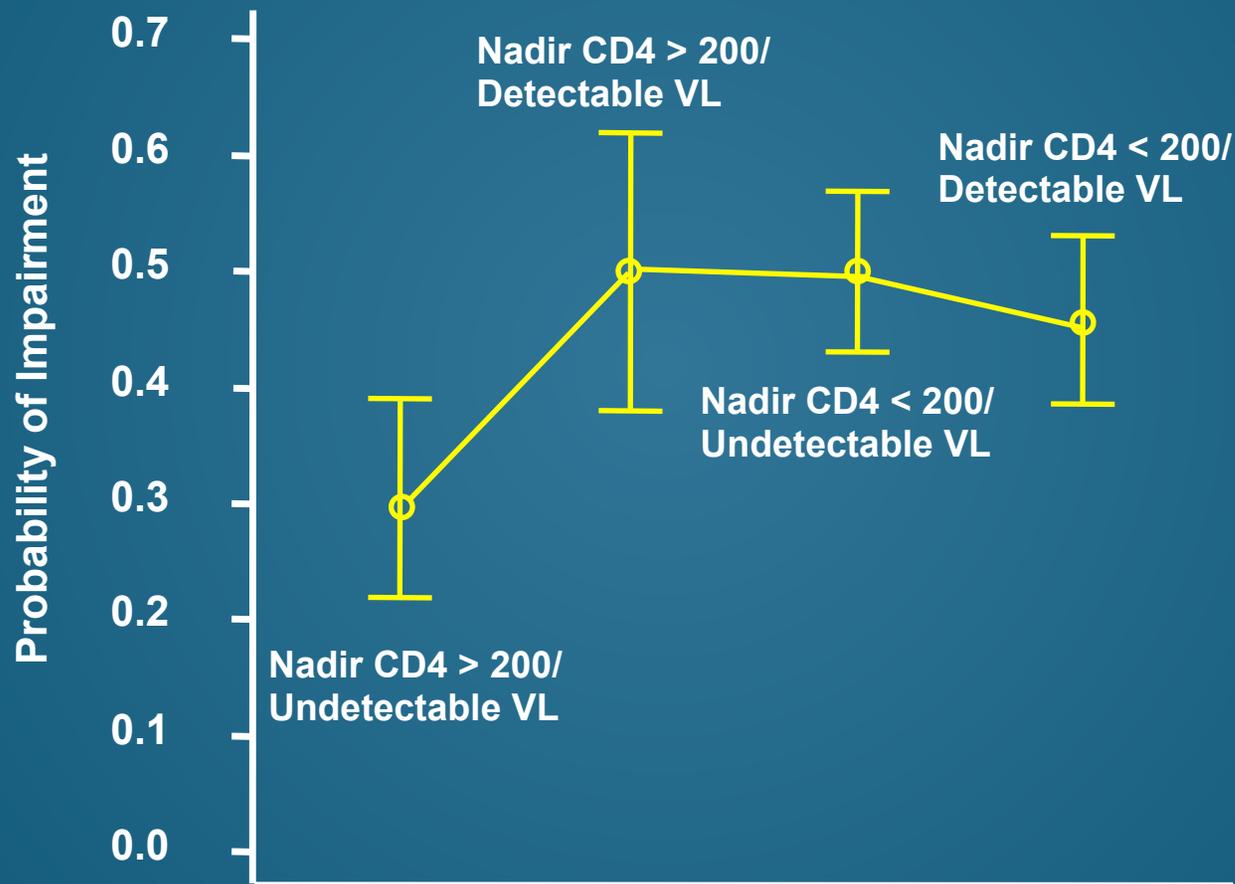
**5B:** Higher anti-toxo IgG levels were associated with worse GDS

*Bharti, et al., in prep*

# Have modern ARV regimens affected HAND?

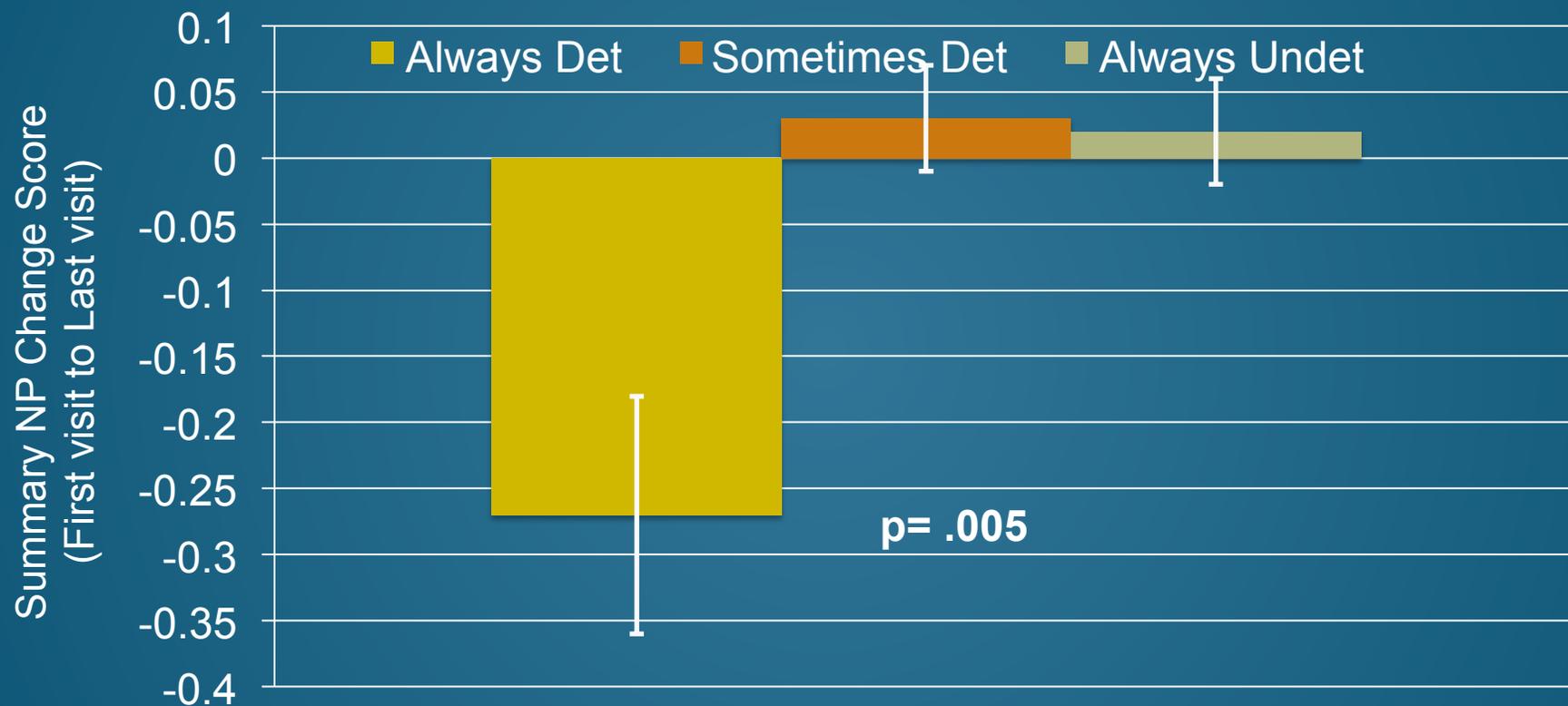
- Yes: CNS opportunistic disease markedly reduced, eg., toxo, PML etc
- Yes: severe dementia has dropped from estimated 15% pre combination ART to <5% now
- BUT: moderate and mild forms of neurocognitive impairment remain prevalent

# Early neurodamaging events? Reduced risk of HAND in those with absent history of severe immunosuppression and good virologic control



Heaton et al., *Neurology*; 2010; 75(23): 2087-96

# Over repeated evaluations during several years persons who remain chronically viremic are most likely to decline cognitively

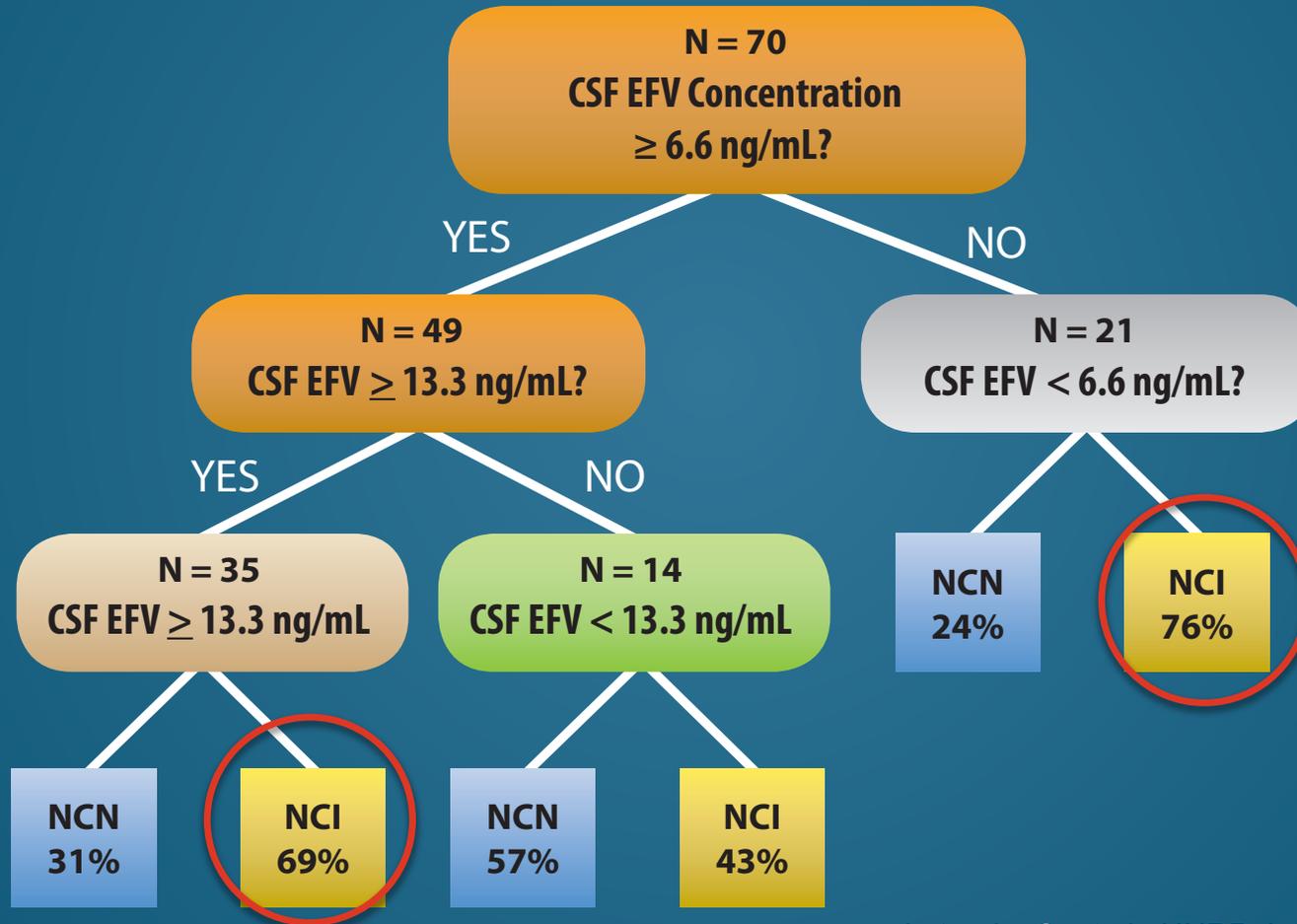


Always Detectable decline > Sometimes Detectable or Always Undetectable

Heaton et al., *CID*; 2015; 60(3): 473-480

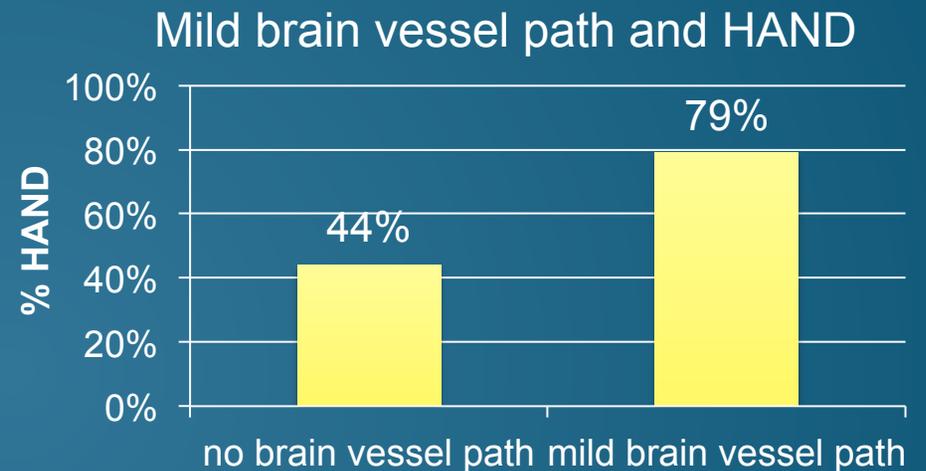
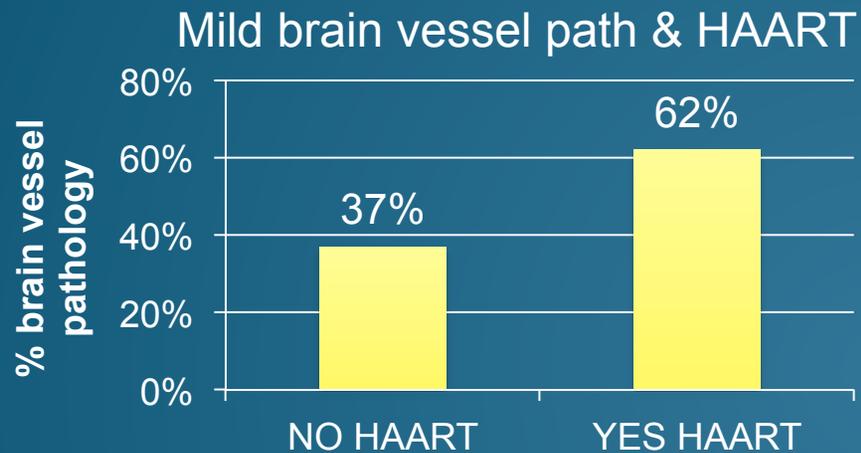
# Is there a “neurotherapeutic window”?

Both high and low CSF Efavirenz associated with higher % of patients showing neurocognitive impairment

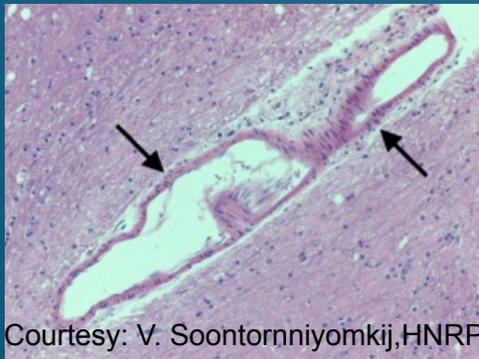


Letendre S, et al., HNRP data .

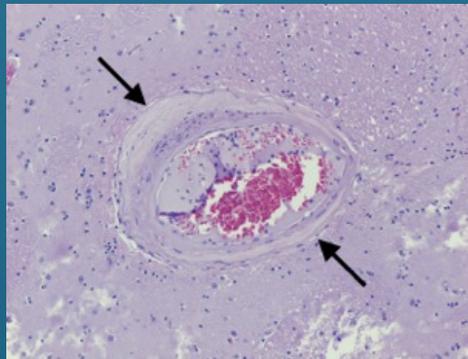
# Could ART be implicated in cerebrovascular pathology: another link to HAND?



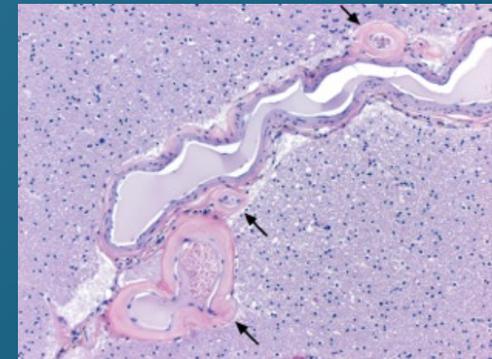
Brain vessel pathology: Absent



Brain vessel pathology: Mild



Brain vessel pathology: Mod.-Sev.



# Specific neuroprotective agents?

## Not yet

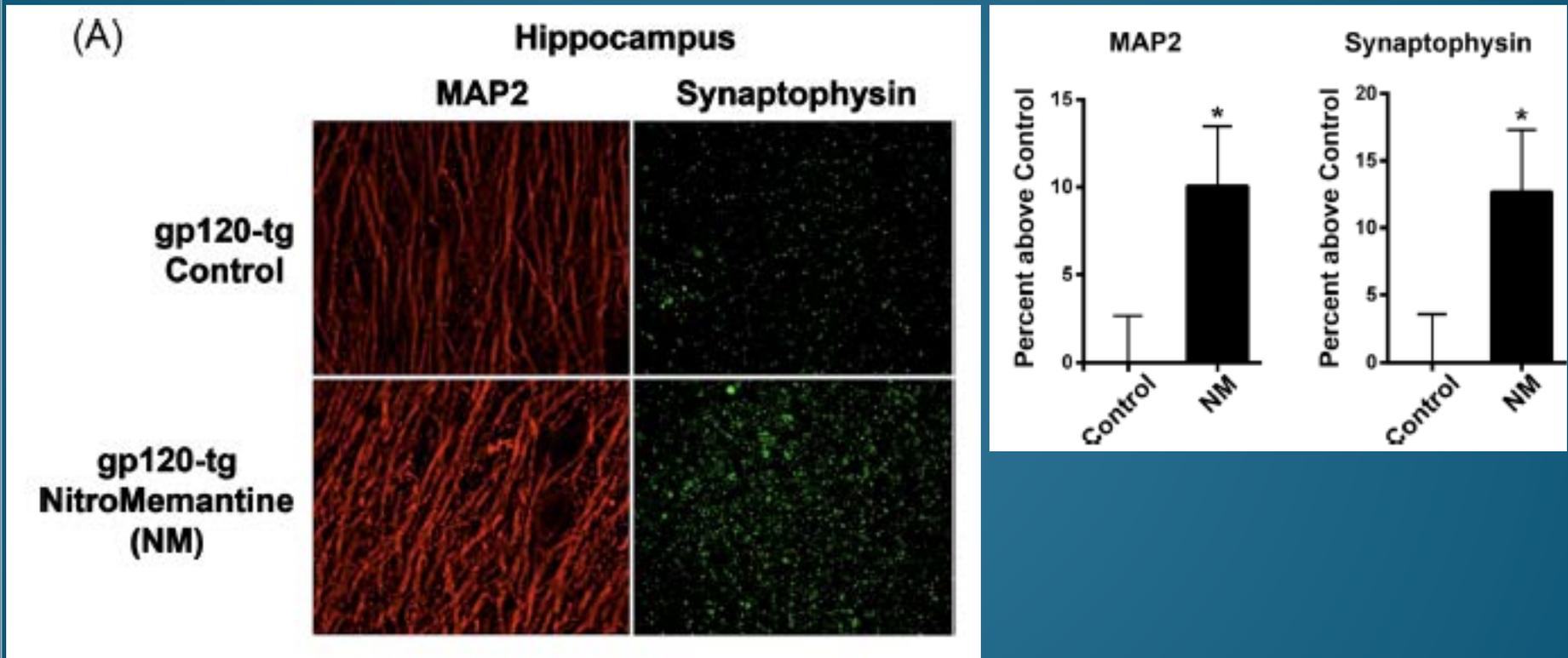
Trials of various antioxidants, anti inflammatory drugs, etc have been largely negative

Drug	Report	Finding
Selegeline	Dana <i>Neurology</i> 1998; Schifitto <i>Neurology</i> 2007	+/-
Thioctic Acid	Dana Consortium <i>Neurology</i> 1998	no effect
Peptide T	Heseltine <i>Arch Neurol</i> 1998	-/+
Lithium	Letendre <i>AIDS</i> 2006	+
Memantine	Schifitto <i>AIDS</i> 2007	no effect
Minocycline	Nakasujja <i>Neurology</i> 2013	no effect
Rivastigmine	Simioni <i>Neurology</i> 2013	no effect

Possible new directions aimed at correcting processes of glutamate hyperexcitability [eg., nitromemantine] or CDK5 inhibitors [eg., sunitimib] are in proof of principle stage

Behavioral techniques, eg., cognitive retraining, exercise based interventions, might have value

# Nitromemantine, which blocks extrasynaptic NMDA receptors, may promote synaptic integrity in study with gp120 transgenic mouse model of HIV



*Nakanishi (2015) J Mol Neurosci*

# Summary

- **HAND persists despite combination antiretroviral therapy (CART)**
- **Even milder HAND produces behavioral and functional impairments that are significant to the individual and society, thus of public health importance**
- **Synaptodendritic injury is one of the substrates of HAND.**
- **Causes of neuronal injury are likely multiple, including viral products, inflammatory molecules, disruption in trophic factors, disturbed protein management, brain small vessel pathology; these processes, incl. expression of viral products may persist despite apparent control of viral replication**
- **Comorbidities (eg. drug abuse) may increase risk of HAND, and its progression**

## Summary (cont.)

- HAND amplified by age related neurologic, vascular and metabolic changes. Comorbidities may further accelerate age related neurocognitive declines
- Neurocognitive health best preserved in those who never have CD4 nadirs <200 and are currently virologically suppressed (implication: treat HIV as soon as possible)
- While continuous virologic suppression is associated with least likelihood of neurocognitive decline over time, ART neurotoxicity or vascular toxicity need to be considered
- No currently accepted neurotherapeutics; need new concepts, and possibly novel delivery systems to brain
- Non pharmacologic (eg., cognitive rehabilitation) strategies may have promise

# Acknowledgements

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- Ned Sacktor
- Ann Collier
- Allen McCutchan
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- ...Neurological Disorders and Stroke
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# Go Russia R21 Team!

(sponsored by NIDA via Office on AIDS Research)



# NeuroAIDS in the modern treatment era

## Thank you!

Igor Grant, MD,  
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Director

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University of California, San Diego