NeuroAIDS in the modern treatment era

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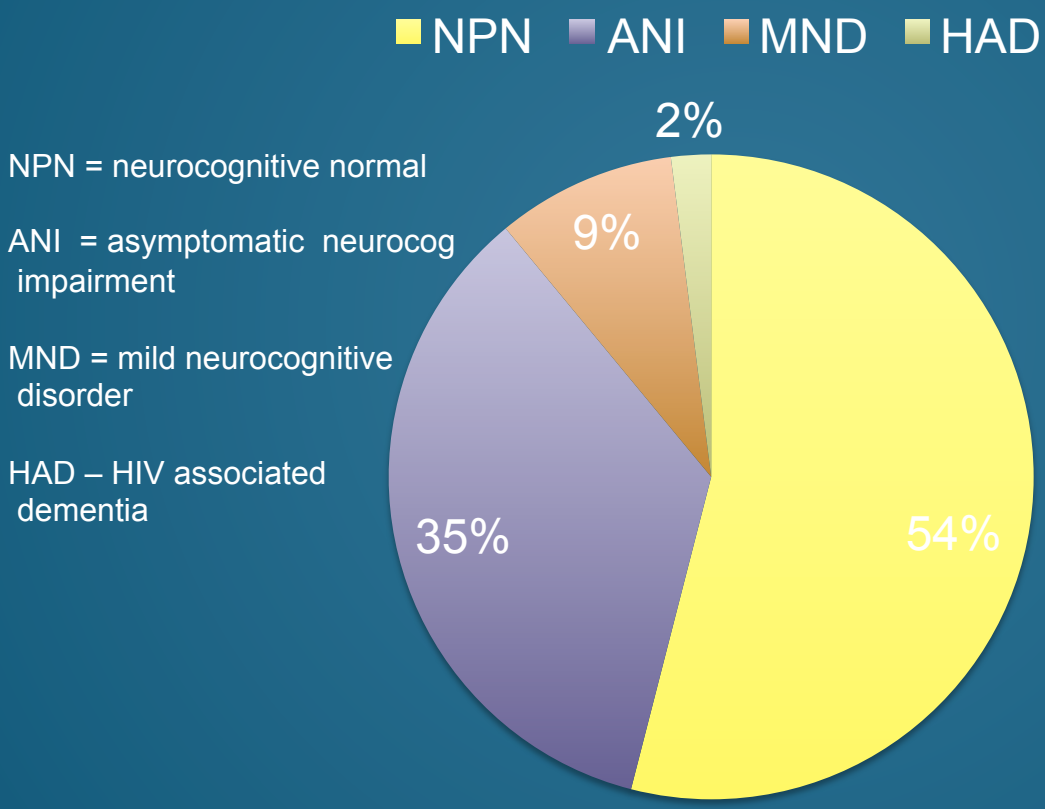
NIH – RFBR Collaborative Research Partnership
St Petersburg, Russian Federation, 14 April 2016

HIV brain disease in the modern treatment era

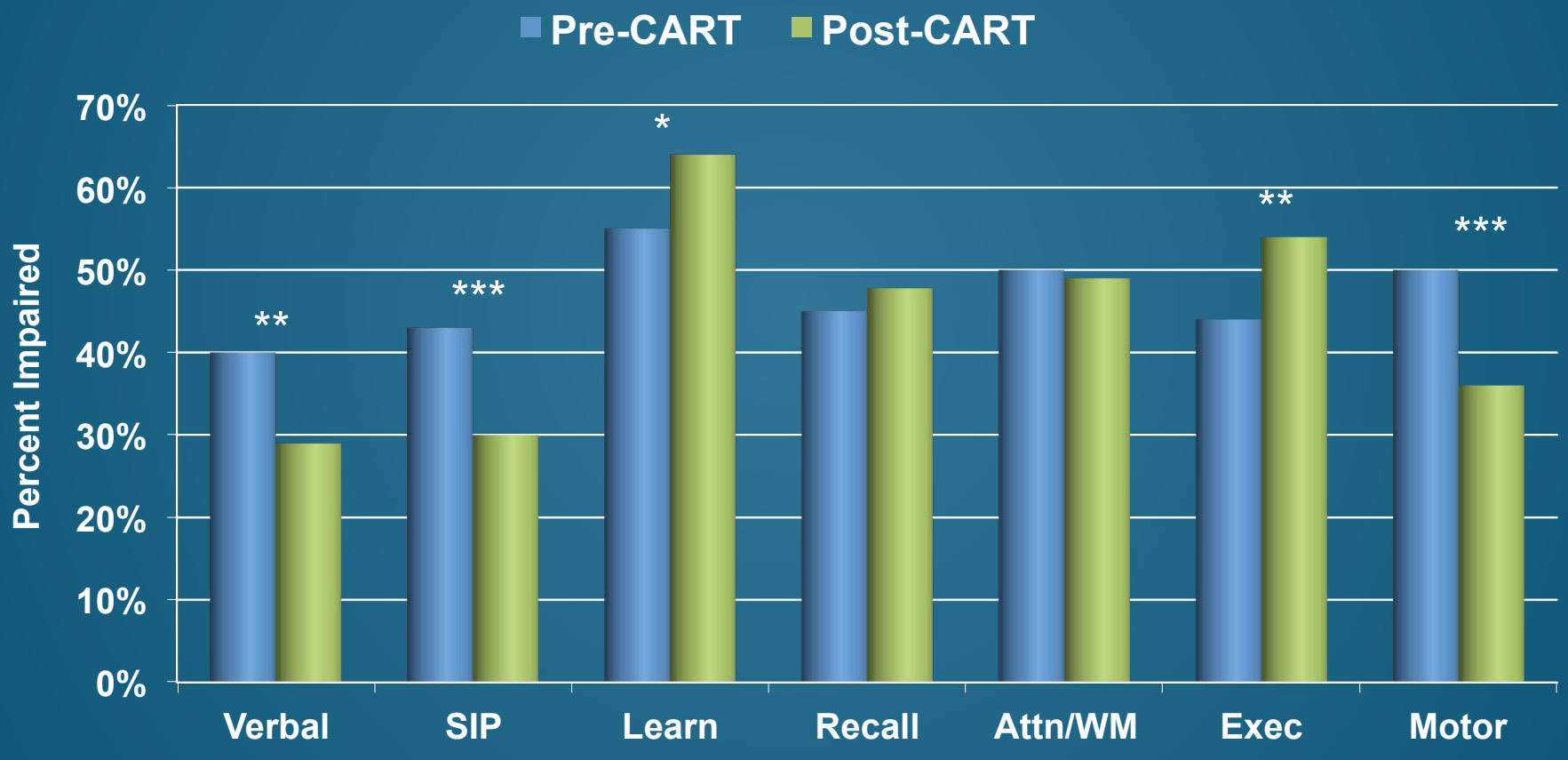
- Although modern ARV treatment has markedly reduced brain disease from opportunistic infections, HIV associated neurocognitive disorders (HAND) remain prevalent, affecting about 40% of HIV+
- HAND still occurs in successfully treated [plasma HIV undetectable] individuals
- As HIV+ people survive longer, 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

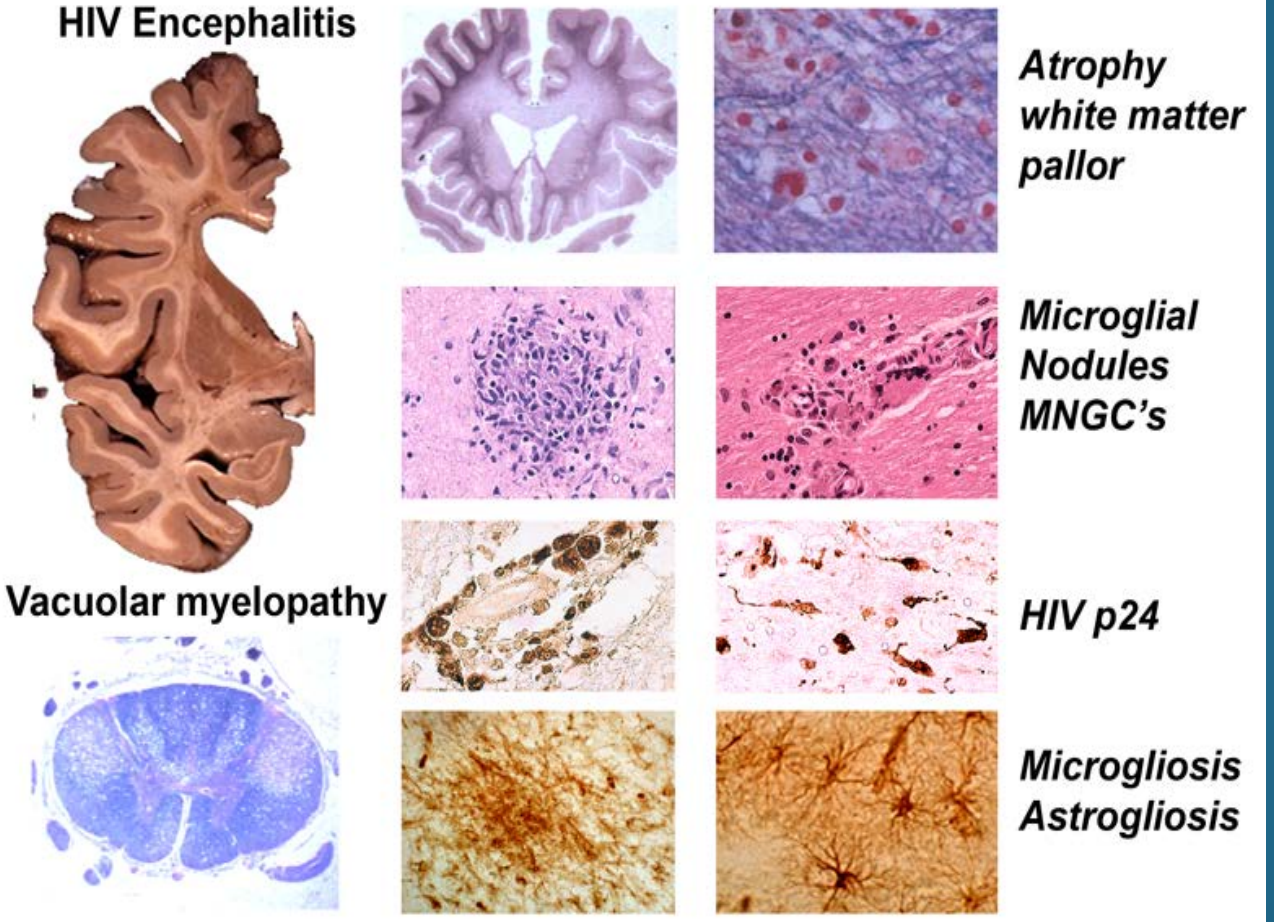


SIP=speed of information processing

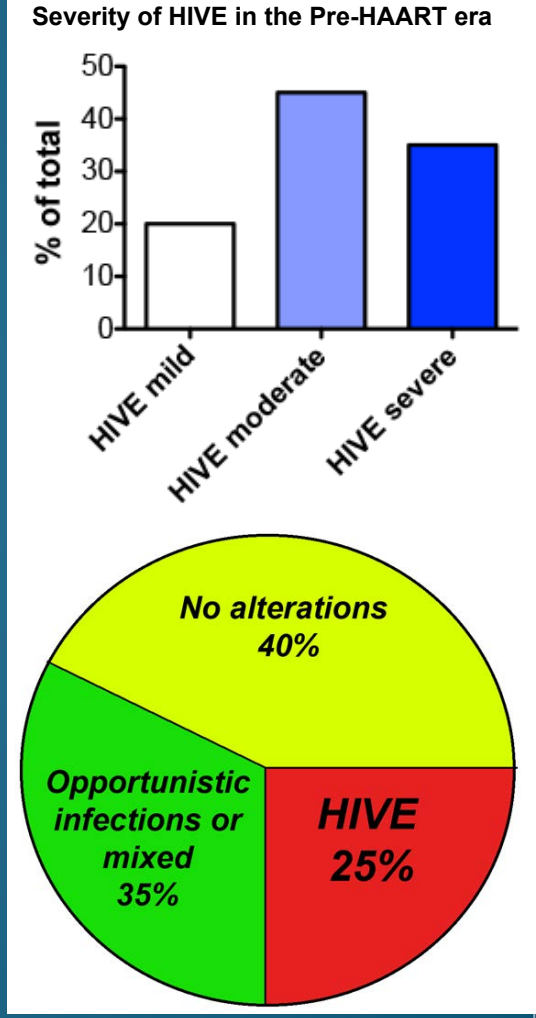
* p<.05; ** p<.01; ***p<.001

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

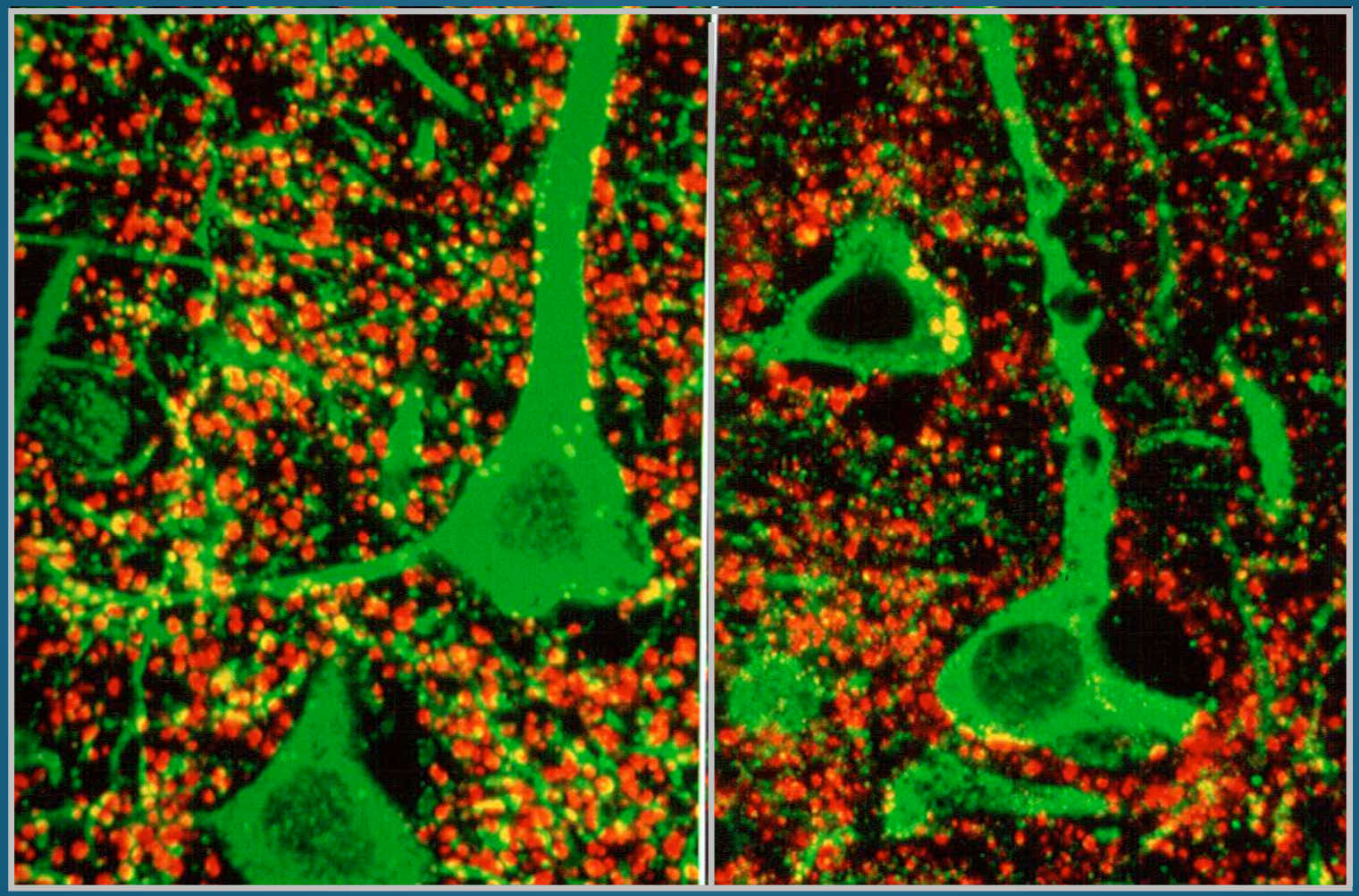
Neuropathology of HIV in the pre-HAART era



Courtesy Eliezer Masliah, UCSD HNRP



Loss of synapses and dendrites in HIV+

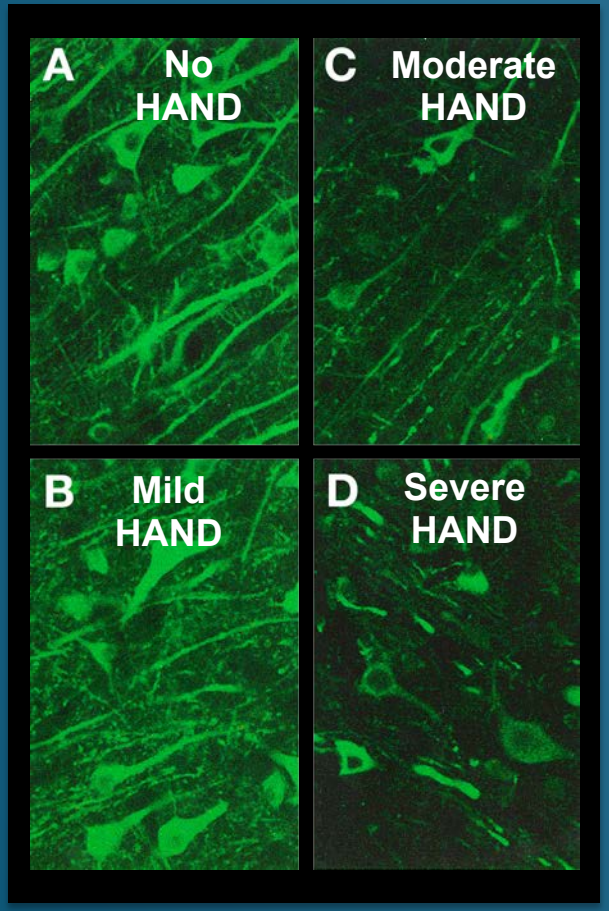


HIV-

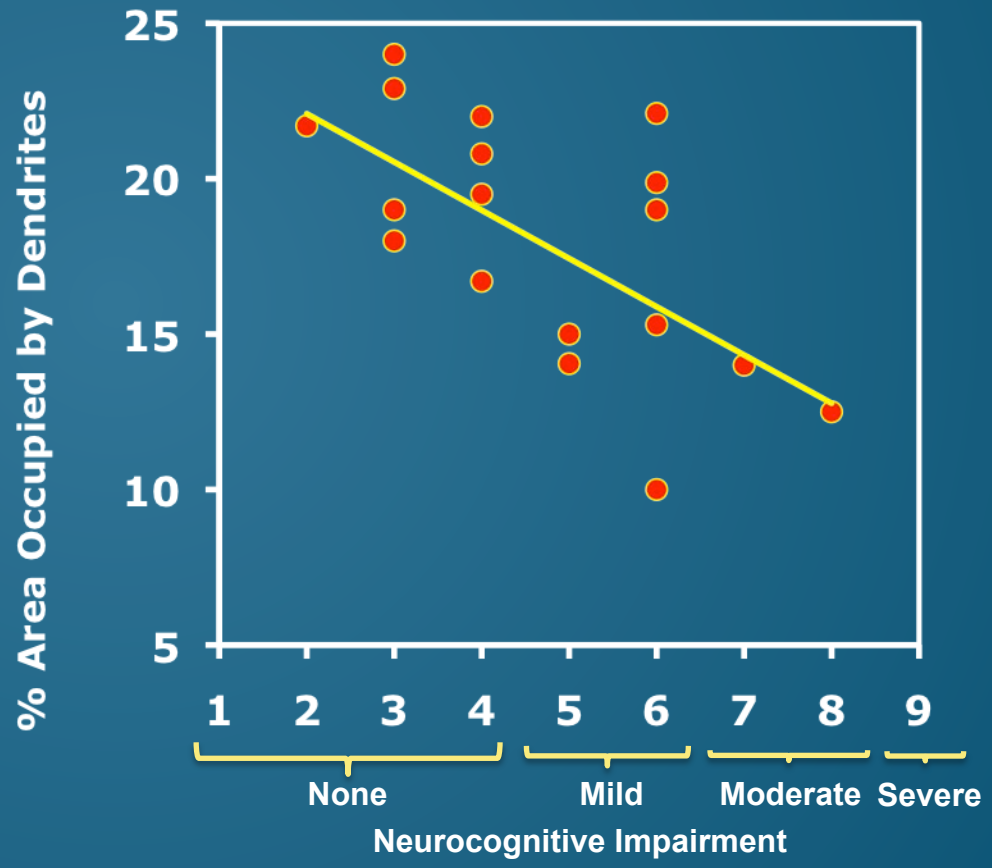
HIV+

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

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

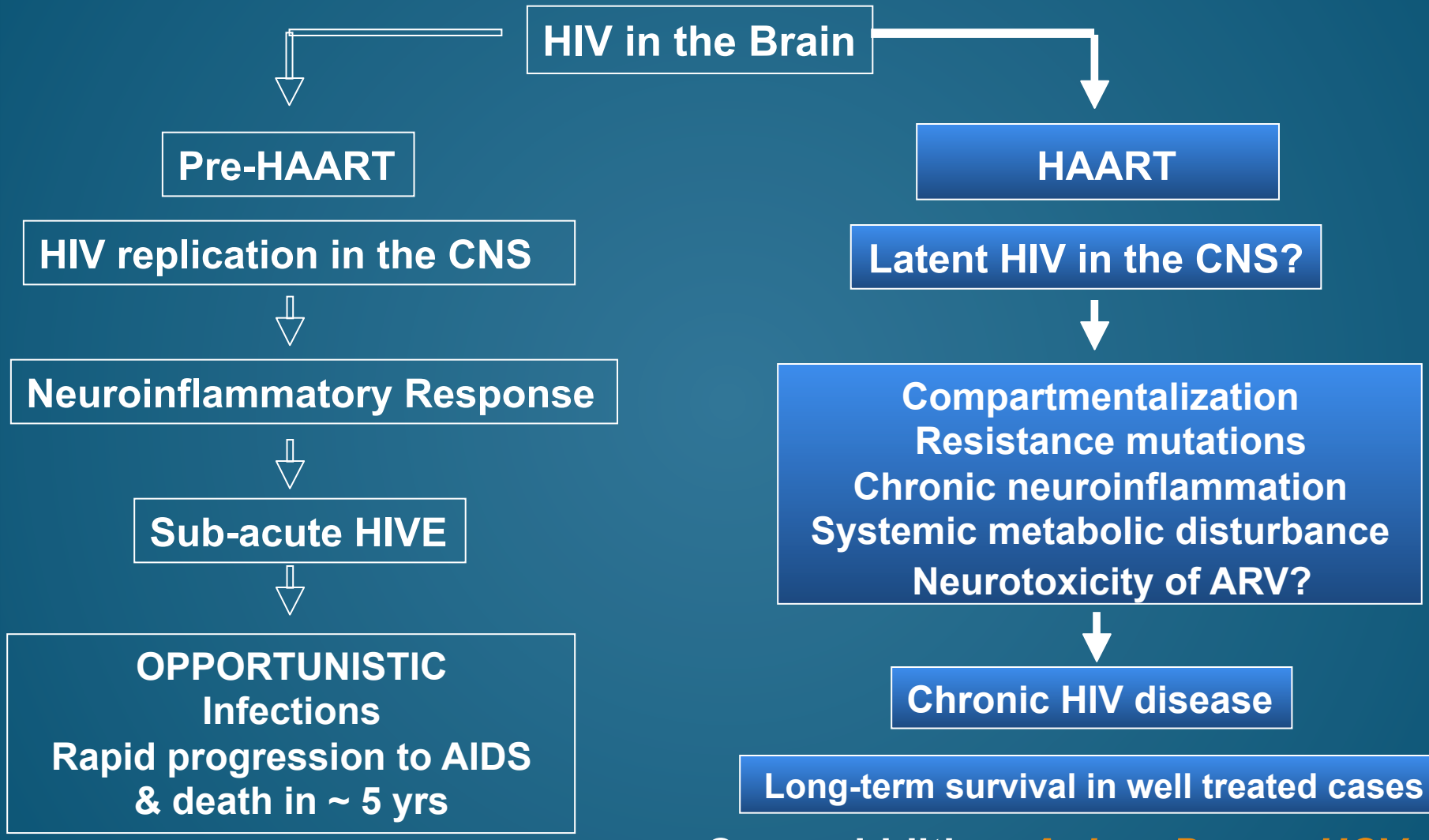


Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss



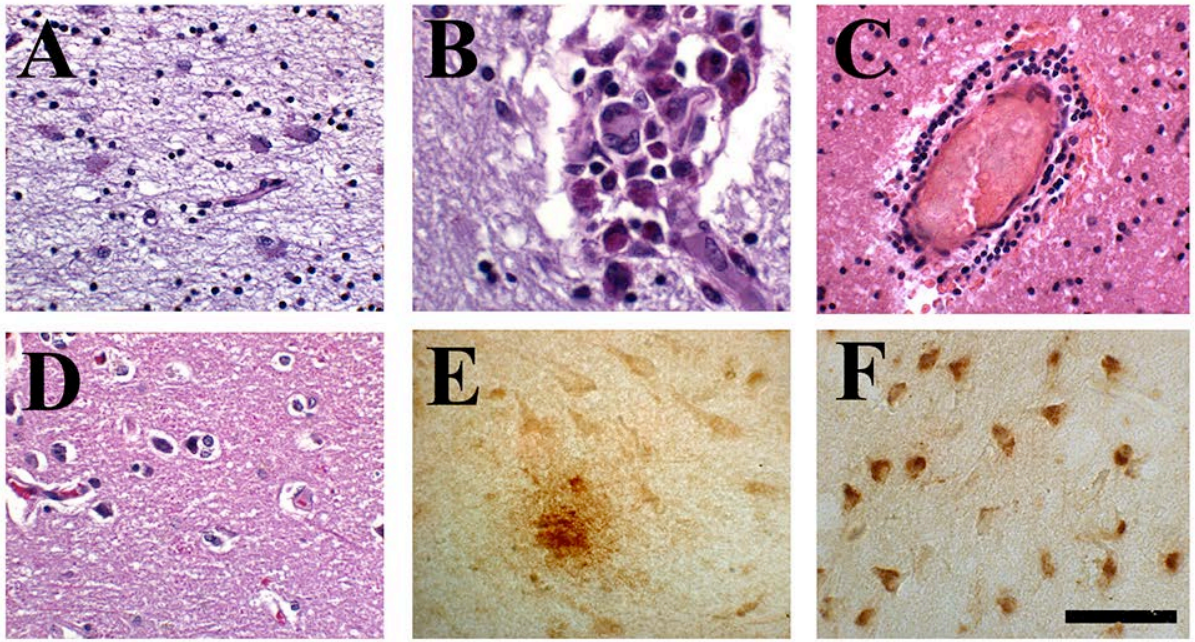
Masliah, et al. Ann Neurol.1997, 42(6): 963-72

HIV: from subacute to chronic disease



Courtesy Eliezer Masliah, HNRP UCSD

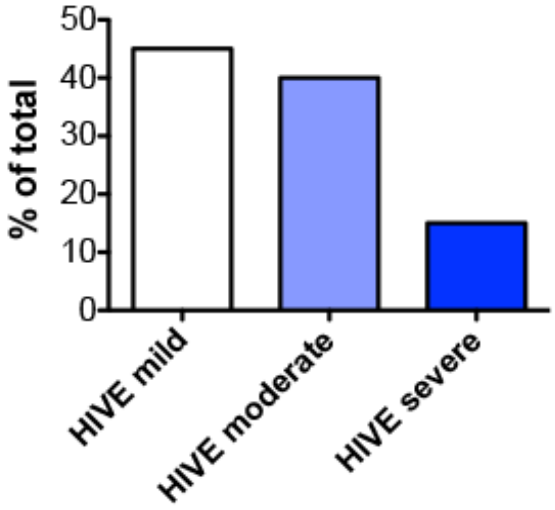
Neuropathology of HIV in the HAART era

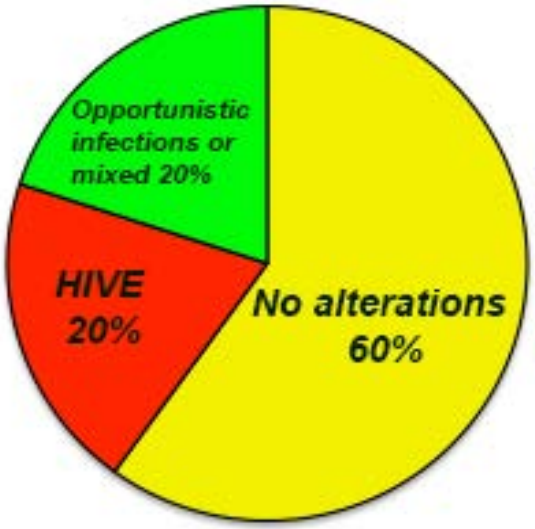


(A) Severe white matter injury with astrogliosis (LFB). (B) Vascular infiltration in the white matter by macrophages (PAS). (C) Lymphocytic perivascular infiltration (H&E). (D) 'Burnt-out' form with neuronal atrophy (H&E). (E) Plaque-like lesions (anti-Aβ, 4G8). (F) Intra-neuronal Aβ (anti-Aβ, 4G8).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

Courtesy Eliezer Masliah, HNRP UCSD

Severity of HIVE in the HAART era



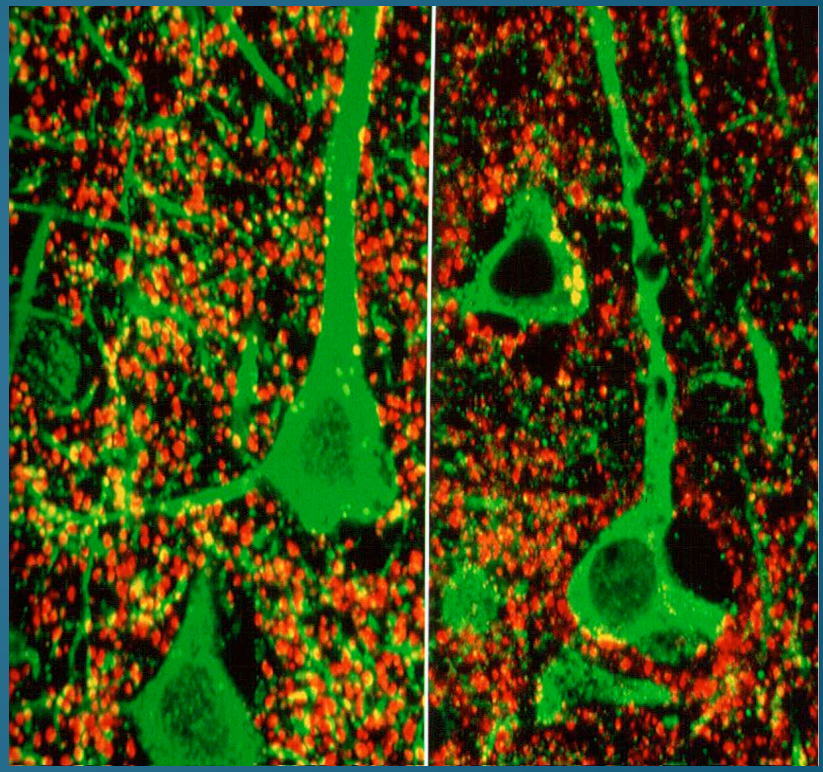


What factors are associated with HAND?

- 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

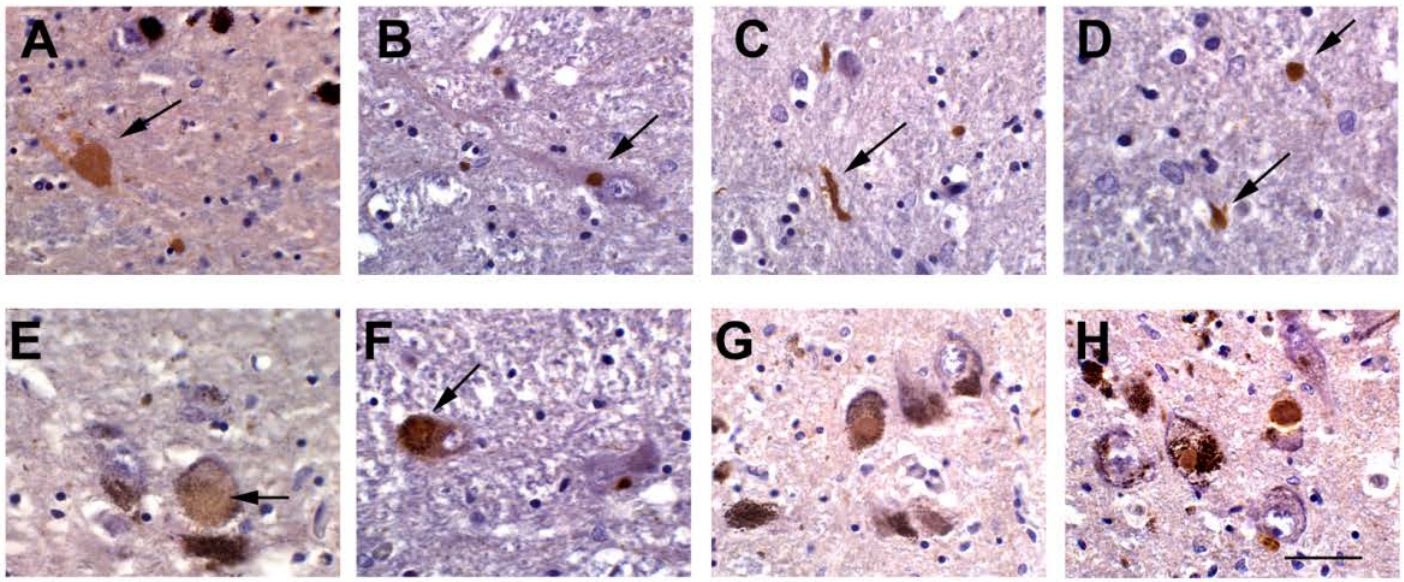
- activate apoptotic pathways
- dysregulate calcium homeostasis
- promote oxidative stress
- alter cell cycle signaling pathways such as CDK5, leading to protein phosphorylation and misfolding
- interfere with clearance pathways such as autophagy, leading to abnormal protein aggregation



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

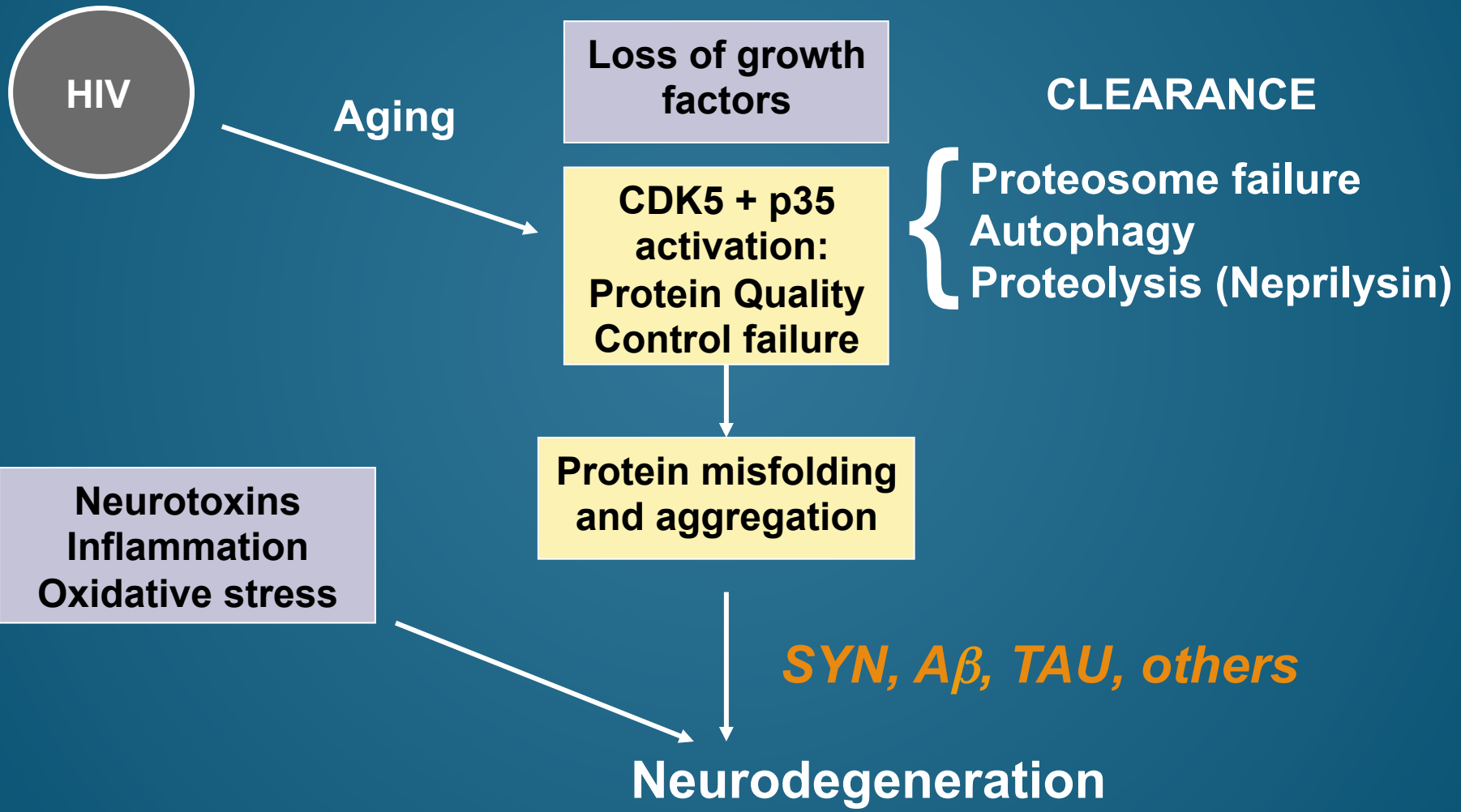
Increased neuritic alpha synuclein expression in brains of 55-65 year olds; accelerated age related "protein mismanagement" in brains of HIV+?

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

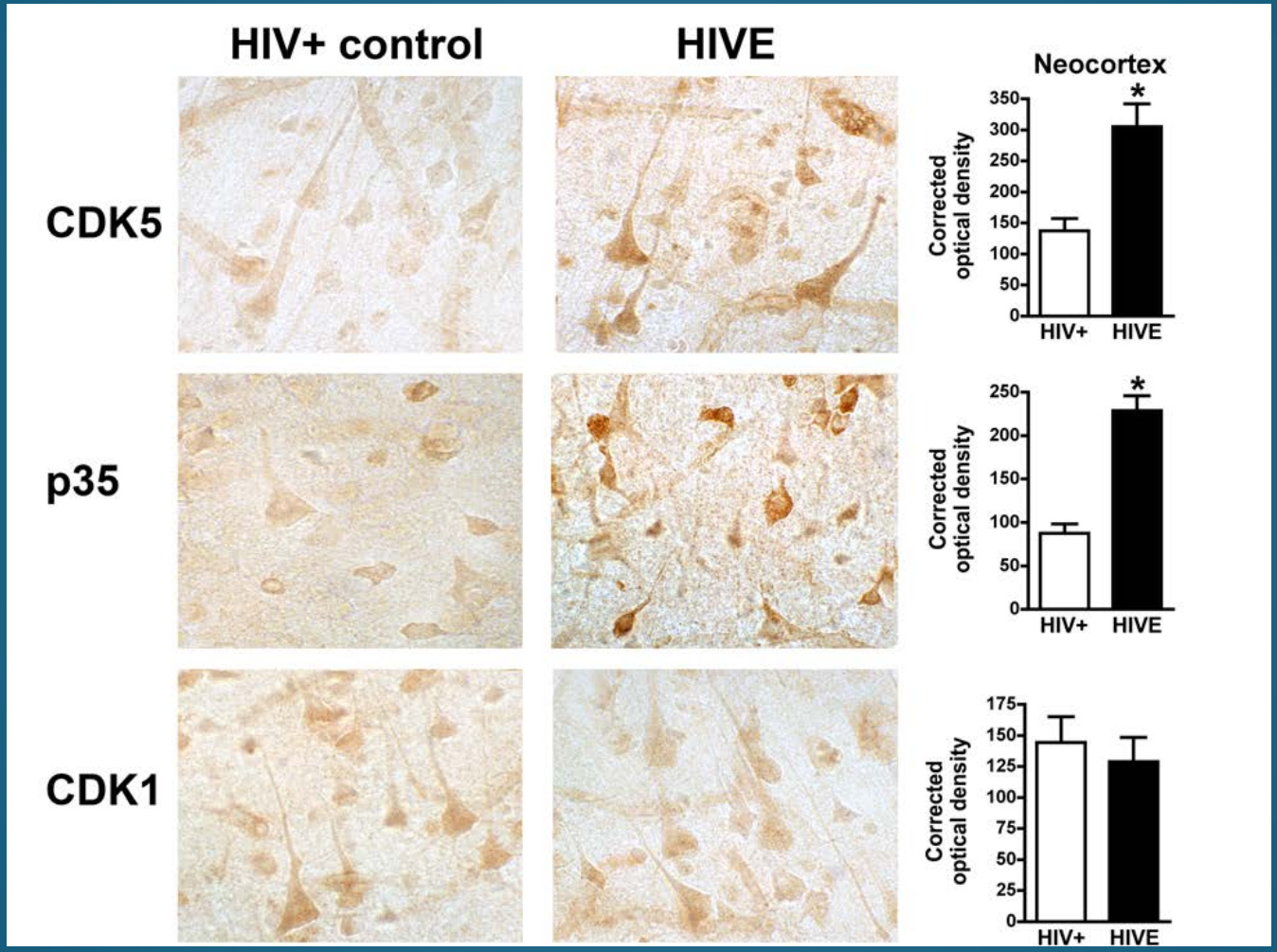


Khanlou et al., J Neurovirol; 2009;15(2):131-138

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



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



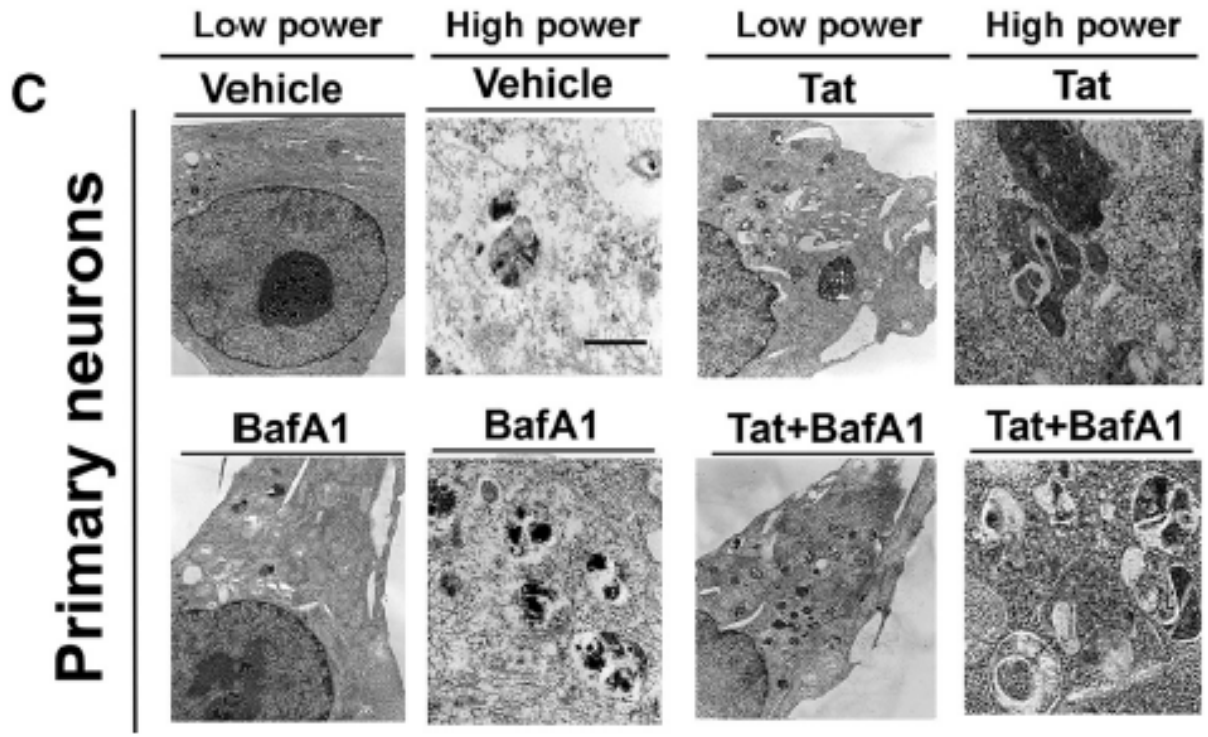
Patrick et al Am J Pathol; Crews et al CDD 2012, 2013

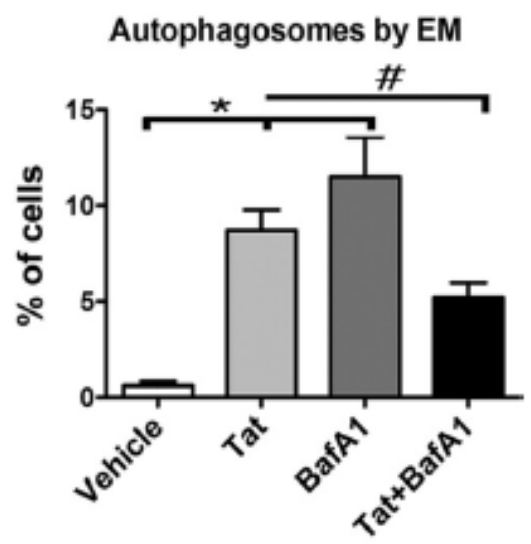
Productive and latent forms of HIV in the brain can release viral proteins that

- 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

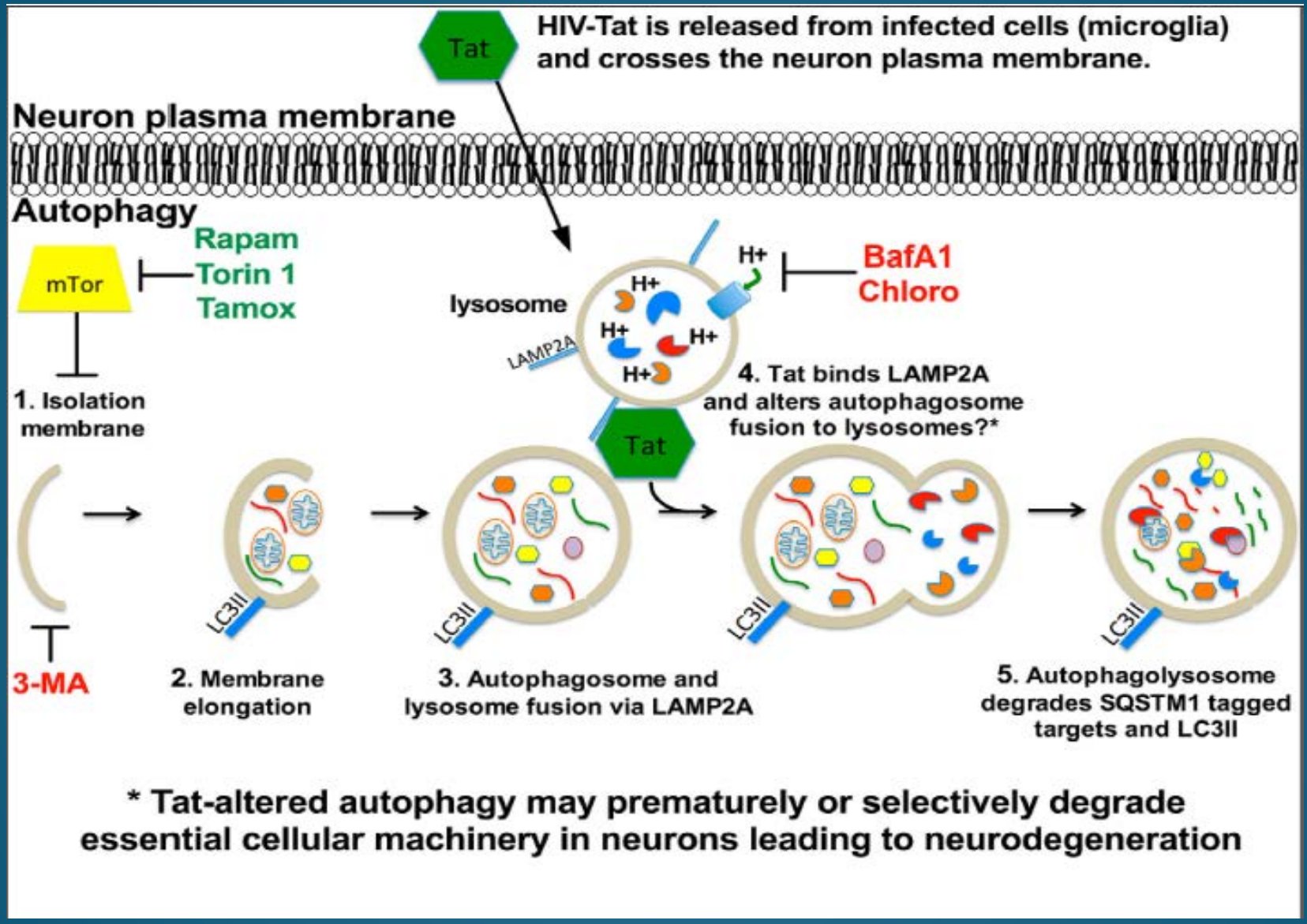
Thereby contributing to synaptodendritic injury

Abnormal accumulation of autophagosomes in Tat treated mouse neuronal cells





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



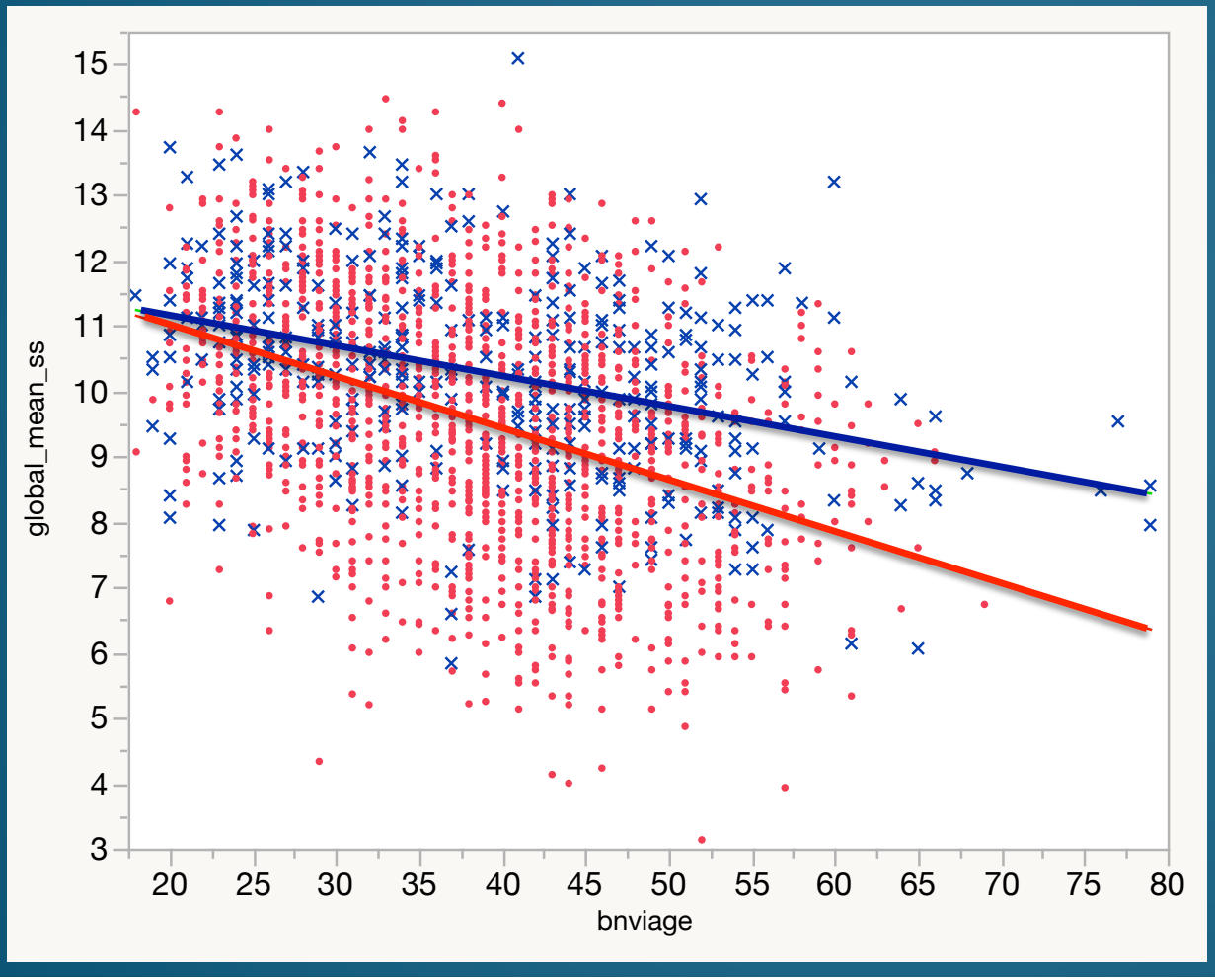
How Tat may interfere with neuronal autophagy. *From Fields (2015) J Neurosci, 35(5):1921-38*

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

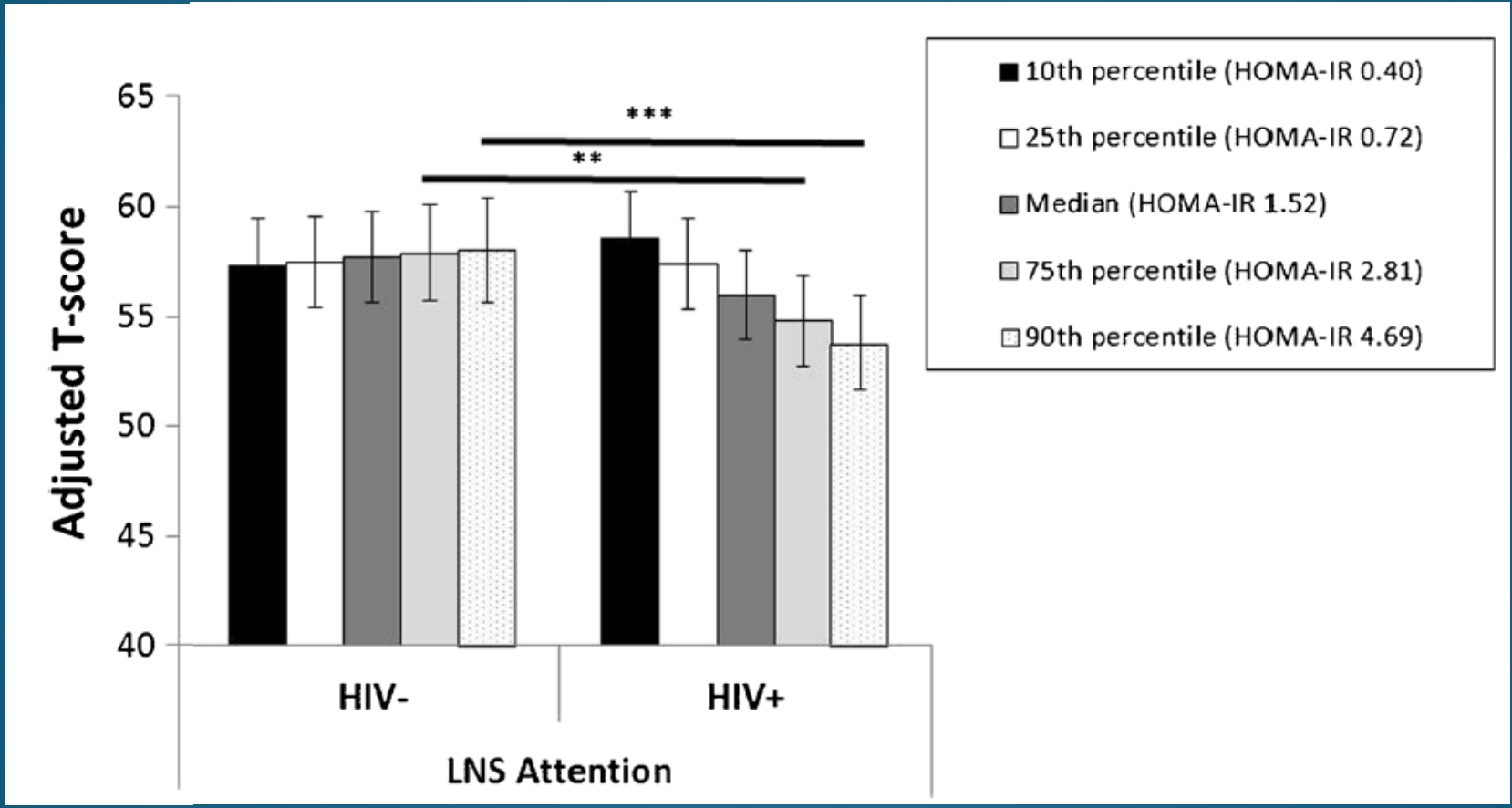


HIV-

HIV+

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-



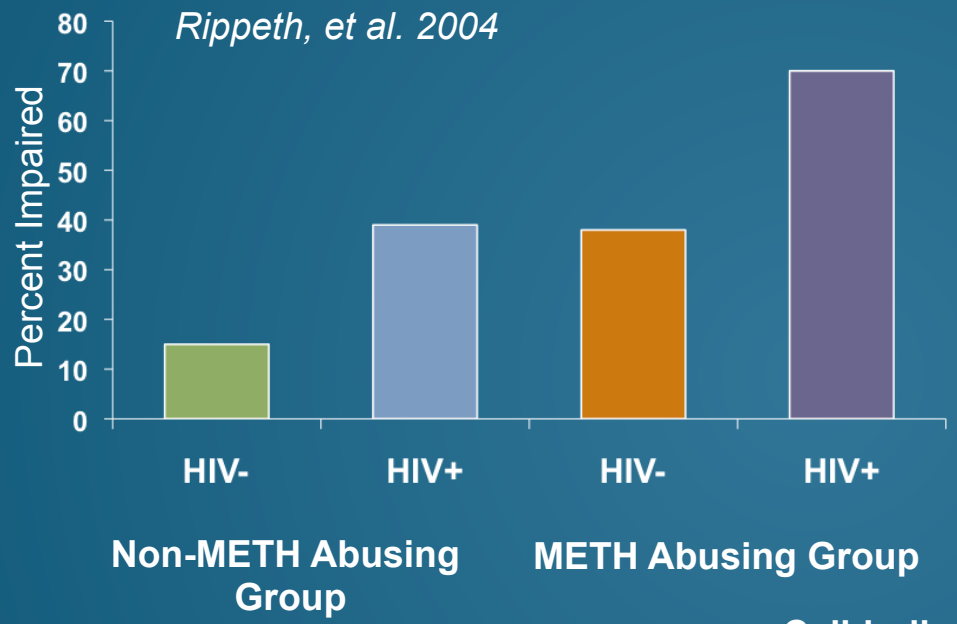
The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function

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

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

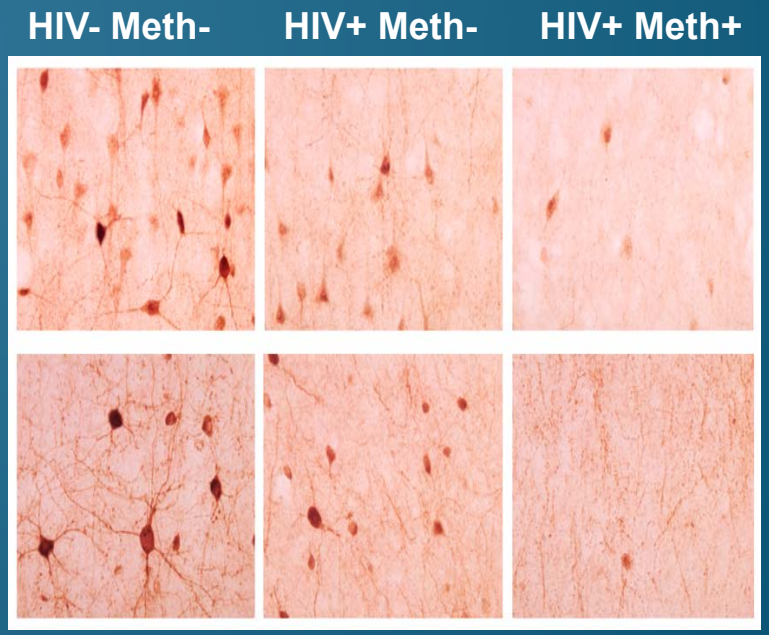
Drug	Evidence for Brain damage? Neurocognitive Impairment (NCI)?	HIV X drug?
Alcohol	Well documented in long term alcoholics	maybe
Methamphetamine	Well documented in extensive users	yes
Cocaine	Data are mixed. Animal and imaging data on potential damage not consistently supported by neurocognitive reports	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



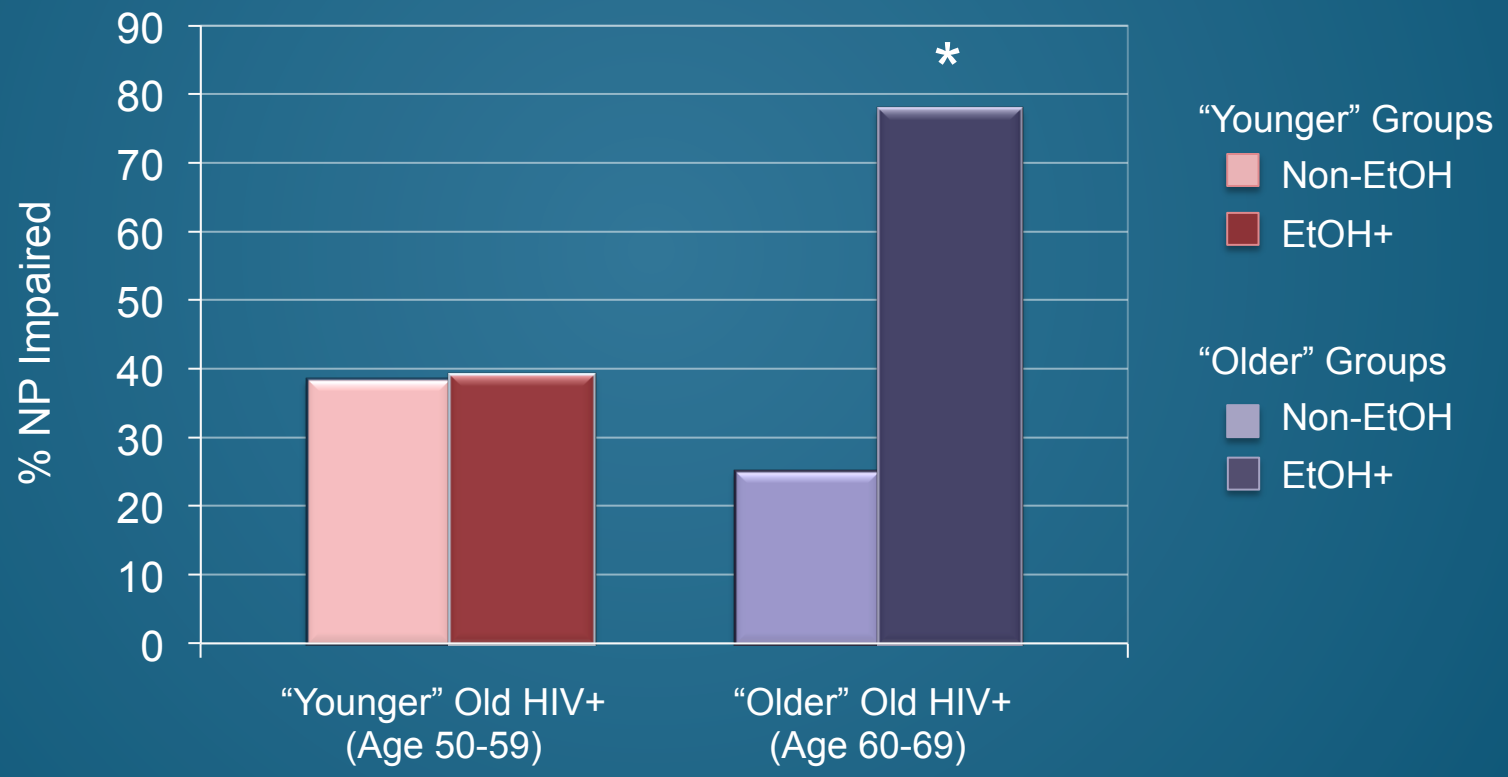
- Increased rates of neurocognitive impairment in HIV+ METH+

- Marked reduction in interneurons in HIVE+ METH+



Chana et al (2006)

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

*$p < 0.01$

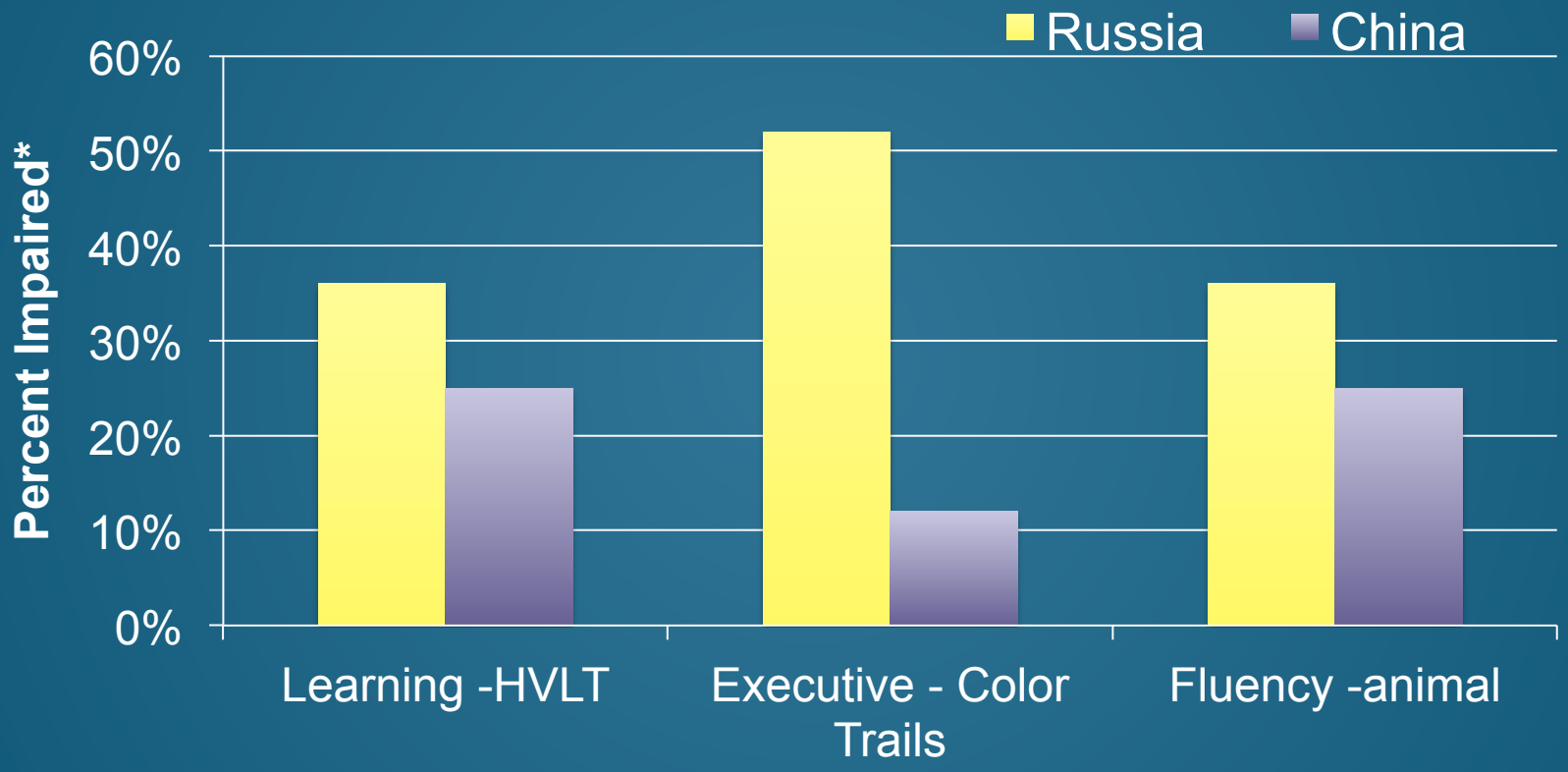
Opioid using HIV+ in Russia and China

	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_{10})	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?



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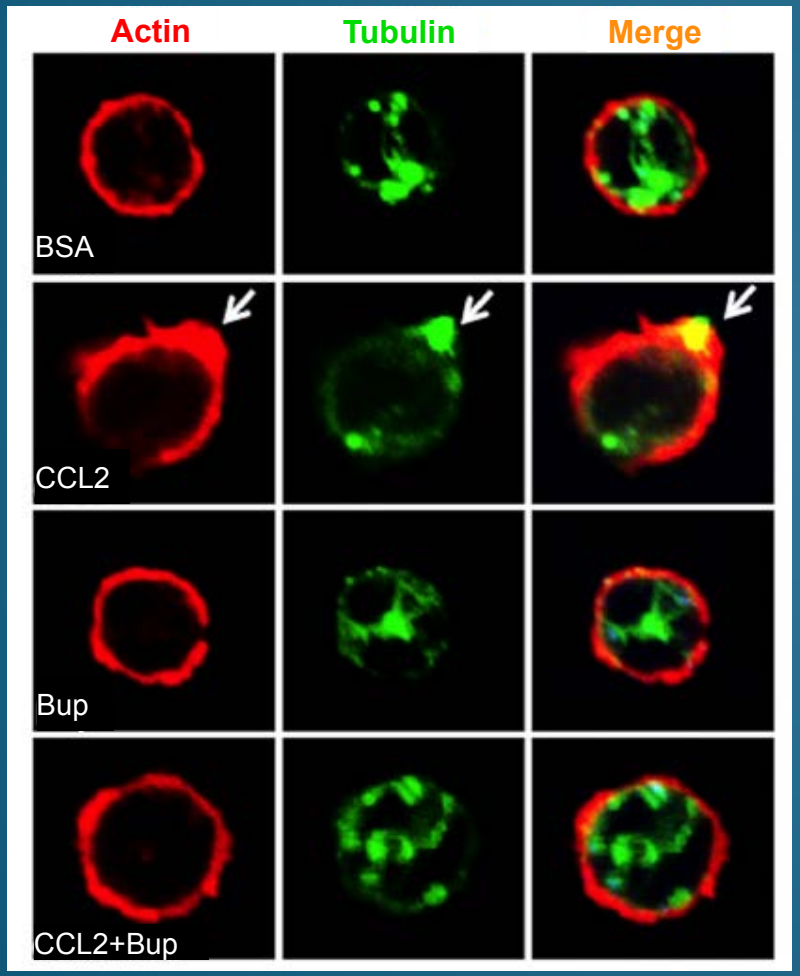
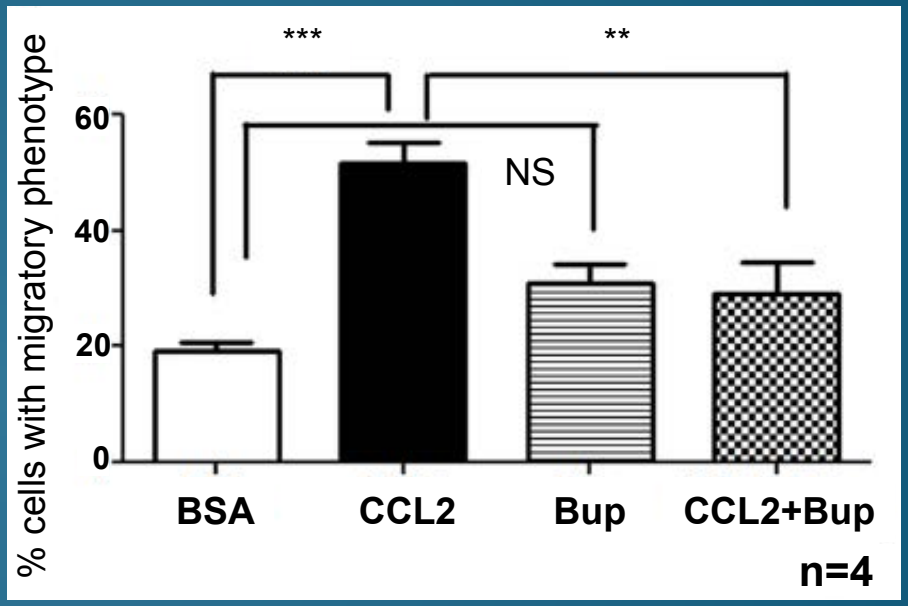
*Uses US normative corrections

Opioid partial/full agonists may inhibit chemokine CCL2-MCP1 induced monocyte migration

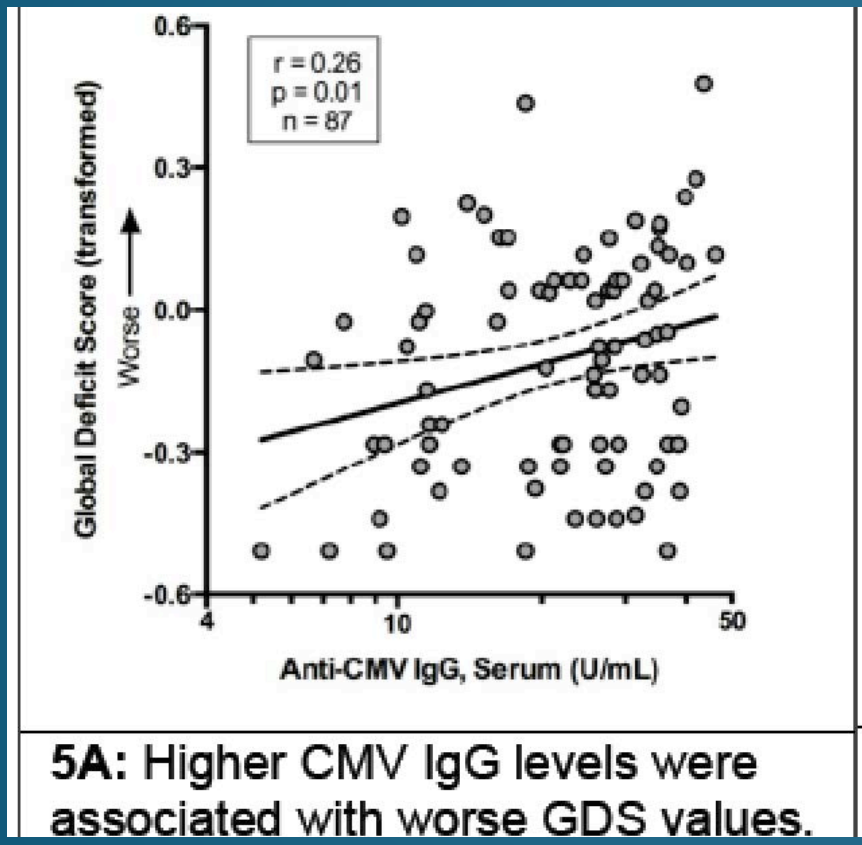
possible neuroprotective effect in HIV infection?



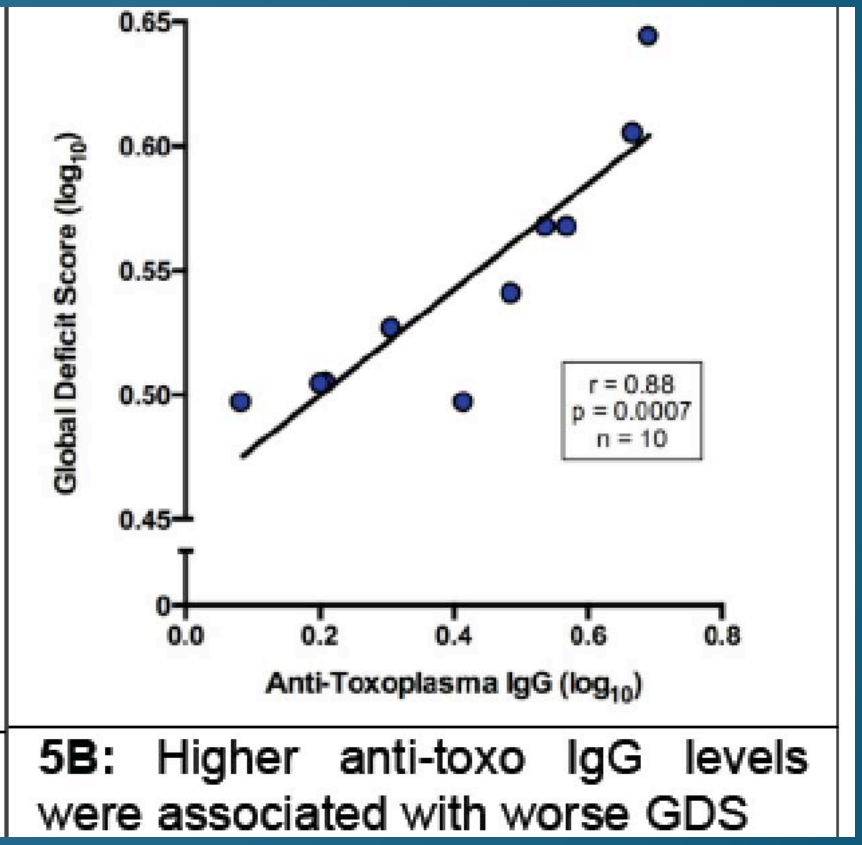


Cavallo et al., J Immunol; 2015; 194(7): 3246-3258

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



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



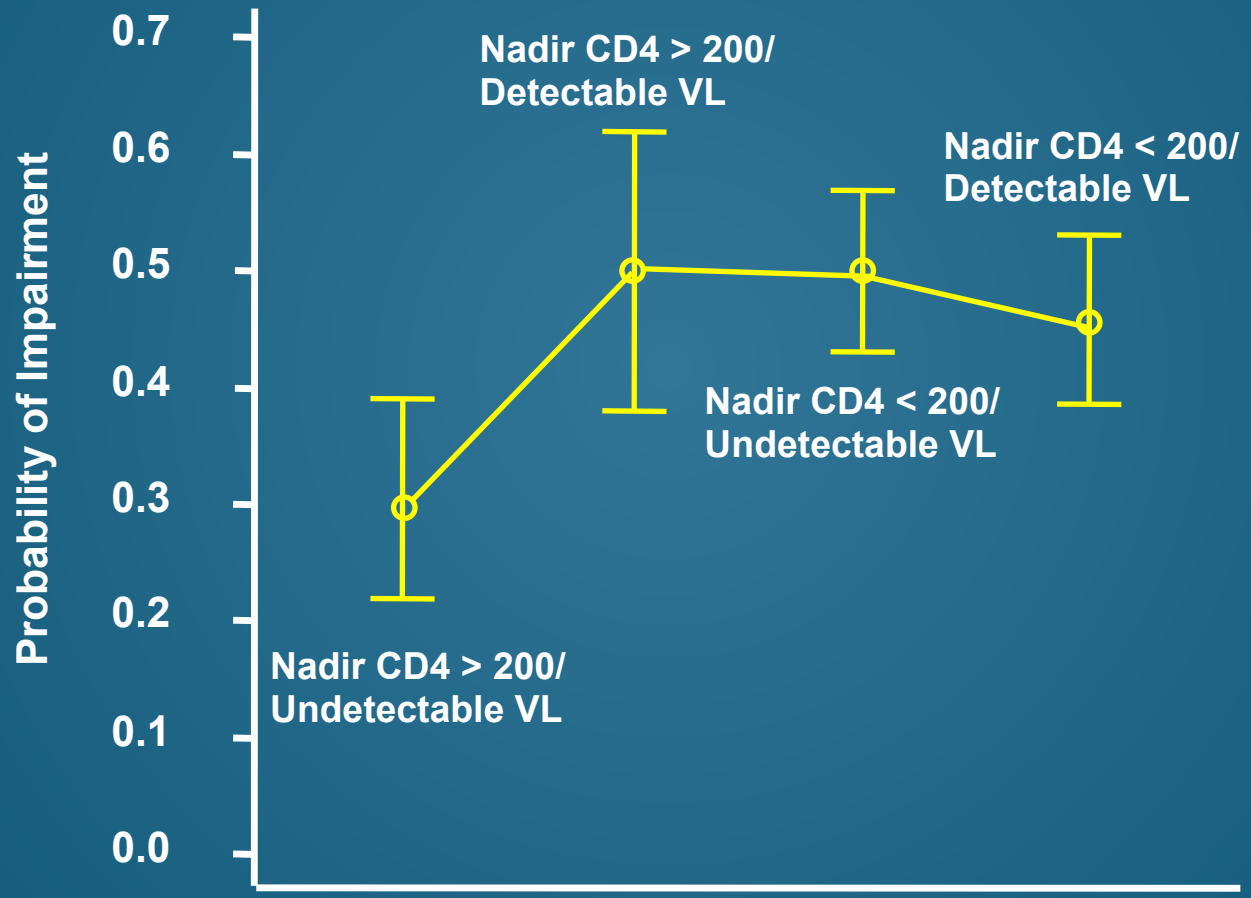
5B: Higher anti-toxo IgG levels were associated with worse GDS

Bharti, et al., in prep

Have modern ARV regimens affected HAND?

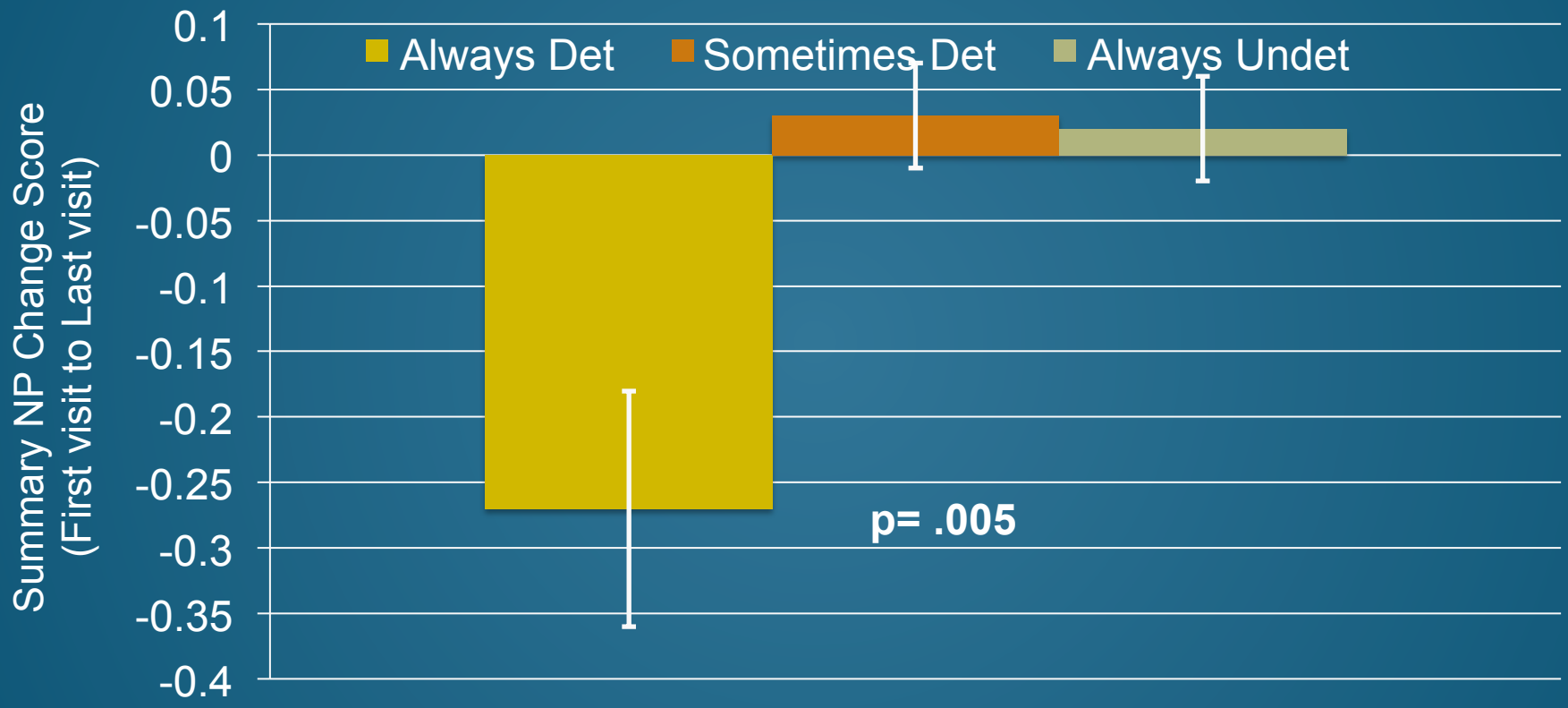
- Yes: CNS opportunistic disease markedly reduced, eg., toxo, PML etc
- Yes: severe dementia has dropped from estimated 15% pre combination ART to <5% now
- BUT: moderate and mild forms of neurocognitive impairment remain prevalent

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

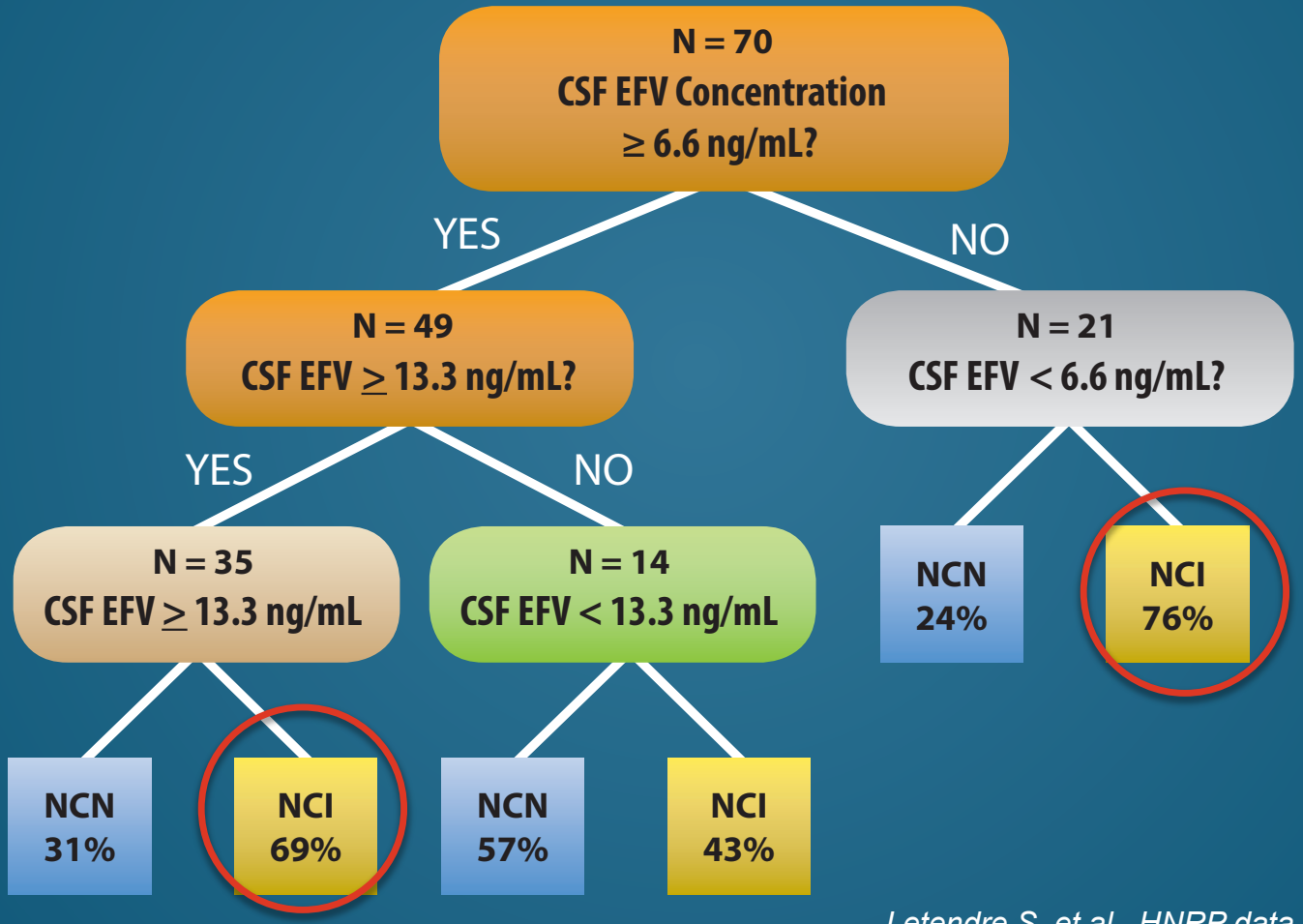
Over repeated evaluations during several years persons who remain chronically viremic are most likely to decline cognitively



Always Detectable decline > Sometimes Detectable or Always Undetectable

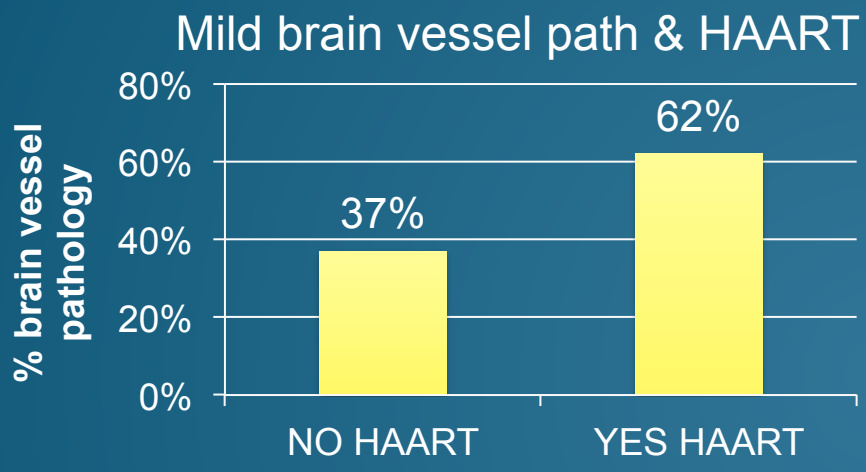
Heaton et al., CID; 2015; 60(3): 473-480

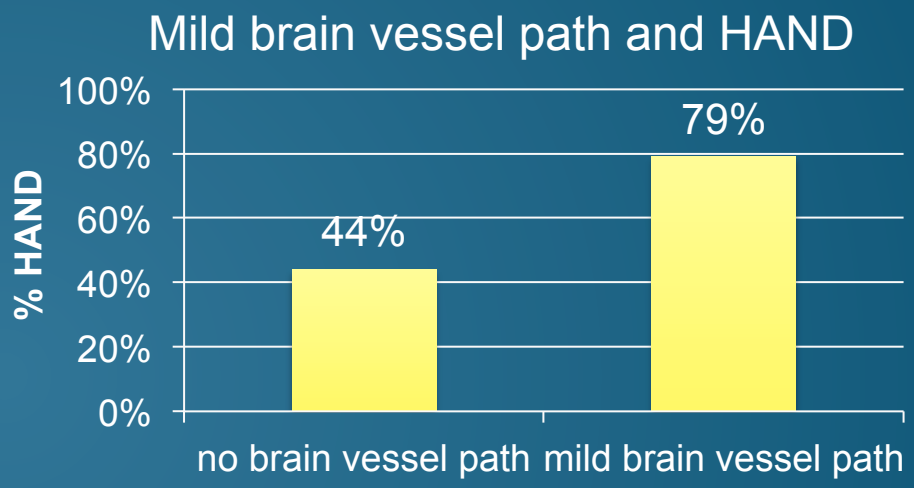
Is there a "neurotherapeutic window"? Both high and low CSF Efavirenz associated with higher % of patients showing neurocognitive impairment



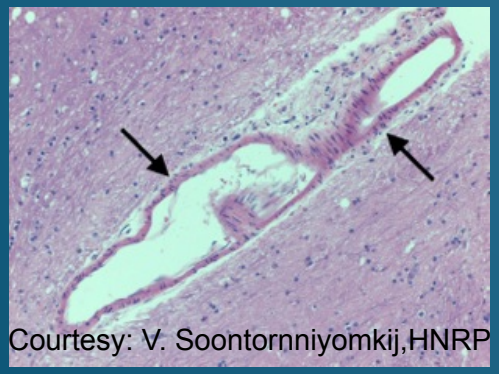
Letendre S, et al., HNRP data .

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



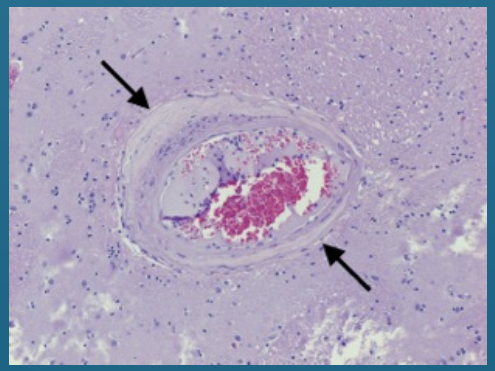


Brain vessel pathology: Absent

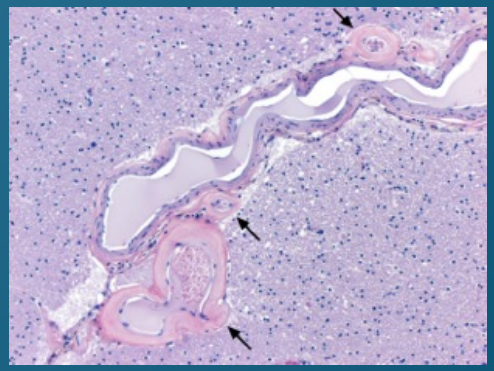


Courtesy: V. Soontornniyomkij,HNRP

Brain vessel pathology: Mild



Brain vessel pathology: Mod.-Sev.



Specific neuroprotective agents? Not yet

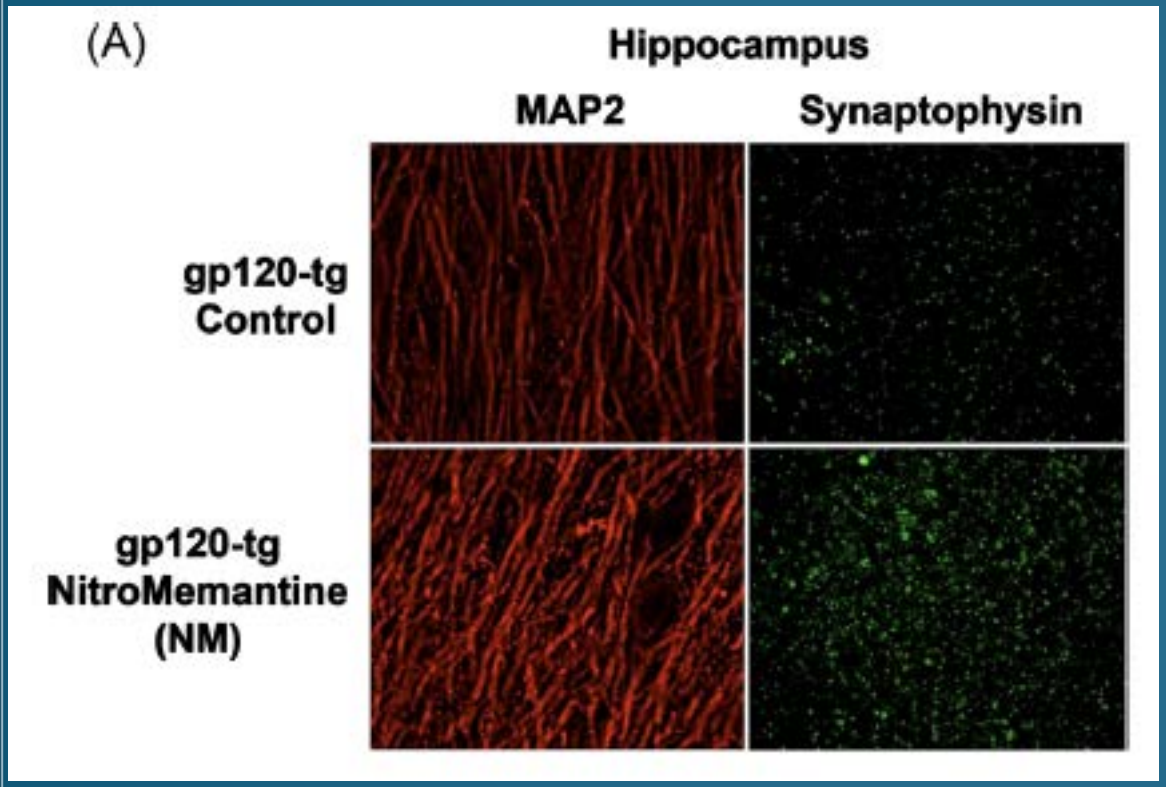
Trials of various antioxidants, anti inflammatory drugs, etc have been largely negative

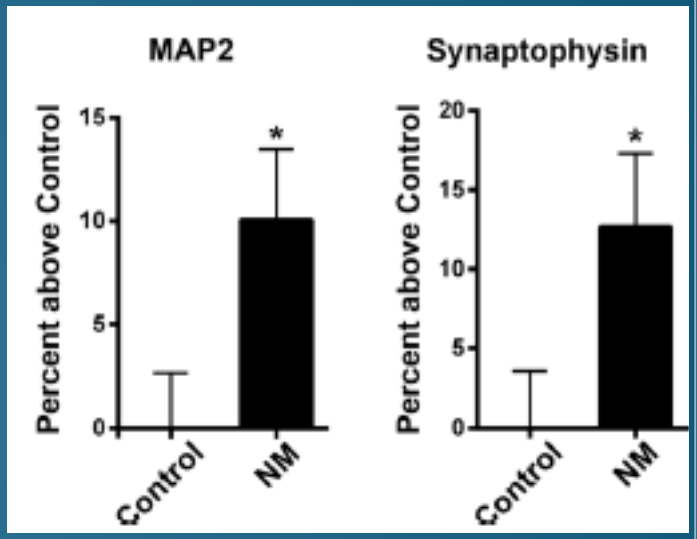
Drug	Report	Finding
Selegeline	Dana *Neurology* 1998; Schifitto *Neurology* 2007	+/-
Thioctic Acid	Dana Consortium *Neurology* 1998	no effect
Peptide T	Heseltine *Arch Neurol* 1998	-/+
Lithium	Letendre *AIDS* 2006	+
Memantine	Schifitto *AIDS* 2007	no effect
Minocycline	Nakasujja *Neurology* 2013	no effect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

Much of the Data Presented was with thanks to all our Study Volunteers and to Collaborating Investigators and Sponsors

UCSD HNRP (I. Grant, Director)

- Scott Letendre
- Ron Ellis
- Bob Heaton
- V. Soontornniyomkij
- Brookie Best
- David Moore
- Hamp Atkinson
- Davey Smith
- Tom Marcotte
- Cris Achim
- Steven Woods
- Eliezer Masliah
- Mariana Cherner
- Allen McCutchan

CHARTER (I. Grant, PI)

- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier
- Allen McCutchan
- Christina Marra
- Susan Morgello
- David Simpson
- Ben Gelman

National Institutes of Health

- ...Mental Health
- ...Drug Abuse
- ...Neurological Disorders and Stroke
- US Office on AIDS Research

- Donald Franklin for assistance in data compilation and slide preparation
- Eliezer Masliah for sharing his slides on changing concepts in HIV neuropathogenesis
- Evgeny Krupitsky, Edwin Zvartau, Dmitry Lioznov, Elena Blokhina and members of "Russia R21" team

Go Russia R21 Team!

(sponsored by NIDA via Office on AIDS Research)

NeuroAIDS in the modern treatment era

Thank you!

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