Clinical Perspectives – NeuroAIDS Research Needs in the Era of HAART

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No disclosures

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MEDICINE

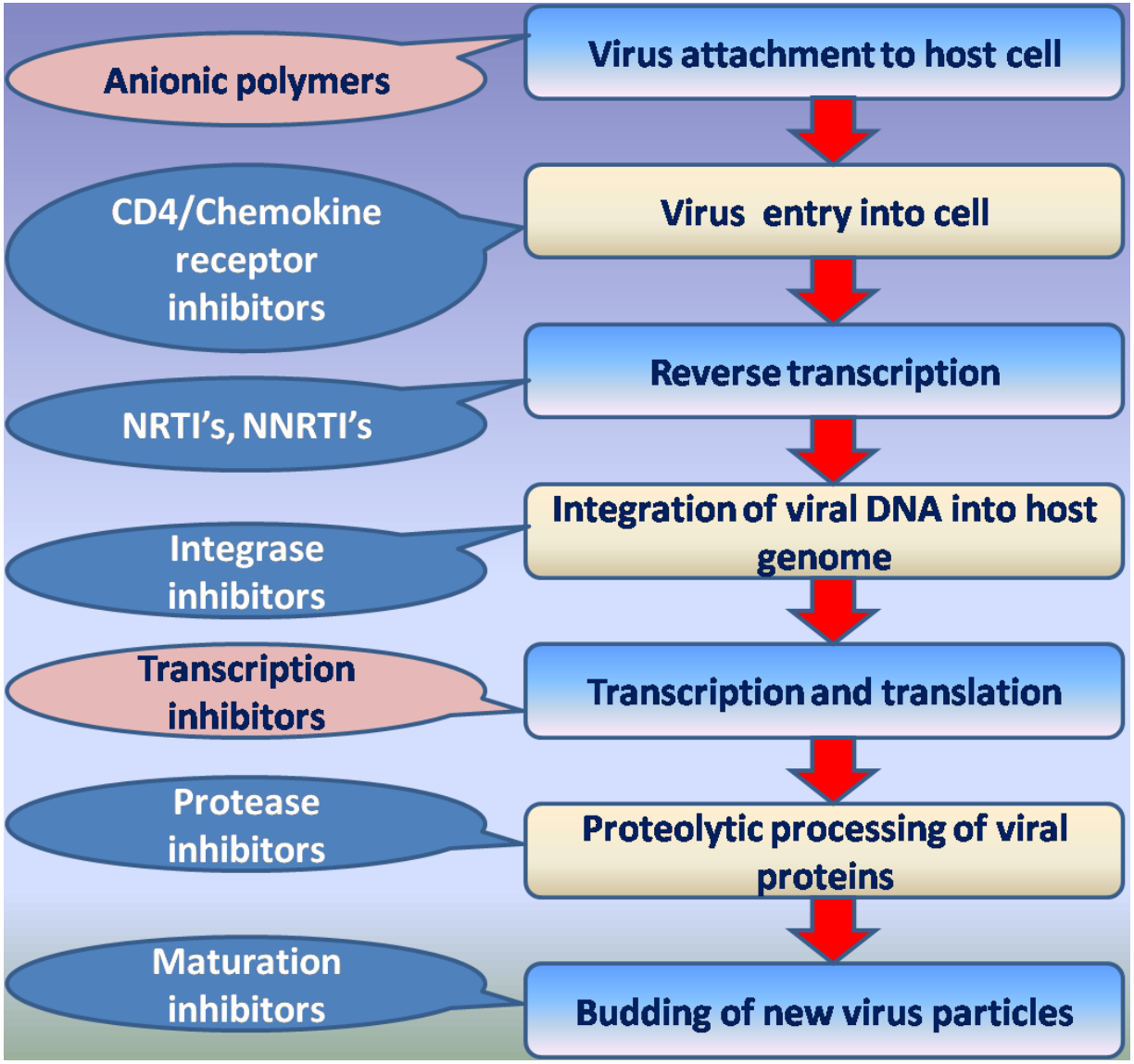
Objectives ~ the state of the HIV epidemic and changing concepts of neuropathogenesis of HIV-associated neurocognitive disorders

- Changing epidemiology in US and globally
- Evolving concepts in HIV neuropathogenesis
- Implications for research ~ addressing the therapeutic gap

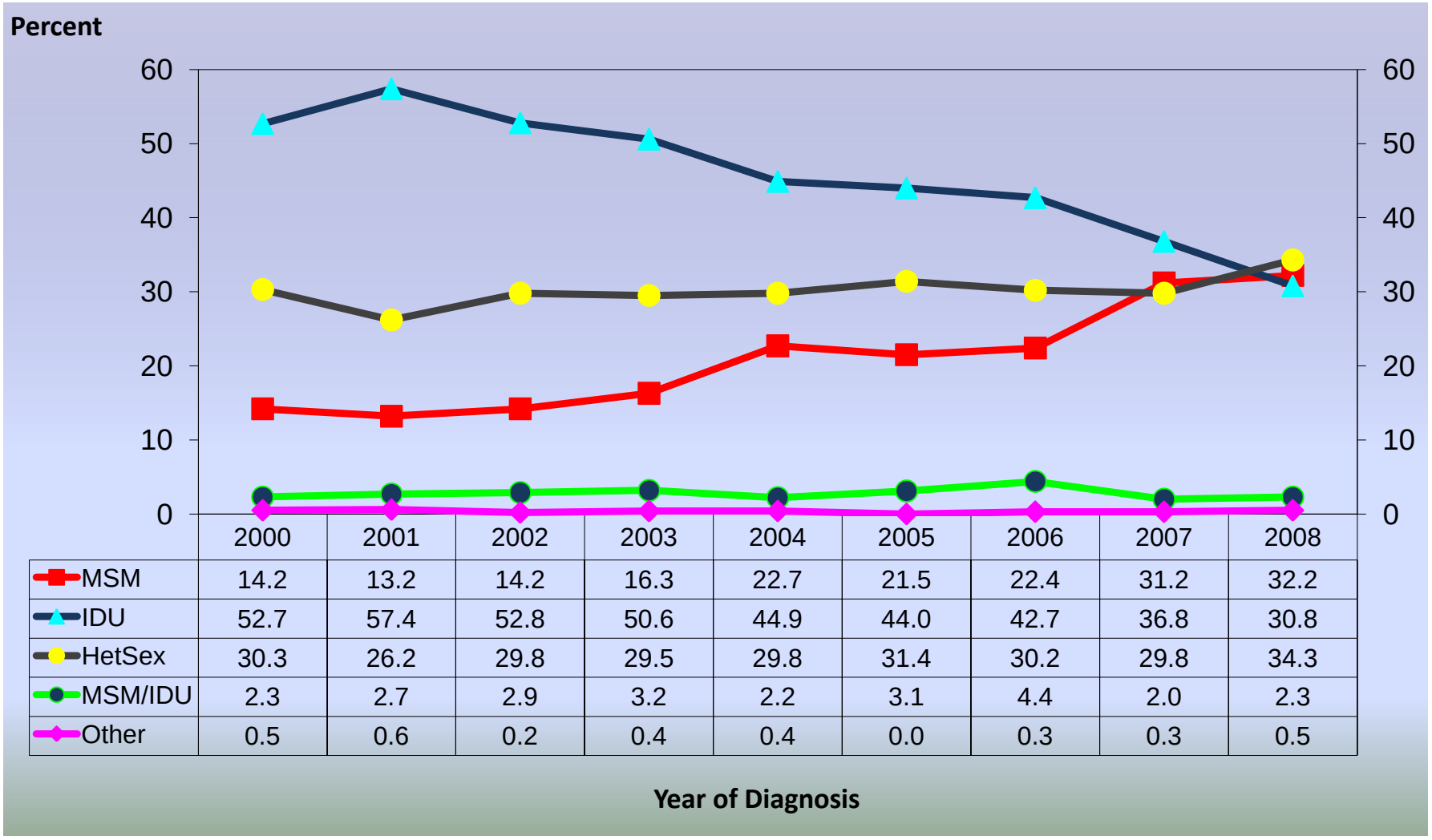
Implications for research…..

- HIV Associated Neurocognitive Disorder [HAND] persists despite ARV
- The phenotype of HAND may be changing: less severe dementia with marked motor signs; more milder cognitive disturbances
- Neuropathology in HAART era: less OI, neuronal loss, gliosis, microglial activation; synaptodendritic damage persists
- Long term survival with chronic immune activation, aging in HIV+ associated with increased likelihood of abnormal protein deposition in brain
- Increasing salience of comorbid conditions: age related metabolic changes [eg. insulin resistance], hypertension, mitochondrial aging, substance abuse, viral coinfections [HCV], toxicity of ARVs
- Continued need for robust biomarkers of HAND predisposition, detection, and monitoring.
- Opportunities and challenges for research in resource-limited settings: need for norms for NP tests

Targets of antiretrovirals

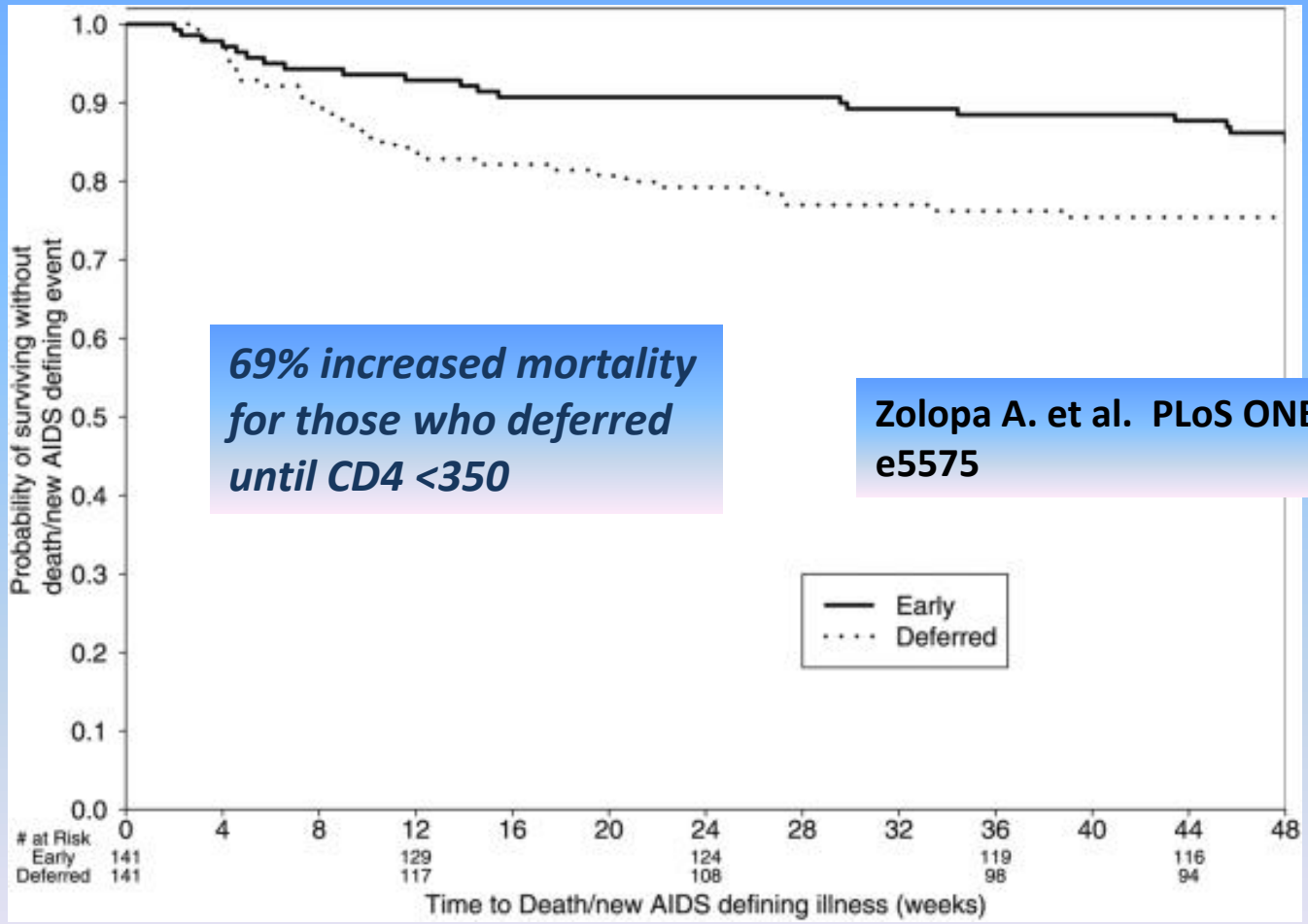


Baltimore: the changing epidemic ~ *MSM rates have doubled in past decade, while IDU rates have halved*



	2000	2001	2002	2003	2004	2005	2006	2007	2008
MSM	14.2	13.2	14.2	16.3	22.7	21.5	22.4	31.2	32.2
IDU	52.7	57.4	52.8	50.6	44.9	44.0	42.7	36.8	30.8
HetSex	30.3	26.2	29.8	29.5	29.8	31.4	30.2	29.8	34.3
MSM/IDU	2.3	2.7	2.9	3.2	2.2	3.1	4.4	2.0	2.3
Other	0.5	0.6	0.2	0.4	0.4	0.0	0.3	0.3	0.5

Early vs. deferred treatment for HIV infection ?



69% increased mortality for those who deferred until CD4 <350

Zolopa A. et al. PLoS ONE. 2009; 4(5): e5575

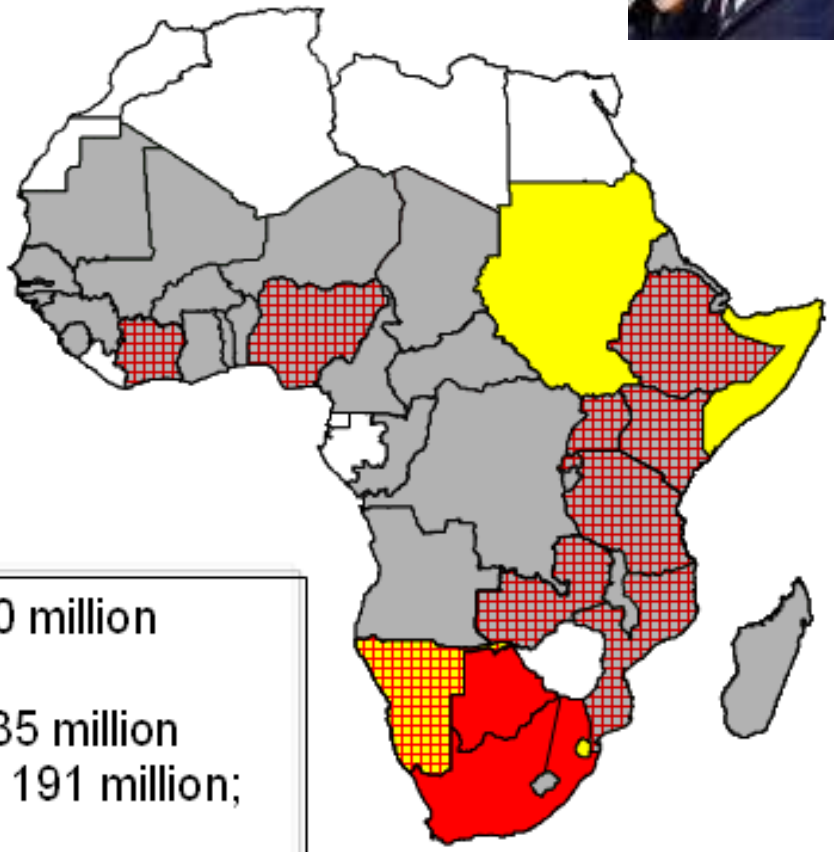
Time to AIDS progression or death.

HR=0.53 Early versus Deferred ART [95%CI 0.30–0.92 p=0.023].

Worldwide, only 15% of 39m HIV-infected are being treated……

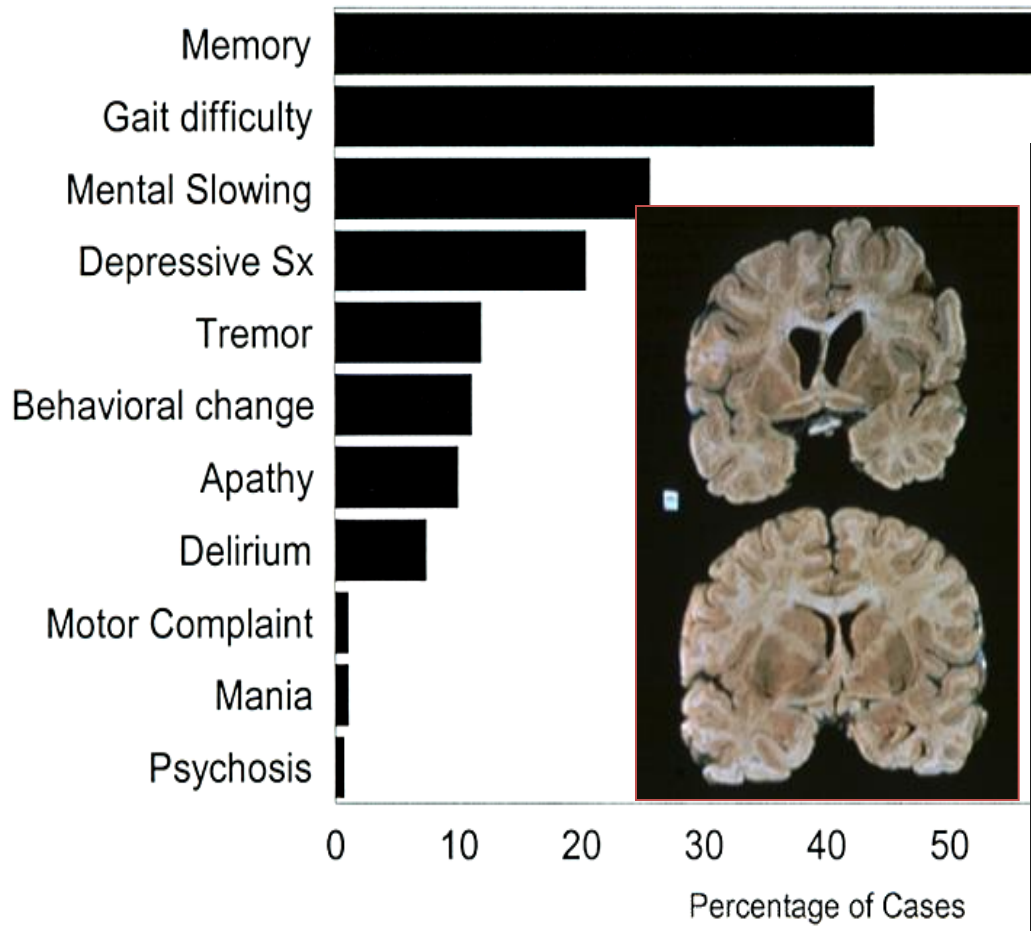
World Bank and PEPFAR Countries (May 2005)

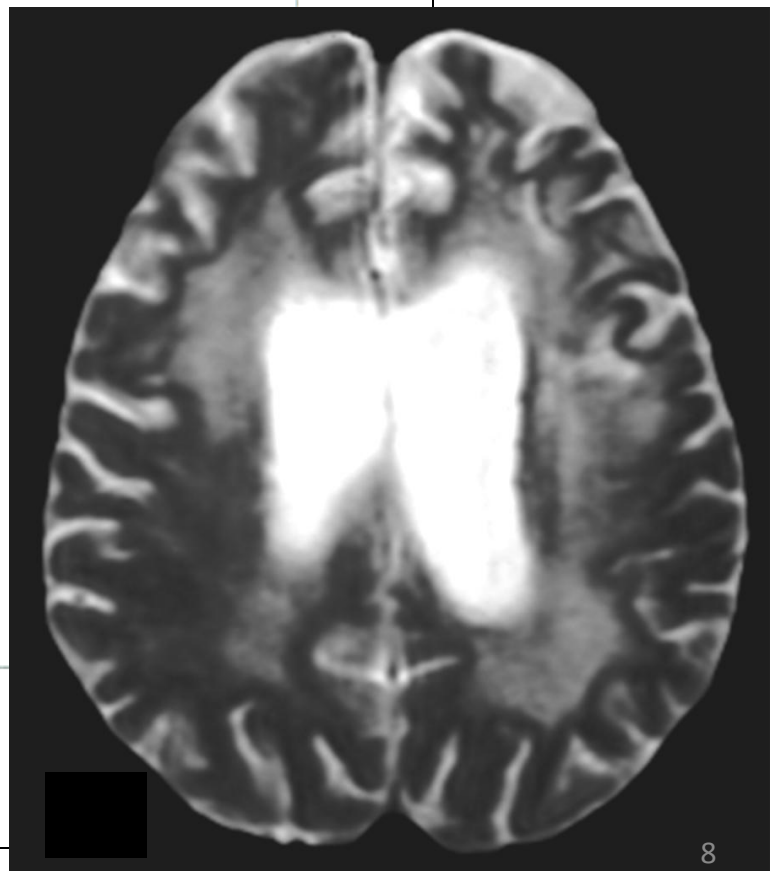
- WB MAP Country and Regional Projects
- WB MAP and PEPFAR
- WB Capacity Building Grants
- WB Capacity Building Grants and PEPFAR
- PEPFAR



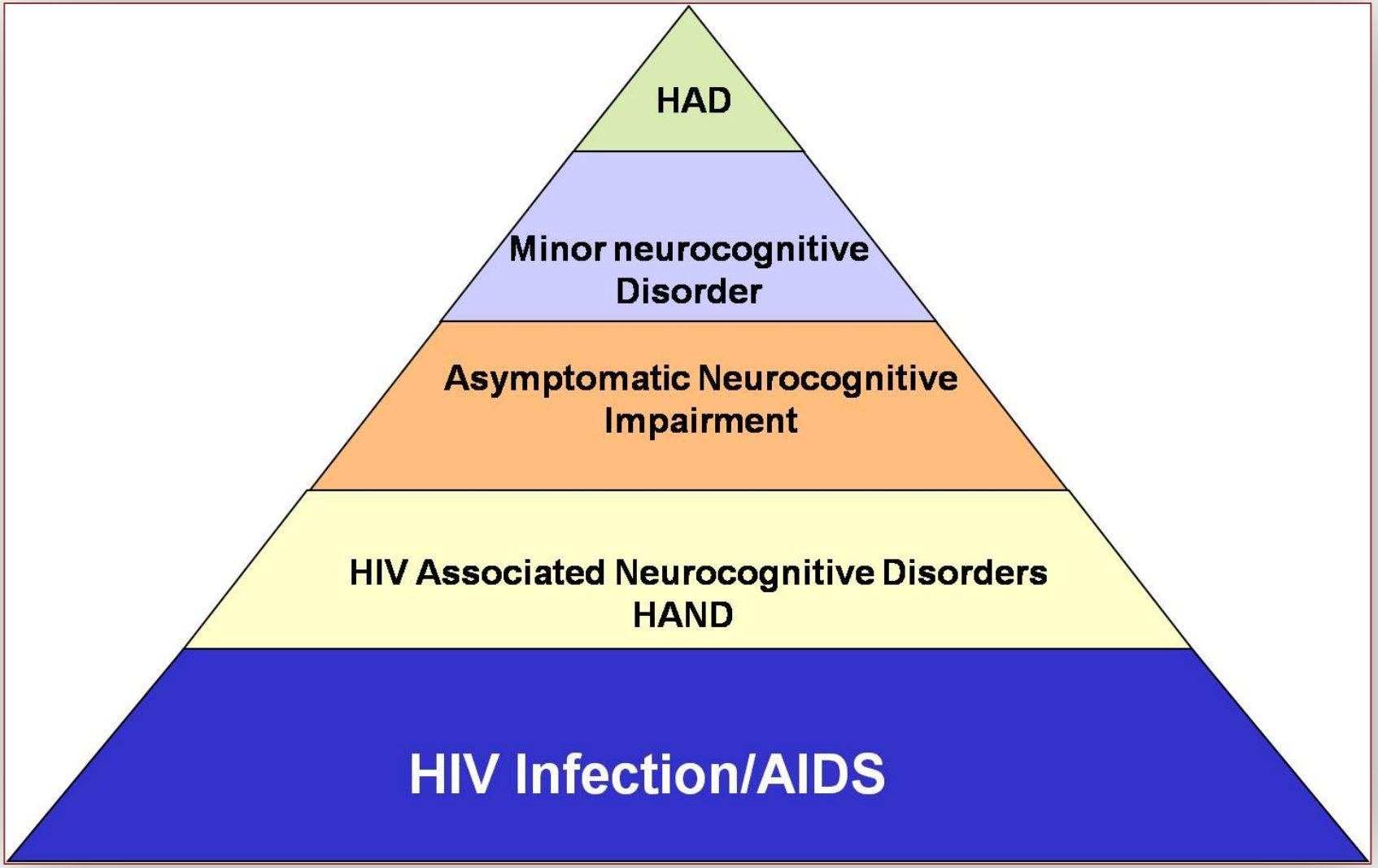
Guyana: Caribbean MAP, US$ 10 million
Haiti: PEPFAR
Vietnam: HIV/AIDS Project, US$ 35 million
India: AIDS Prevention II, US$ 191 million; AIDS III in the pipeline

*The old days….*frequency of clinical features in JHU HIV-D cases (n=300)

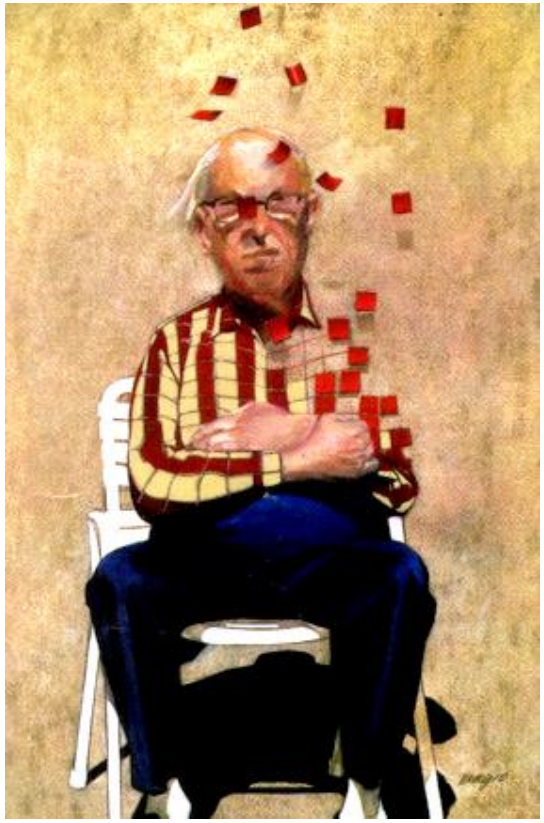




Hierachy of HAND



Today….changes in HIV dementia with HAART



5 months mean survival in 1993-1995 to 38.5 months in 1996-2000.

(Dore, AIDS 2003)

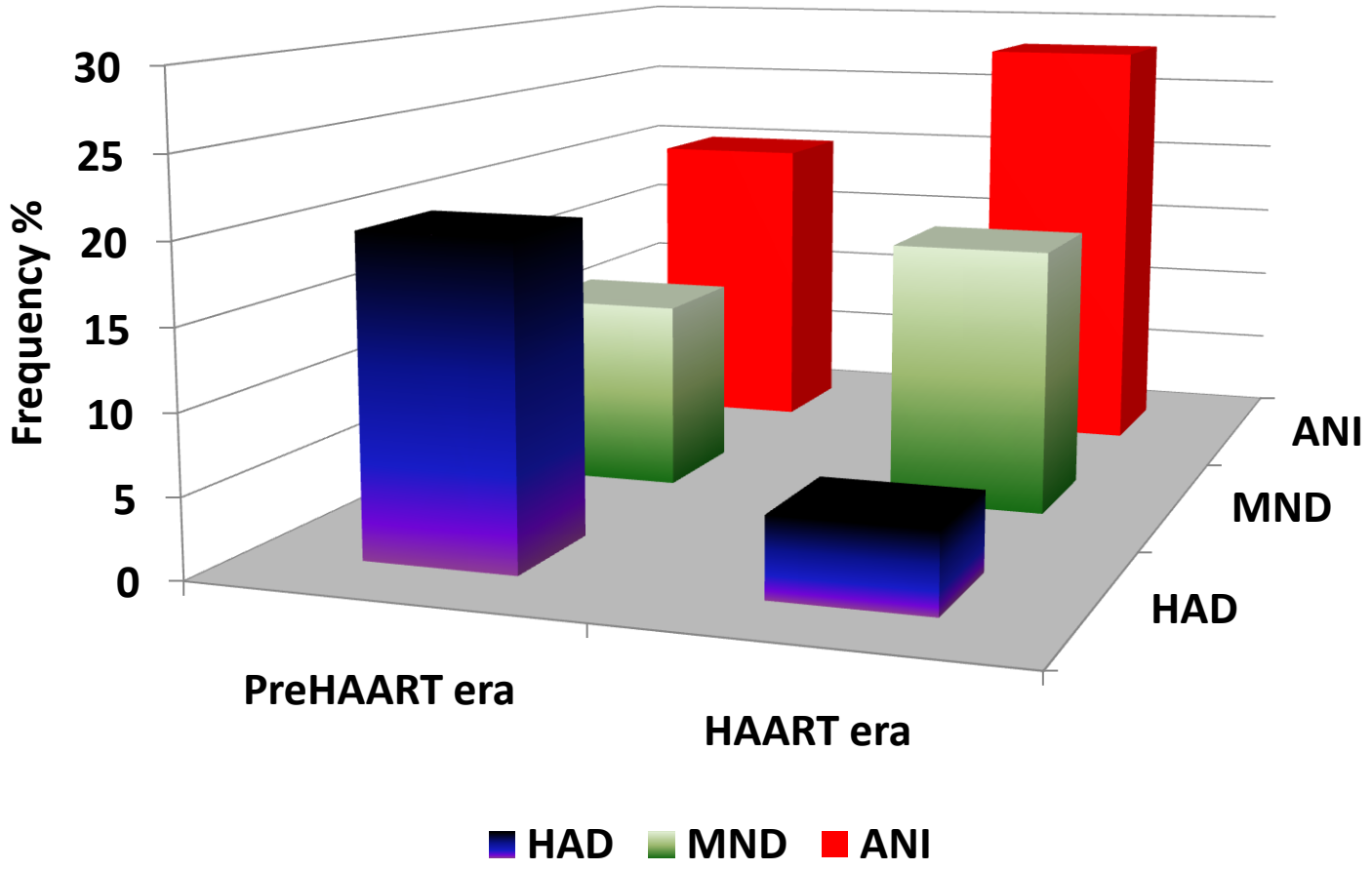
Before HAART:

- **'Sub-cortical': apathy and severe psychomotor slowing, memory loss. Typically progressive.**
- **Multinucleated giant cell encephalitis with neuronal loss.**

After HAART:

- **Mixed 'cortical and subcortical' features, with milder phenotype and frequent transitions and reversals.**
- **Synaptodendritic injury with less CNS HIV replication.**

Changing prevalence of HAND



Modified from Heaton R., et al: HIV-associated neurocognitive disorders (HAND) persist in the era of potent antiretroviral therapy: The CHARTER Study; and Heaton R., *J Int Neuropsychol Soc.* May 1995;1(3):231-251)).

HAND is relatively refractory to HAART

Persistence of Neuropsychologic Deficits Despite Long-Term Highly Active Antiretroviral Therapy in Patients With HIV-Related Neurocognitive Impairment

Prevalence and Risk Factors

Valerio Tozzi, MD, Pietro Balestra, PsyD,* Rita Bellagamba, MD,* Angela Corpolongo, MD,* Maria Flora Salvatori, DSc,* Ubaldo Visco-Comandini, PhD,* Chrysoula Vlassi, MD,* Marinella Giulianelli, PsyD,* Simonetta Galgani, MD,† Andrea Antinori, MD,* and Pasquale Narciso, MD*

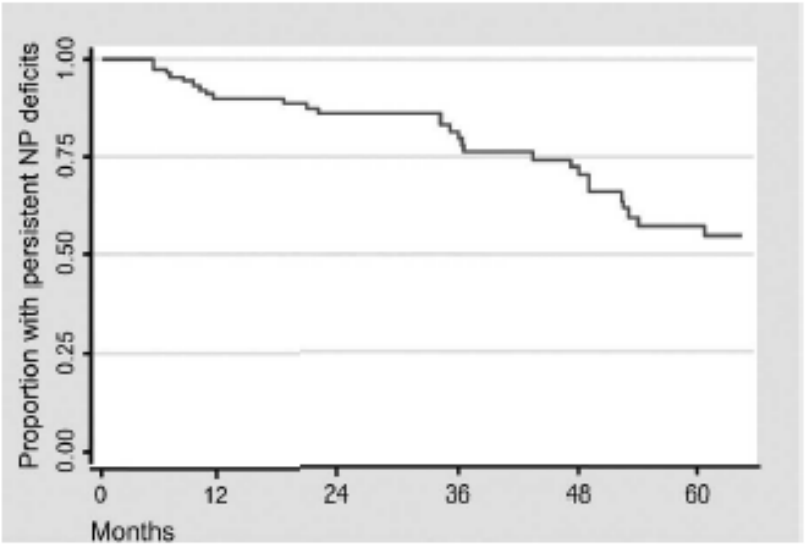


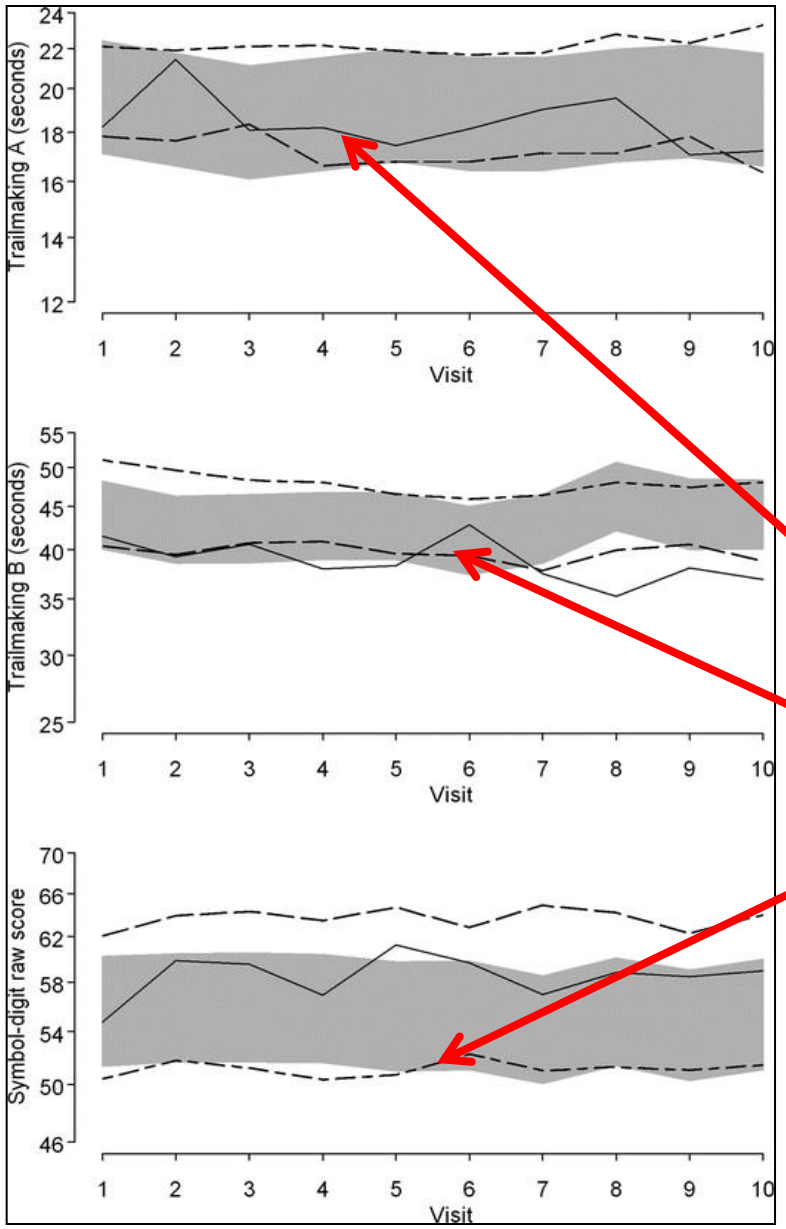
FIGURE 1. Kaplan-Meyer plot of the probability of showing persistent NP deficits by month of follow-up in the 94 study patients with HIV-related NCI treated with HAART.

TABLE 5. Factors Associated With Persistent NP Deficits in the 94 Impaired HIV-Positive Patients: Results of Multivariable Cox Model

Factor	OR	95% CI	P
Male gender	1.18	0.23 to 5.88	0.844
Education (for 1-year decrease)	1.14	0.98 to 1.30	0.072
HCV-positive serology	0.96	0.34 to 2.76	0.937
CD4 count at last visit (for 1-cell increase)	1.00	0.99 to 1.00	0.205
NPZ8 baseline score (for 1° decrease)	3.07	1.54 to 6.08	0.001

Conclusions: The severity of NCI at HAART initiation seems to be the strongest predictor of persistent NP deficits despite long-term HAART. Our data indicate that HAART should be initiated as soon as NCI is diagnosed to avoid potentially irreversible neurologic damage.

Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals
Cole, M et al. Neurology. 69(24):2213-2220, December 11, 2007.



Adjusted geometric means of Trail Making Test A, Trail Making Test B, and Symbol Digit Modalities test raw score by MACS visit

Trail Making Test A (top panel)
Trail Making Test B (middle panel)
Symbol Digit Modalities (bottom panel)

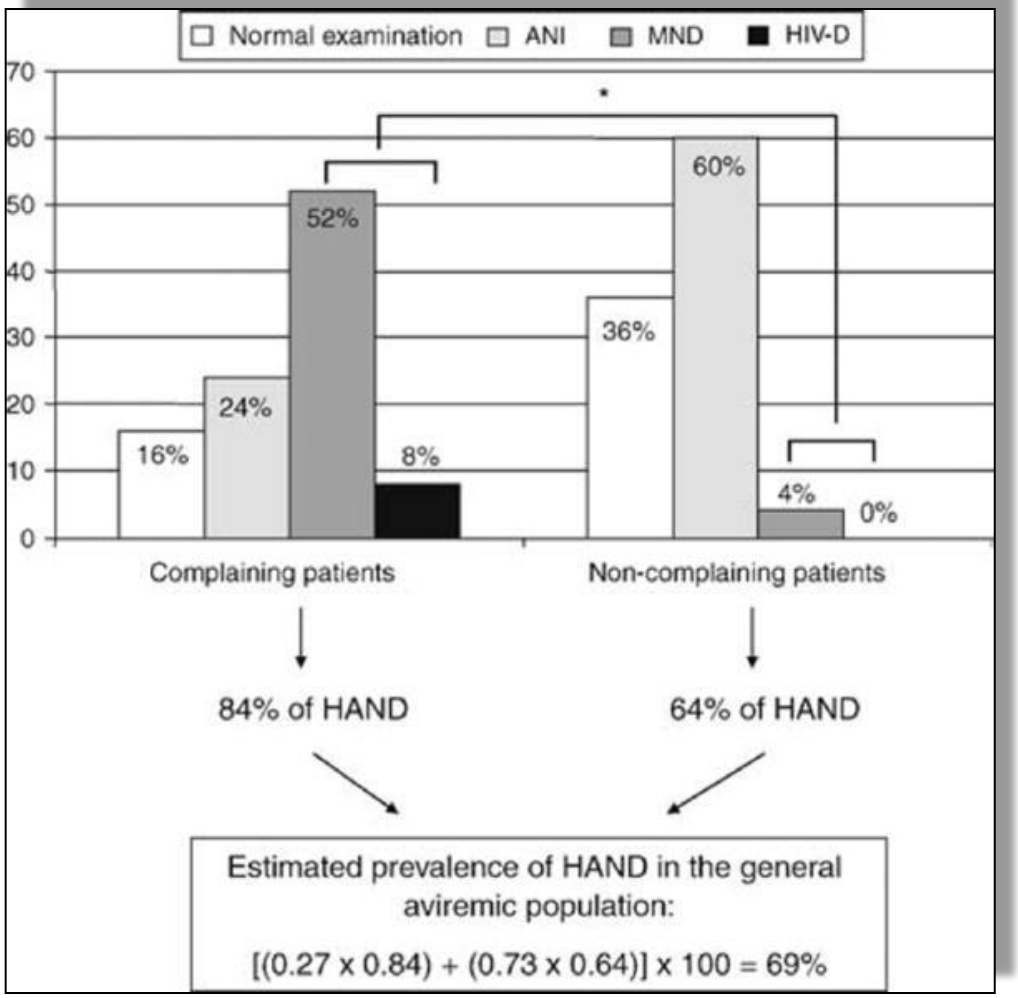
Solid line = long-term disease non-progressors (LTDNP) who have not received HAART (n=29)

Line with long dashes = HIV-positive participants receiving HAART with long-term undetectable viral loads (n=83)

Line with short and long dashes = HIV-positive participants who were healthy and CD4/AIDS-free (n=233)

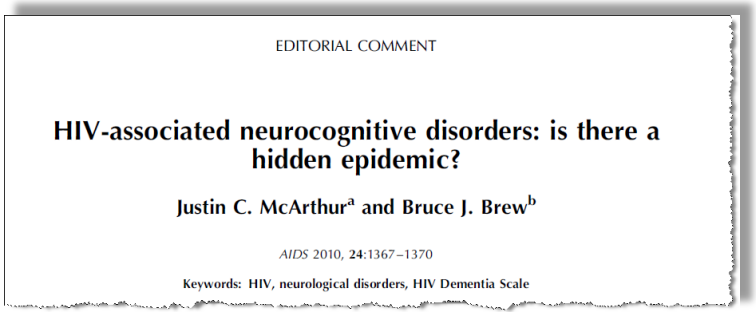
Gray shaded area covers the adjusted geometric means of HIV-negative group obtained from the three separate analyses (n=237)

Prevalence of HIV-associated neurocognitive disorders in complaining and noncomplaining aviremic HIV-positive patients



Cognitive dysfunction in HIV patients despite long-standing suppression of viremia.
Simioni, S., et al

AIDS. 24(9):1243-1250, June 1, 2010.



EDITORIAL COMMENT

HIV-associated neurocognitive disorders: is there a hidden epidemic?

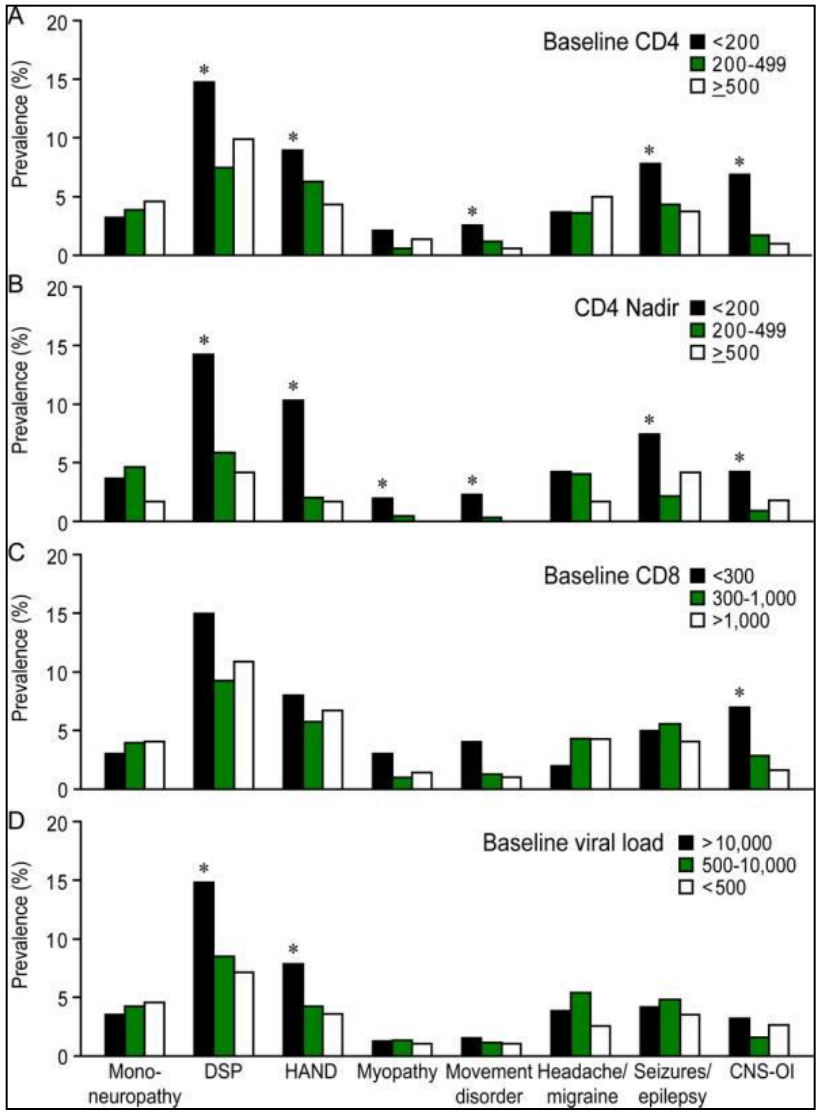
Justin C. McArthur[a] and Bruce J. Brew[b]

AIDS 2010, **24**:1367–1370

Keywords: HIV, neurological disorders, HIV Dementia Scale

Neurologic disease burden in treated HIV/AIDS predicts survival: A population-based study

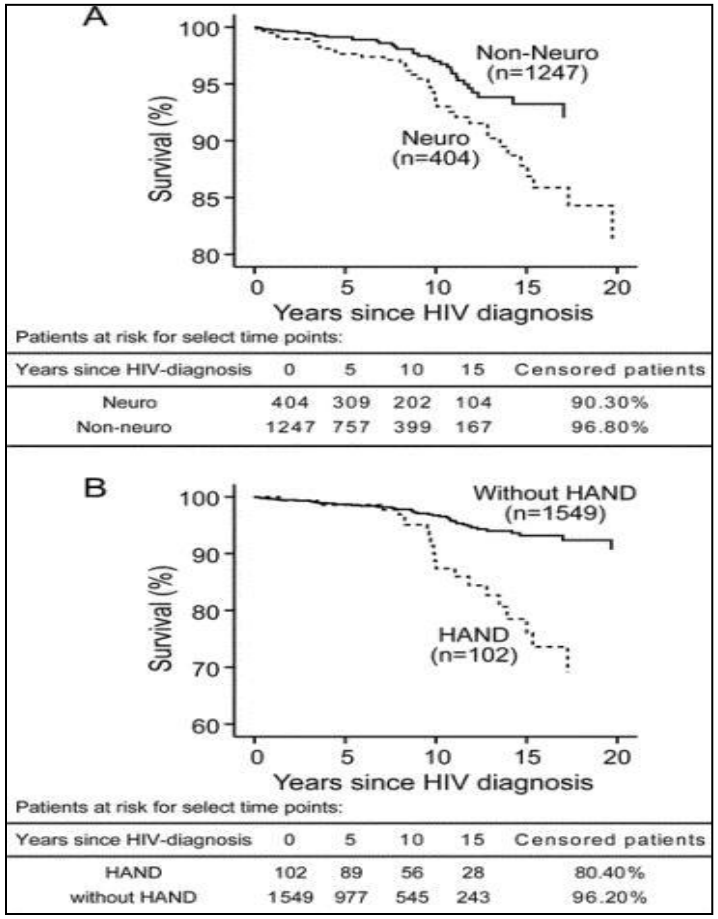
Vivithanaporn, P et al Neurology. 75(13):1150-1158, 2010.



The risks of distal sensory polyneuropathy (DSP), HIV-associated neurocognitive disorders (HAND), movement disorders, seizure, and CNS opportunistic infection (CNS-OI) were greater among persons with baseline and nadir CD4+ T-cell levels below 200 cells/mm3

Neurologic disease burden in treated HIV/AIDS predicts survival: A population-based study

Vivithanaporn, P et al Neurology. 75(13):1150-1158, 2010.



Patients at risk for select time points:

Years since HIV-diagnosis	0	5	10	15	Censored patients
Neuro	404	309	202	104	90.30%
Non-neuro	1247	757	399	167	96.80%

Patients at risk for select time points:

Years since HIV-diagnosis	0	5	10	15	Censored patients
HAND	102	89	56	28	80.40%
without HAND	1549	977	545	243	96.20%

HAND increased the risk of mortality by approximately 3-fold, after accounting for demographic, immunologic, and virologic variables.

Why do people with HAND die at higher rates ?

Pathological findings in the central nervous system of AIDS patients on antiretroviral therapeutic regimens: *retrospective study of 1597 autopsies*

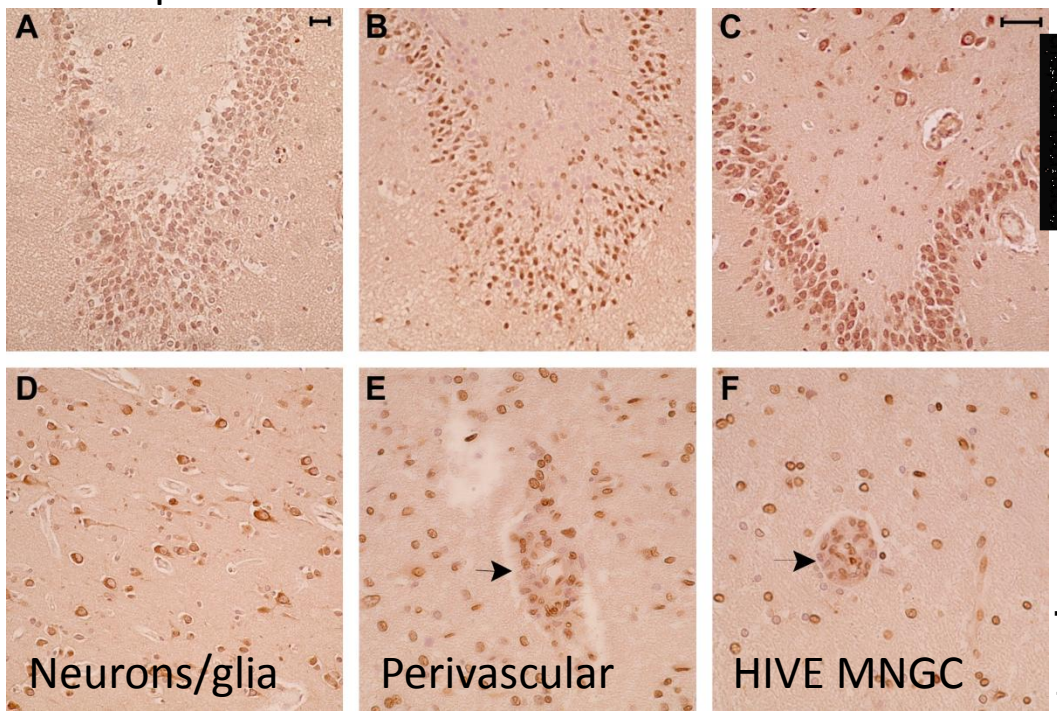
(AIDS, 2002 Vago, L. et al)

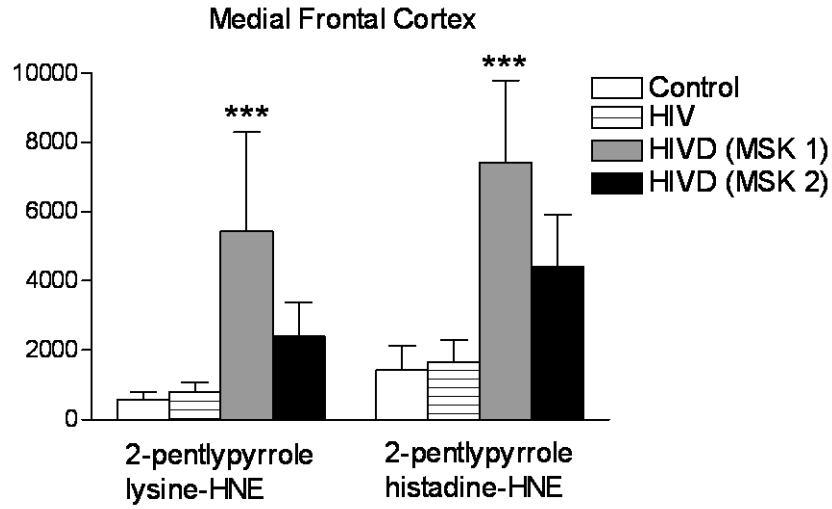
- **Epochs studied:**
  - **1984–1987, no therapy: 54%**
  - **1988–1994, monotherapy : 32%**
  - **1995–1996, dual combination therapy: 18%**
  - **>1996, triple combination therapy: 15%**
- **The prevalence of HIV-encephalitis, with or without OI, was significantly reduced in the subsequent three periods.**

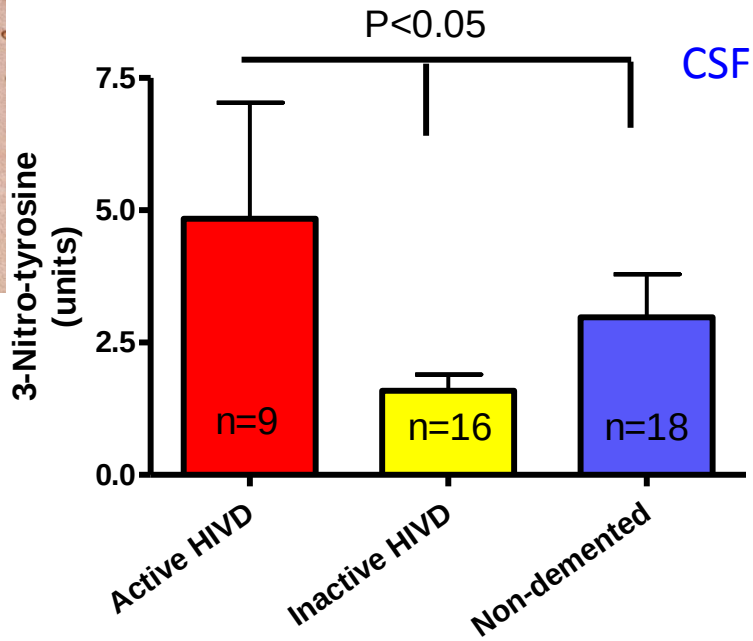
Is inflammation persistent within the CNS…and why ?

- Gisslen M. et al: **neopterin elevated in 60% even after years of HAART-induced aviremia**
- Nguyen T.: **the role of the immunoproteasome**
- Li et al. 2008: **high levels of oxidative stress**

Oxidative and nitrosative stress in HIV encephalitis and dementia (Turchan et al., 2003; Haughey et al, 2004; Wenxue Li et al. 2008)







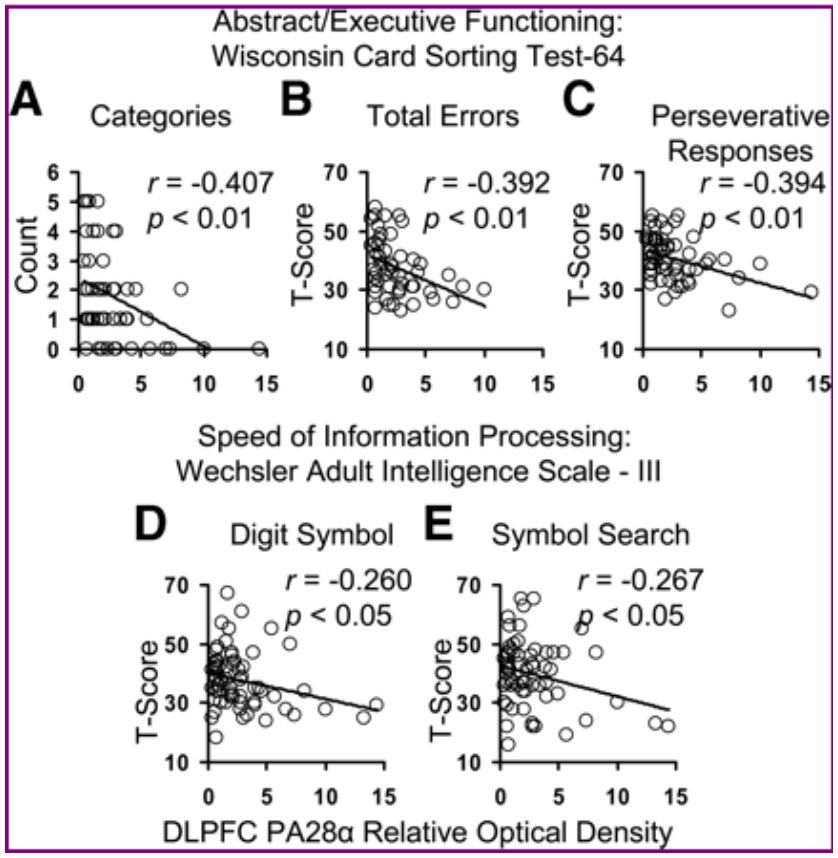
Immunostaining for hydroxynonenal, a marker of lipid peroxidation: *prominent in HIV dementia*

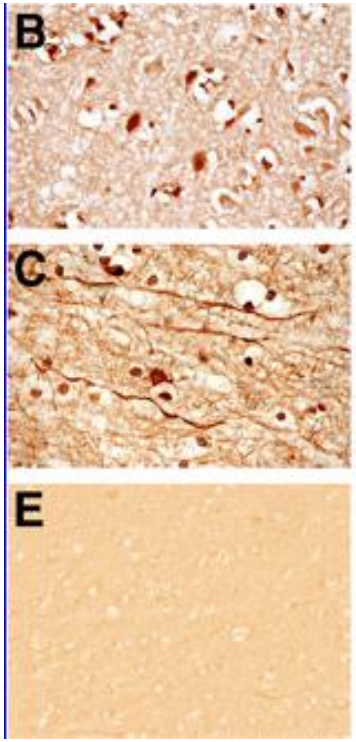
The American Journal of Pathology, Vol. 176, No. 2, February 2010
Copyright © American Society for Investigative Pathology
DOI: 10.2353/ajpath.2010.090590

Neurobiology

Persistent Hijacking of Brain Proteasomes in HIV-Associated Dementia

Trung P. Nguyen,* Vicki M. Soukup,† and Benjamin B. Gelman*
From the Departments of Pathology and Neurology,† the University of Texas Medical Branch, Galveston, Texas*

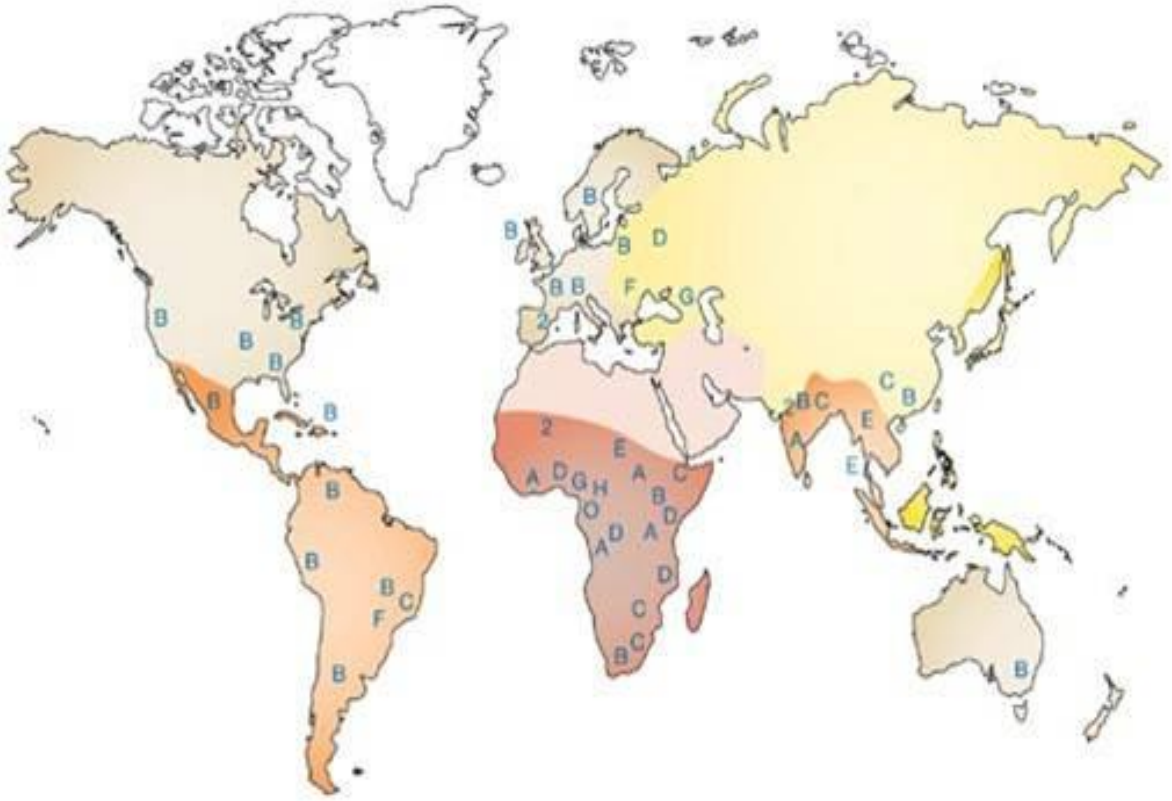




Is there a therapeutic 'gap' for HAND ?

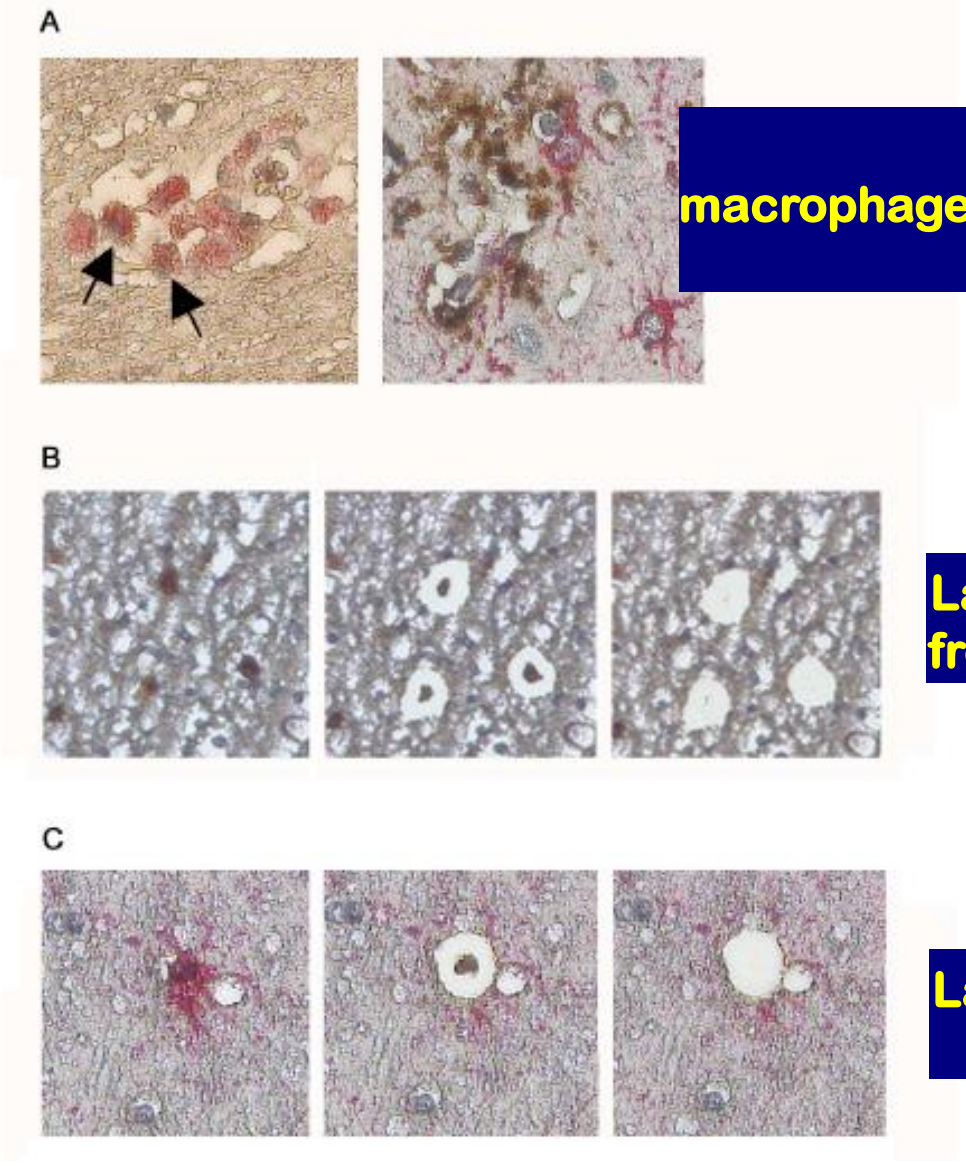
- Despite HAART's effect on incidence, the prevalence of HAND remains high
- Pathological and immunologcal evidence of sustained inflammation or HIVE persists
- Drugs of abuse may be synergistic
- HAART can reverse neurocognitive deficits, but usually is only a partial effect
- Neuronal loss is presumably permanent, even when CNS inflammation is 'burnt out'

Clade differences in neurovirulence



In Ethiopia, clade C appears to be less neurovirulent than Clades A and D seen in sub-saharan Africa. The mechanisms for these clade differences in neurovirulence may be determined by variation in the regulatory viral protein transactivator of transcription (*Tat). Sacktor N., Nature Clin. Pract. Neurology, 2007*

Detection of integrated HIV-1 DNA in astrocytes: A possible permanent reservoir for HIV



CD68+ macrophages and GFAP+ astrocytes

Laser capture microdissection from macrophage lineage cells

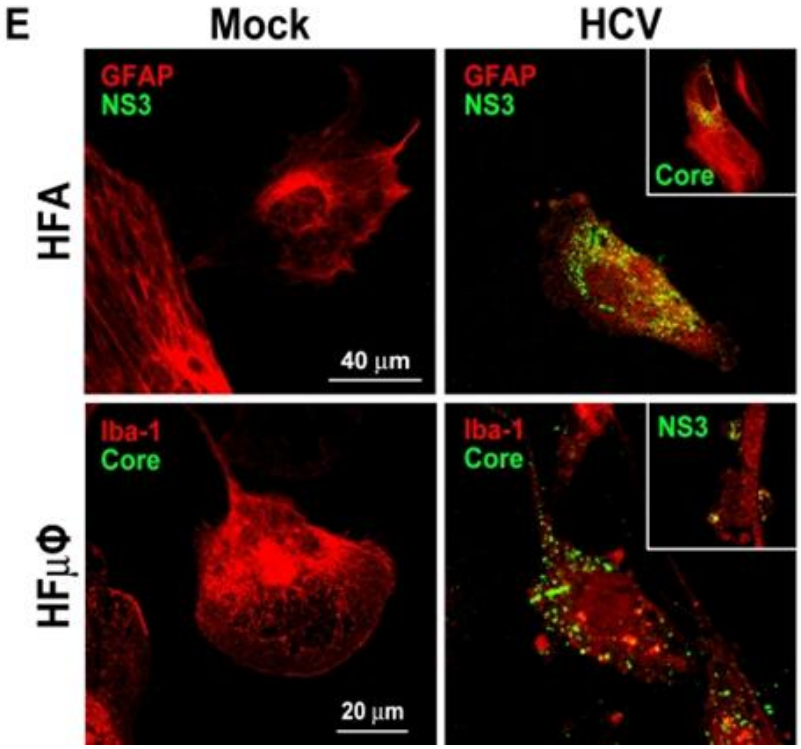
Laser capture microdissection from astrocytes

Churchill M., JNV, 2006

Hepatitis C virus core protein induces neuroimmune activation and potentiates Human Immunodeficiency Virus-1 neurotoxicity

PLoS One. 2010 Sep 21;5(9):e12856

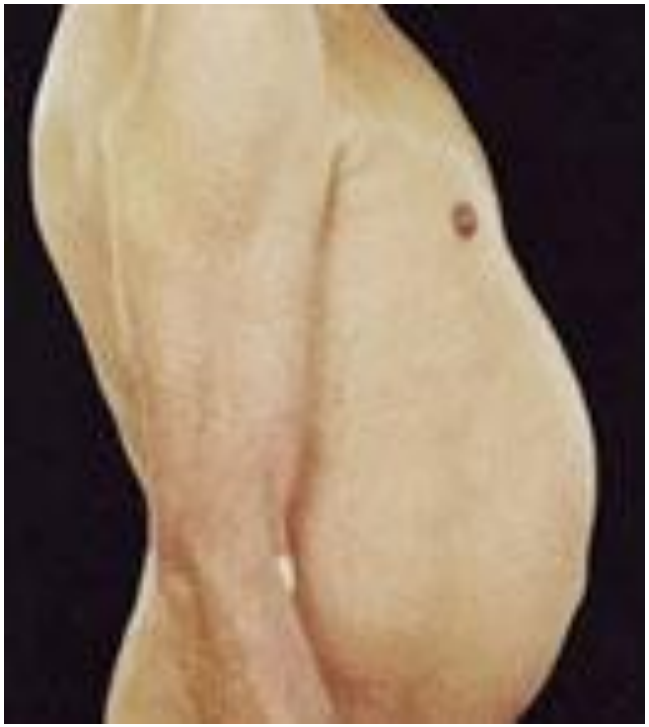
Vivithanaporn P, ……Power C



HCV core protein exposure caused neuronal injury through suppression of neuronal autophagy in addition to neuroimmune activation. The additive neurotoxic effects of HCV- and HIV-encoded proteins highlight extrahepatic mechanisms by which HCV infection worsens the disease course of HIV infection.

Confounding illnesses in the assessment of HIV dementia

- **Metabolic syndrome in HAART recipients and accelerated vascular disease *(Currier, 2003)***



Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men

ABSTRACT

Background: The purpose of this study was to evaluate the relationship between cognitive performance, risk factors for cardiovascular and cerebrovascular disease (CVD), and HIV infection in the era of highly active antiretroviral therapy.

Methods: We evaluated the cognitive functions of men enrolled in the cardiovascular disease substudy of the Multicenter AIDS Cohort Study who were aged ≥40 years, with no self-reported history of heart disease or cerebrovascular disease. Results from comprehensive neuropsychological evaluations were used to construct composite scores of psychomotor speed and memory performance. Subclinical CVD was assessed by measuring coronary artery calcium and carotid artery intima-media thickness (IMT), as well as laboratory measures, including total cholesterol, fasting glucose, glycosylated hemoglobin, glomerular filtration rate (estimated), and standardized blood pressure and heart rate measures.

Results: After accounting for education, depression, and race, carotid IMT and glomerular filtration rate were significantly associated with psychomotor speed, whereas IMT was associated with memory test performance. HIV serostatus was not significantly associated with poorer cognitive test performance. However, among the HIV-infected individuals, the presence of detectable HIV RNA in plasma was linked to lower memory performance.

Conclusions: These findings suggest that HIV infection may not be the most important predictor of cognitive performance among older gay and bisexual men in the post–highly active antiretroviral therapy era, at least among those with access to medical care and to appropriate medications. Medical factors associated with normal aging are significantly associated with performance on neuropsychological tests, and good clinical management of these factors both in HIV-infected individuals and those at risk for infection may have beneficial effects in the short term and could reduce the risk of subsequent cognitive decline. *Neurology*® 2009;73:1292–1299

Confounding illnesses in the assessment of HIV dementia

- Metabolic syndrome in HAART recipients and accelerated vascular disease *(Currier, 2003)*
- **Immune restoration syndrome**
- **CNS escape**
- **Alcohol and other drugs of abuse**
- **Hepatitis C co-infection**
- **Age-related cognitive changes**
- **Vitamin, endocrine and nutritional deficiencies**
- **Resource-limited countries ~ TB, nutrition**

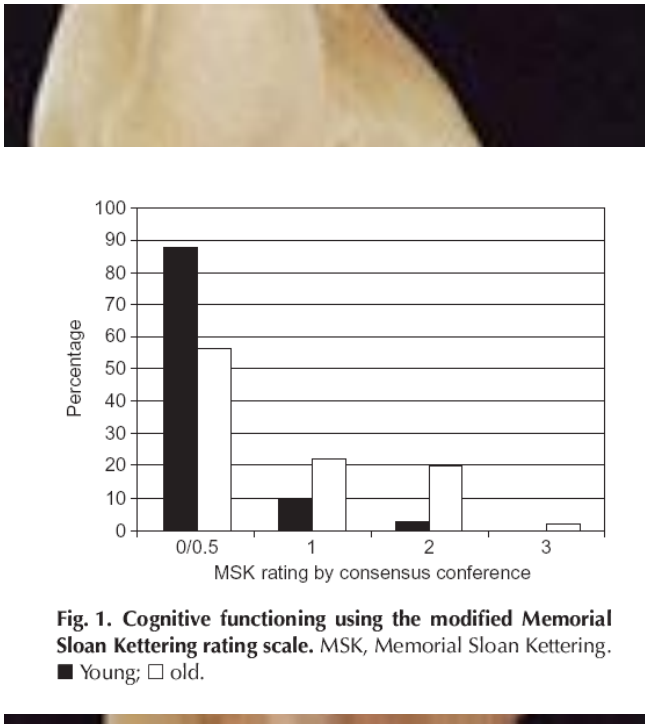
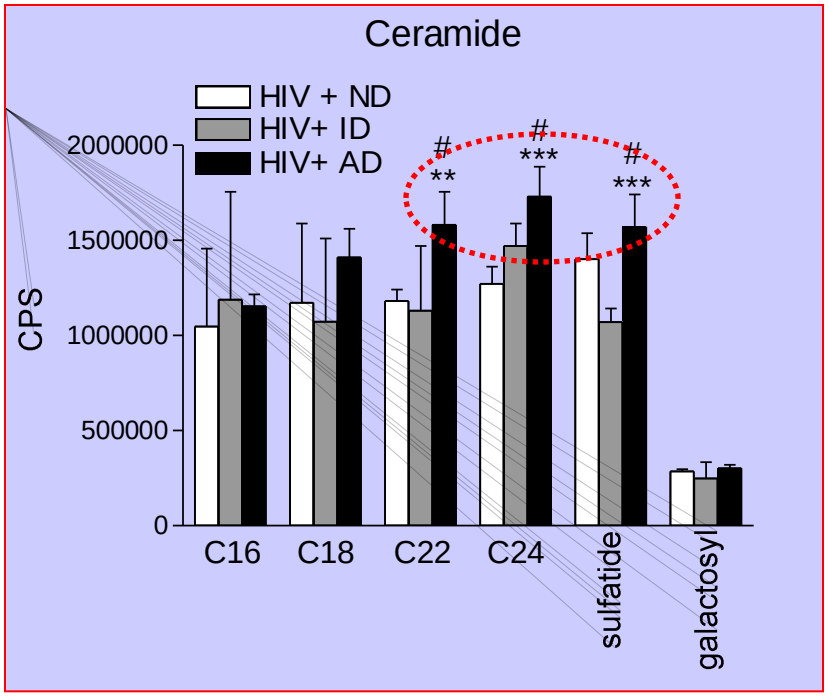
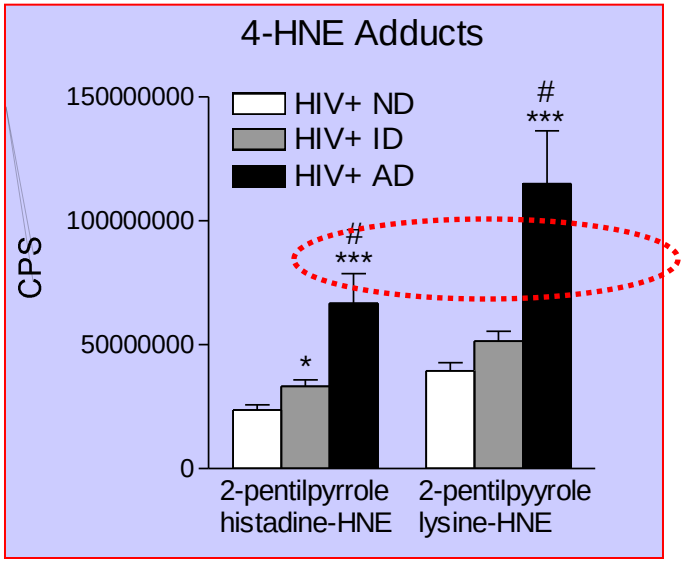


Fig. 1. Cognitive functioning using the modified Memorial Sloan Kettering rating scale. MSK, Memorial Sloan Kettering. ■ Young; □ old.

Biomarkers of oxidative stress can differentiate HAND phenotype: significant elevations of ceramide, and 4-HNE in 'progressive' HIV-dementia. *Haughey N, Ann Neurol, 2004*

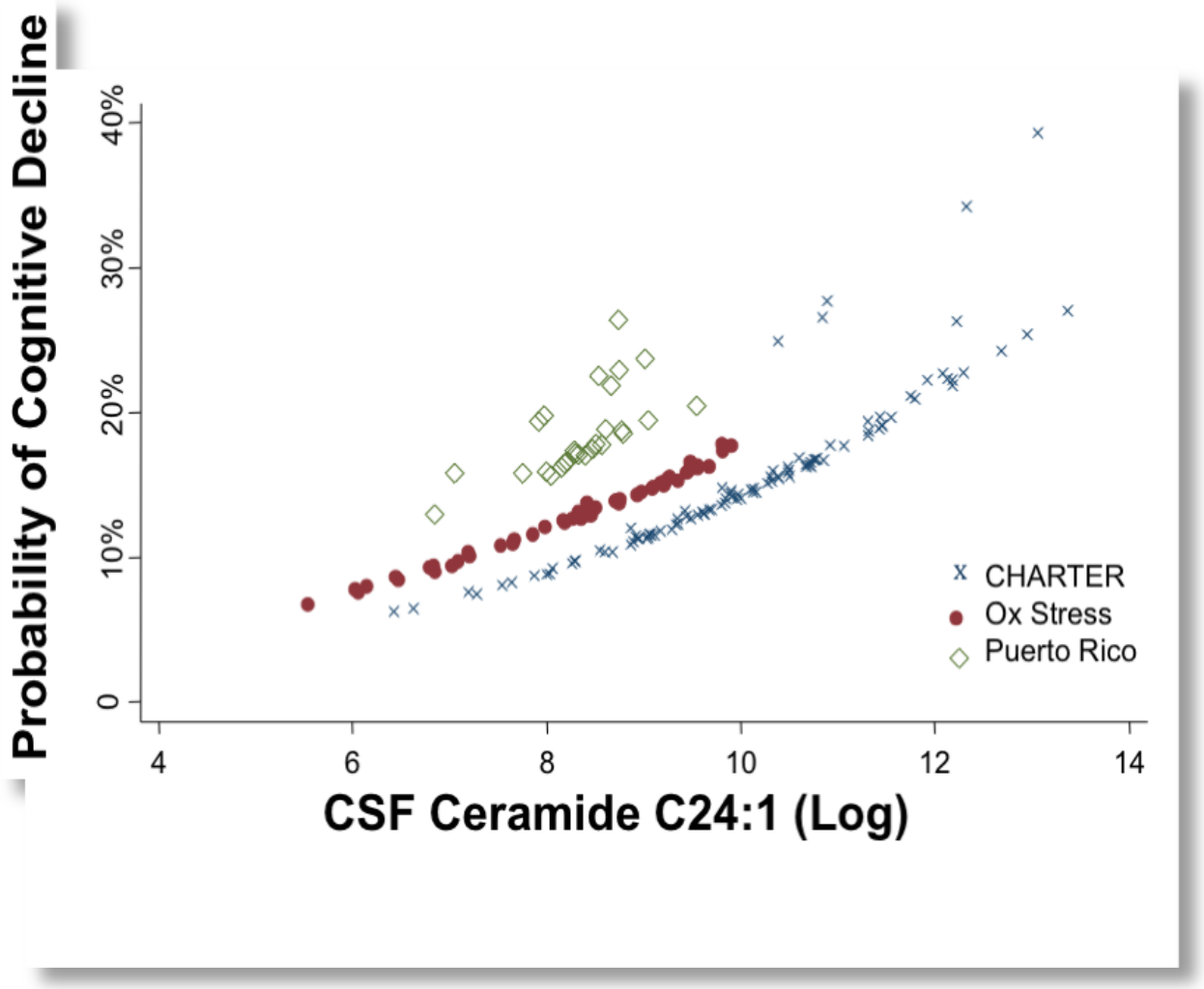
ND = not demented
ID = stable dementia (*no change*)
AD = progressive dementia (*new transition*)



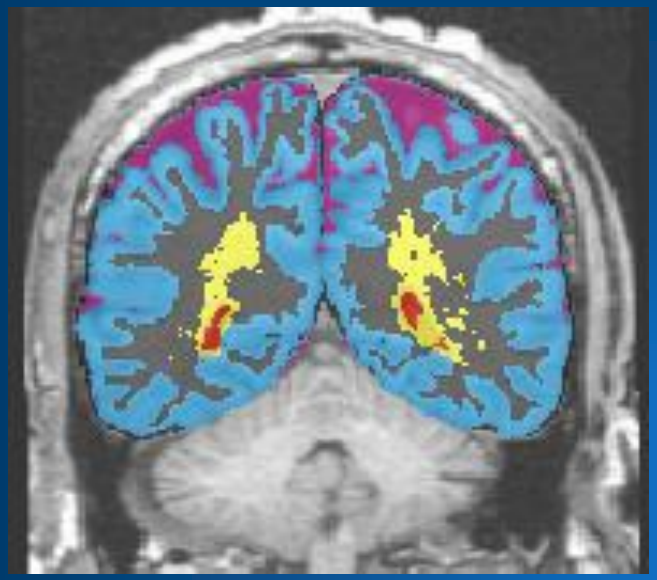


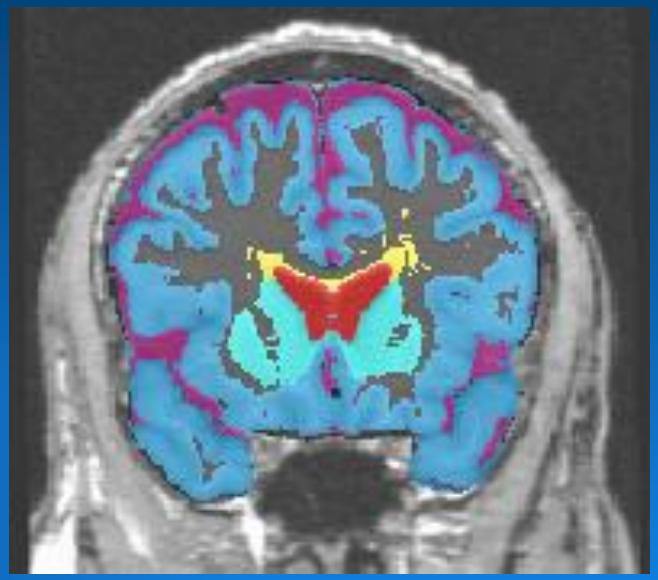
Predictive markers of oxidative stress: probability of cognitive decline. Changes in the sphingomyelin / ceramide ratio for C24:1

(from CHARTER, JHU Oxidative stress and Puerto Rico cohorts, courtesy of N. Haughey)



Morphometry Measures





Abnormal White Matter

Total White Matter

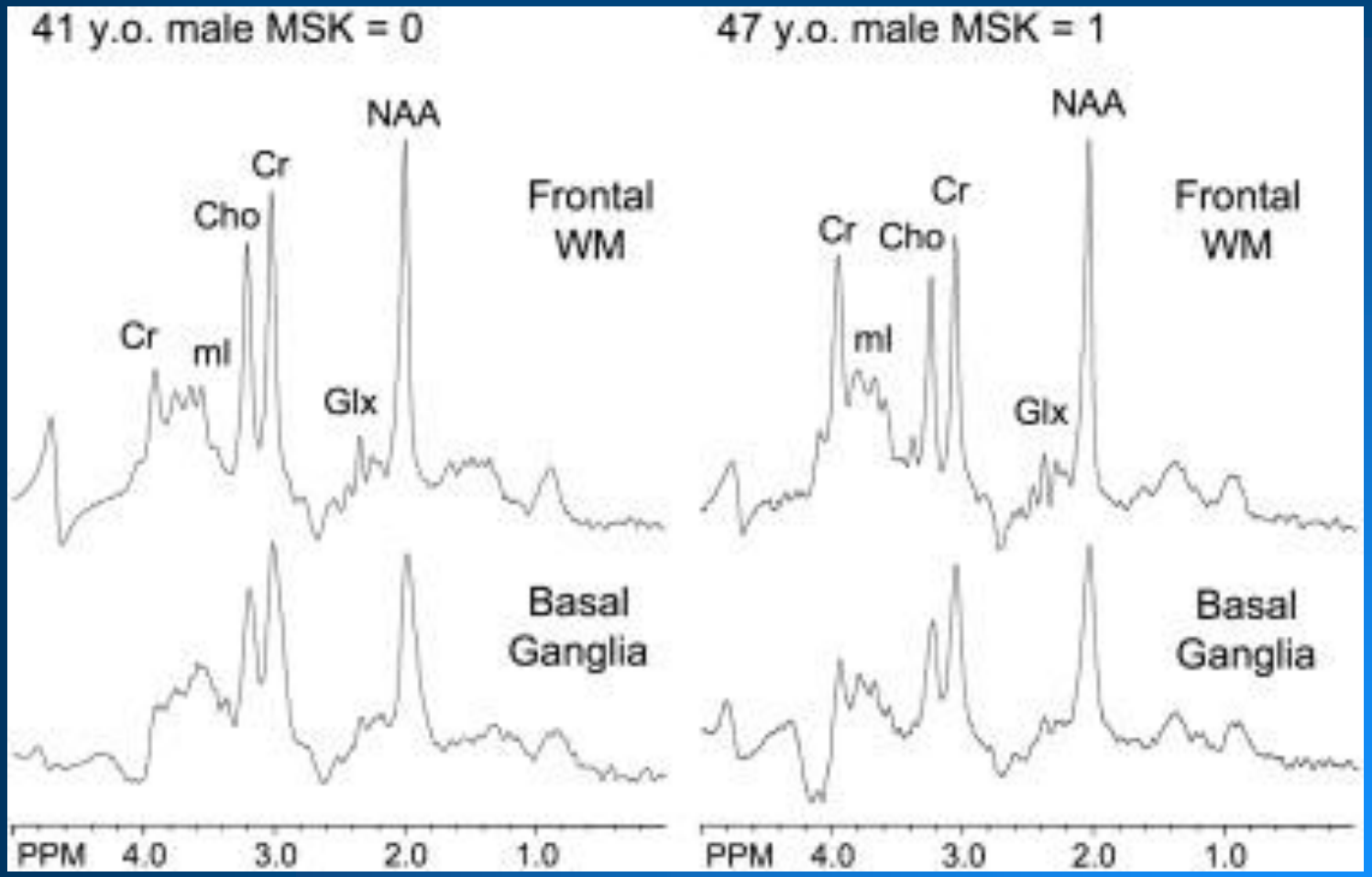
Ventricular CSF

Cortical Gray

Subcortical Gray

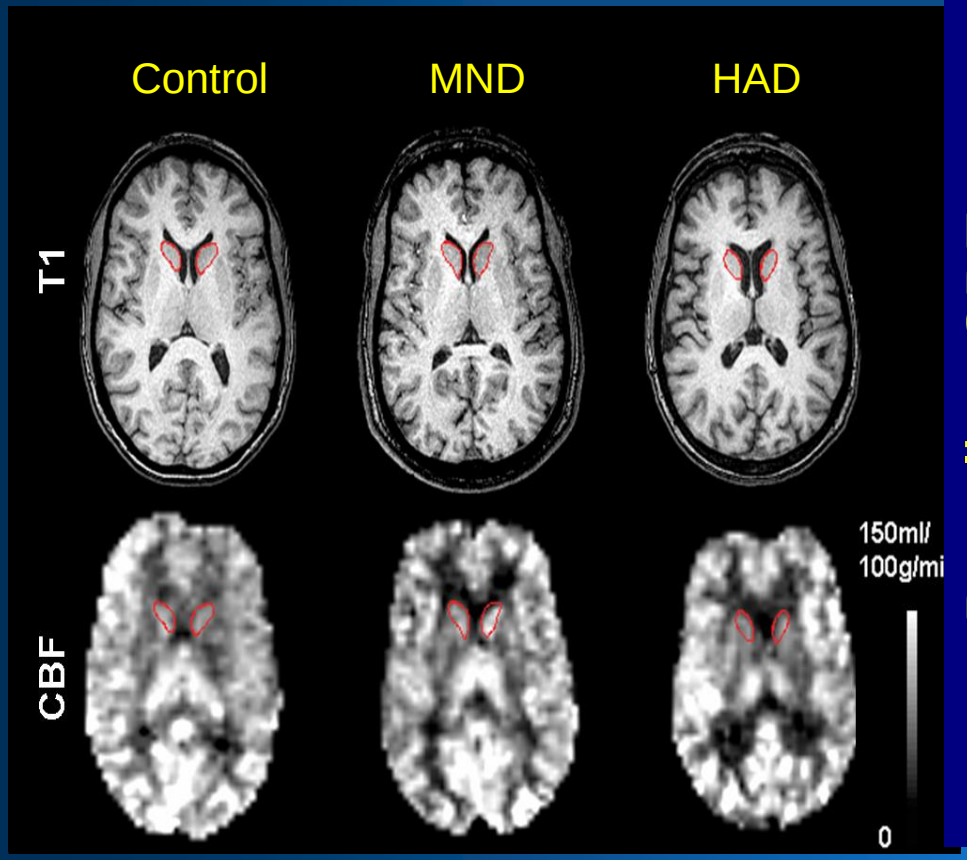
Sulcal CSF

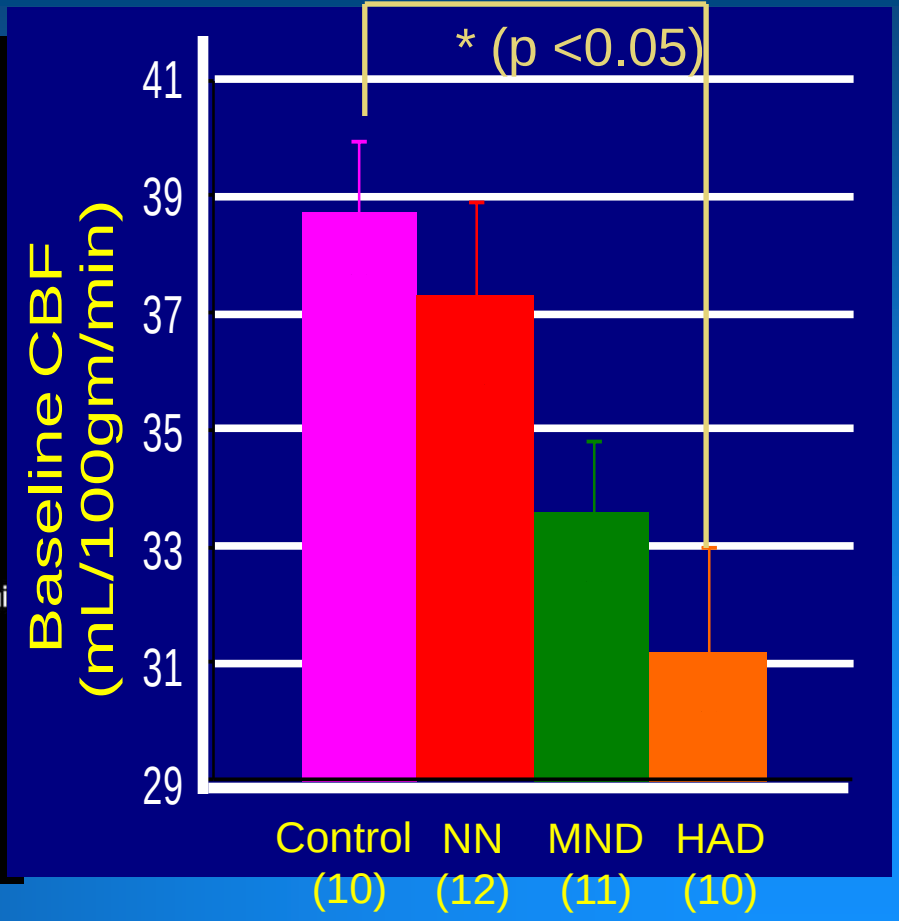
Representative spectra from the frontal lobe and BG in two HIV+ subjects with MSK 0 and MSK 1 (HIV dementia), respectively. Lower levels of glutamate and glutamamine.



Magnetic Resonance Imaging Vol 28, Issue 9. 2010 Mohamed M., et al

Effects of Neurocognitive Impairment on rCBF





Ances et al., *Neurology*, 2006

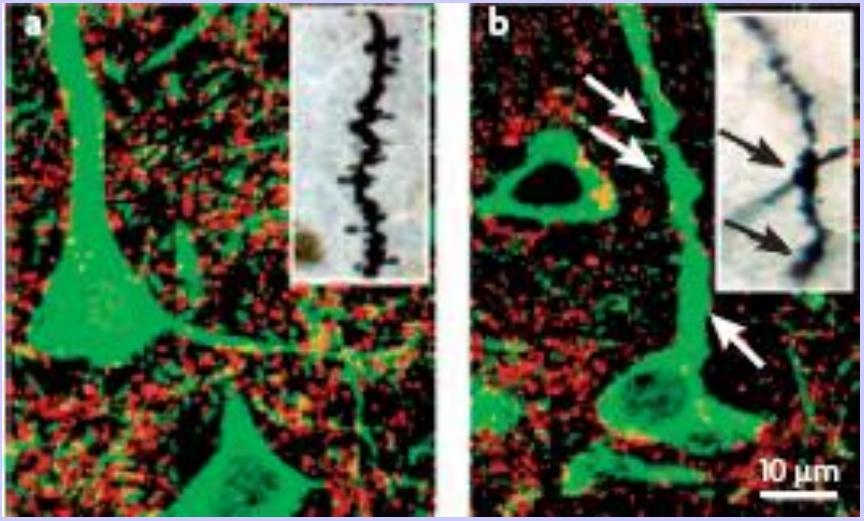
Implications for research and clinical practice

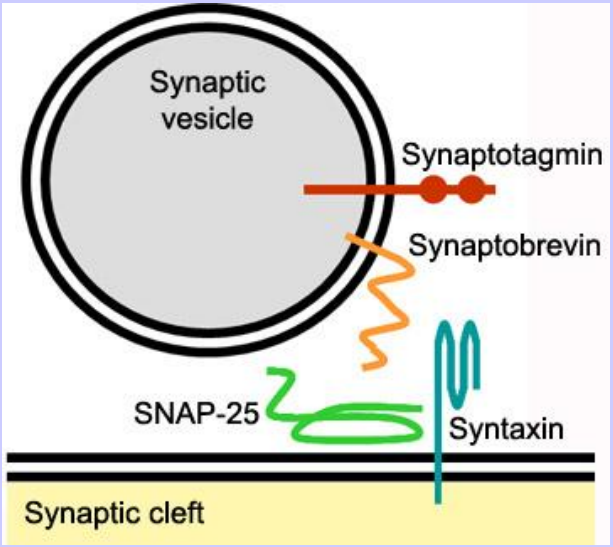
- Oxidative stress may play a critical role in sustaining neurological dysfunction, even in HAART-suppressed individuals
- Imaging measures show promise, but need further validation, and are resource-intensive
- Biomarkers based on oxidative stress may be correlative or even predictive of neurological progression ~ but can they be used as outcome measures in trials ?
- Novel targets based on oxidative stress are being actively explored

Synaptodendritic injury in HIV dementia may be reversible

Ellis, Langford, and Masliah.
Nature Neurosci, Review, 2007

Arek Szklarczyk,, JHU



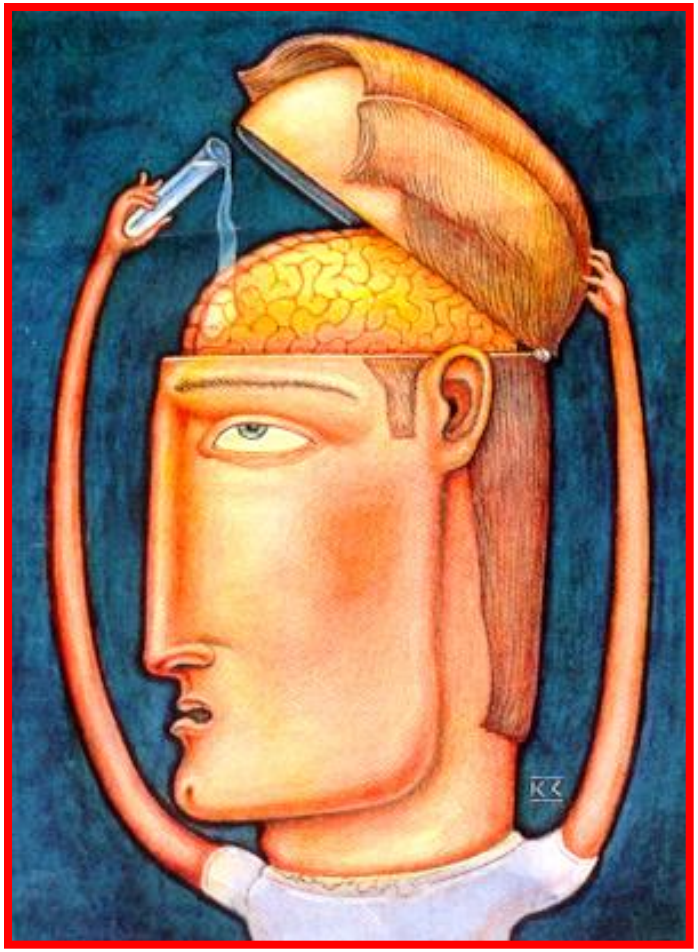


Excess proteolysis
of SYNAPTIC PROTEINS by MMP-7

Implications for research and clinical practice

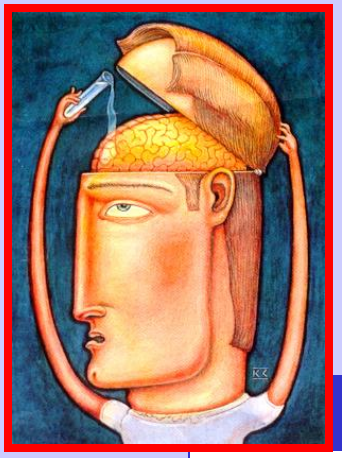
- Other mechanisms for neurological dysfunction may become more important ~ immune reconstitution, synaptic dysfunction
- Synergistic effects of drugs of abuse and co-infections, especially Hep C
- Effects of viral proteins on neurogenesis may have relevance for recovery of function

Choice of optimum HAART regimen for HAND



Does CNS penetration profile matter ?

- ***Sacktor N, 2001:*** **no regimen effect on cognitive improvement**
- ***Cysique L, 2004:*** **regimen effect only in cognitively impaired**
- ***Letendre S., 2007*** **~ index of CNS penetration**



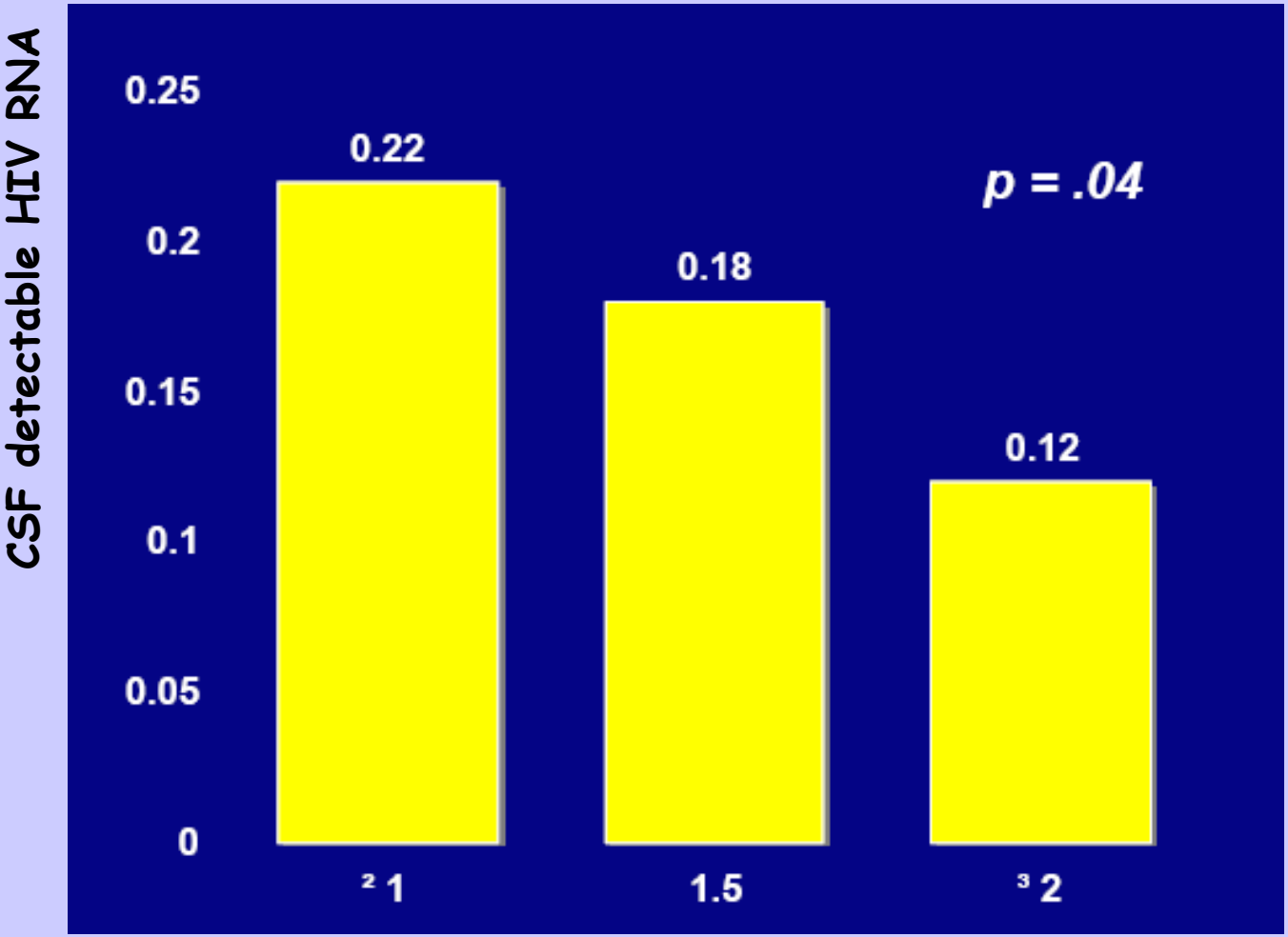
Antiretroviral Effectiveness

CNS Penetration-Effectiveness Score

LeTendre S., et al, Arch Neurol., 2007

	Good	Fair	Poor
	1	0.5	0
NRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine	Efavirenz	
PIs	Indinavir Indinavir-r Lopinavir-r	Amprenavir-r Atazanavir Atazanavir-r Darunavir-r	Amprenavir Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion Inhibitors			Enfuvirtide

Better CNS penetration of ART is associated with better CSF virological suppression



LeTendre S., et al, Arch Neurol., 2007

Implications for research

- CSF HIV RNA is not diagnostic or correlative in HAART-treated individuals
- Highly productive HIV encephalitis is uncommon in HAART-treated individuals, but astrocytes may serve as a reservoir for HIV
- CSF genotyping is not normally useful in the clinical management of HAND
- Relative CNS penetration of ARTs may be important in determining HIV suppression within the CNS

Lessons for HAND from Alzheimer disease and Huntington disease

- Focus on MCI and presymptomatic HD, before transition to symptomatic disease
- Screening tests can identify MRI and PET abnormalities in MCI, or even presymptomatic stages
- Therapy now targeting early stages of AD and HD

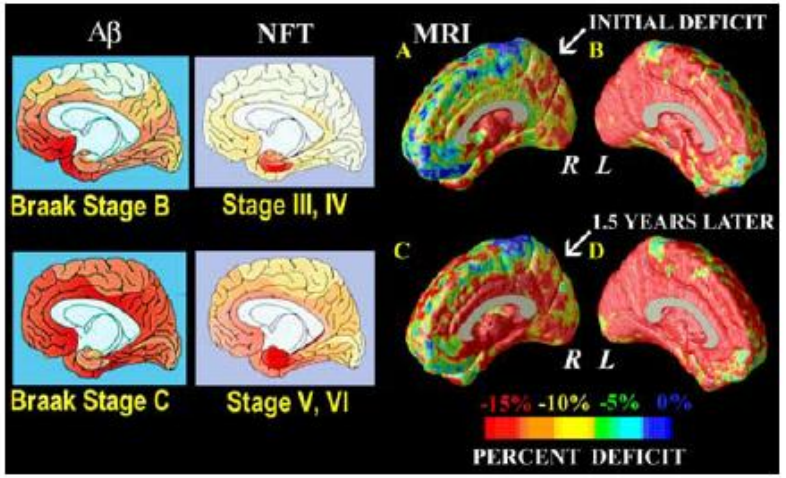


FIGURE 1. Gray matter deficits spread through the limbic system in moderate AD.

Specific Challenges for NeuroAIDS Researchers

- **Clinical**
  - **Develop clinically useful *predictive* markers**
  - **Design and conduct controlled clinical trials *rapidly and with large enough numbers to impact practice***

- **Develop new modes of treatment to**
  - **eliminate viral reservoirs in brain**
  - **control viral replication in brain**
  - **prevent glial cell activation**
  - **modulate inflammatory cascades and prevent neuronal cell loss**

Summary

- **The data suggest that we cannot be complacent and assume that systemic virological and immunological control will uniformly control CNS disease. We cannot ignore the very unique characteristics of the brain as a potential sanctuary for persistent infection and ongoing inflammatory damage**.
- **If indeed there is a 'hidden epidemic' of neurological disease in aviremic individuals, then we must develop and promulgate screening techniques to detect and track HAND and screening should be included in routine care.**
- **Integration of these data into treatment guidelines is important and the assumption that systemic treatment 'will take care of the brain' is dangerous.**
- **Finally, the population of HIV-infected individuals is aging and further study is needed to assess the concatenation of age-related and HIV-related cognitive deterioration.**