Neuro-AIDS in drug users

NIDA conference May, 2007

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HIV Neuroscience Program
NIMH Center for novel therapeutics
Johns Hopkins University

Neuro-AIDS in drug users

- Changes in HIV-D/MCMD/ANI definitions
- Changing phenotype of HIV-D with HAART
- Causes of comorbidity and fluctuations
- Impact of HAND on functional measures
- Surrogate biomarkers
- The treatment' gap' in HAND
- Design issues for treatment trials

Justin C McArthur JHU HIV
Neurosciences Program

Johns Hopkins University: HIV Neurosciences Program and NIMH Center for novel therapeutics

Patients, volunteers, other investigators ~ NARC, NEAD

Clinical research/imaging:
K Carter, D Esposito, M Pomper, N Sacktor, A Venkataramana, R Skolasky, A King, G Mbeo, R Hurley, M Fitchett, M Greene, J Creighton, L Abrams

Neuropathology/Cutaneous Nerve studies: C Pardo, M Polydefkis, D Thomas, P Hauer, JW Griffin, B Freeman, B Dearman, G Ebenezer

Neuroimmunology and Models:
K Conant, S Gartner, N Haughey, A Hoke, A Nath

SIV macaque: J Clements, C Zink, J Mankowski, Laast V

JHU AIDS Service/CFAR:
J Bartlett, R Moore, J Gallant

$$ ~ NINDS, NIAID, NIMH, NARC, NIDA

- Osteopontin
- Mmp7 and snap25
- Peruzzi and synaptic changes.

BRITISH JOURNAL OF PSYCHIATRY (2000), 177, 252–256

The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale

Two methods to assess fluctuating confusion in dementia

M. P. WALKER, G. A. AYRE, J. L. CUMMINGS, K. WESNES, I. G. McKEITH, J. T. O'BRIEN and C. G. BALLARD

2. Fluctuation

(a) Has the patient had a period or periods today when he/she seemed to be confused and muddled and then a period or periods when he/she seemed to be improved and functioning better?

Yes ____ **(1)** No ____ **(0)**

If yes, how much of the day was he/she confused?

(i) 25% (¼) of the day or less ____ **(1)**

(ii) 25–75% (¼–¾) of the day ____ **(2)**

(iii) 75% (¾) or more of the day ____ **(3)**

(b) How great was the difference today between the worst period of function and the best period of function?

(i) a slight degree of variation ____ **(0)**

(ii) a moderate degree of variation which had a clear effect on his/her ability to function at the same level throughout the day ____ **(1)**

(iii) a marked degree of variation which had a large effect on his/her ability to function at the same level throughout the day ____ **(2)**

CLINICAL IMPLICATIONS

- Brief standardised clinical scales are useful for identifying fluctuating confusion in patients with dementia.
- Standardised fluctuation scales may improve the accuracy of differential diagnosis between dementia with Lewy bodies and Alzheimer's disease.
- An electroencephalogram examination also contributes important information to the assessment of fluctuating confusion.

- Fluctuating cognition with pronounced variations in attention and alertness is considered an essential diagnostic feature of DLB.
- FC has been observed in approximately 80% of DLB patients. In the original Consensus Guidelines for the clinical diagnosis of DLB, McKeith et al. described such fluctuations as deficits in cognitive function and global performance that alternate with periods of normal or near-normal performance. The periodicity and amplitude of fluctuations are variable both between subjects and within the same individual. They are described as occurring rapidly, although fluctuations can also be slower (weekly to months). No typical diurnal pattern of fluctuation has been identified in DLB. In the early stages, cognitive disturbances ranging from mild to severe, occurring within a period of a few weeks to a few days and sometimes even within hours, may alternate with periods of normal cognitive performance. A characteristic circadian pattern of presentation has not been described for DLB because the periodicity and range of fluctuation is quite variable within the same individual. In fact, apparent sudden spontaneous remissions are sometimes possible in response to new, unexpected situations in the patient's life, although these are usually short-lasting.

New categorization of HAND

NIMH Frascati conference 2005: updated definitional criteria ~ addition of asymptomatic neurocognitive impairment

Assessment of definitional criteria

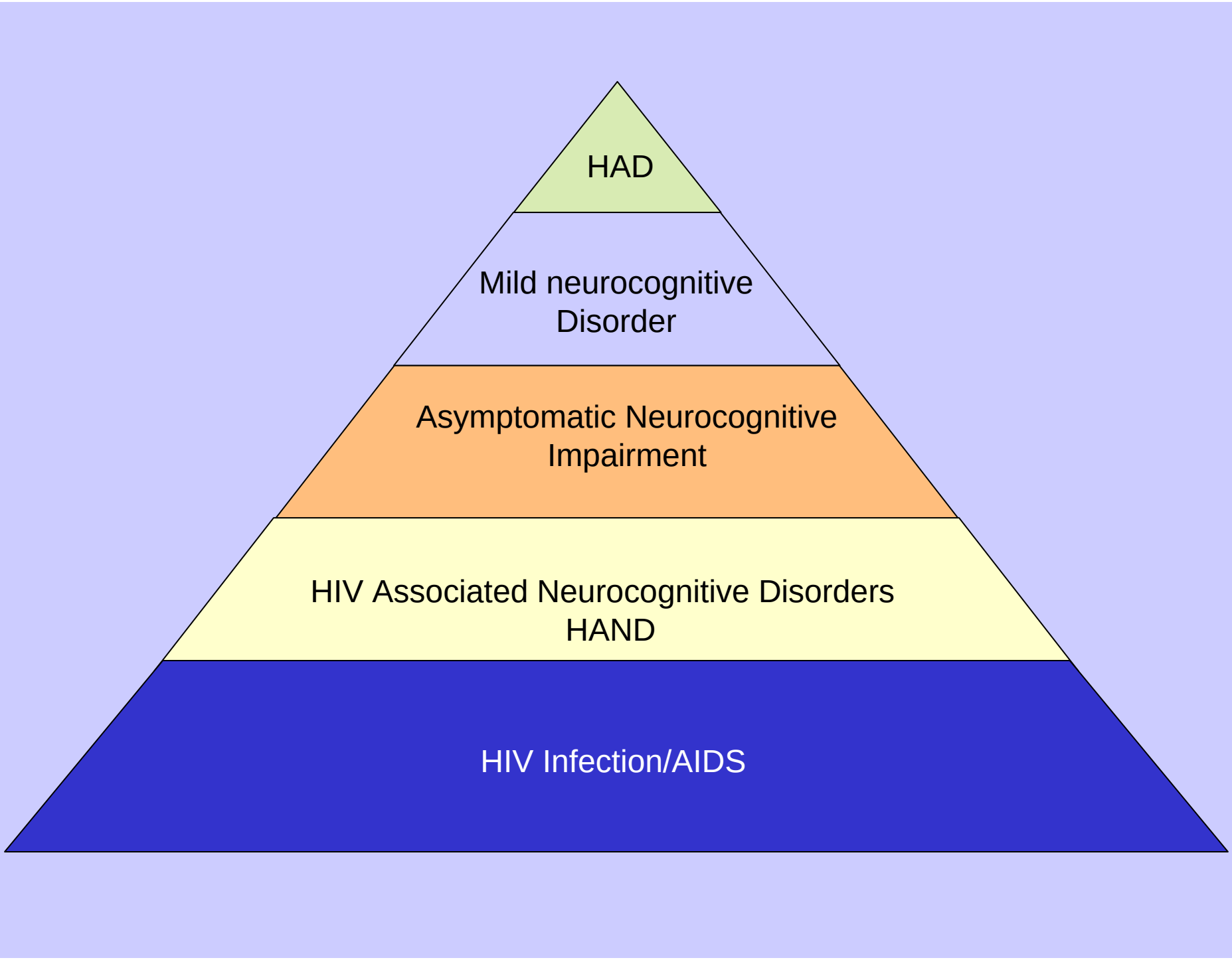
Cherner M., 2002

Improves diagnostic accuracy of AAN and HNRC nomenclatures with respect to post mortem presence of HIV encephalitis

Positive Predictive Power: Number of cases with NP impairment who eventually develop HIVE

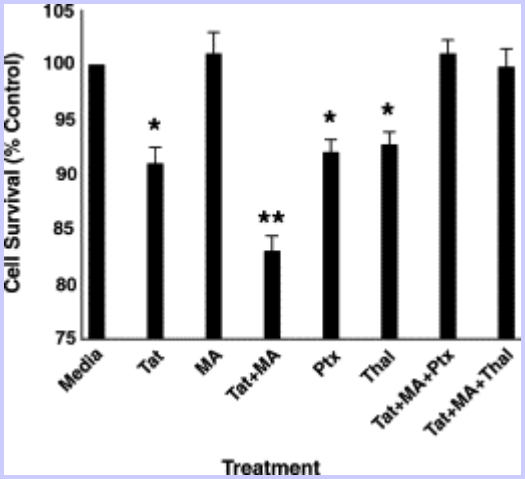
Using AAN criteria: 15/17 = 88%
Using HNRC criteria: 18/19 = 95%

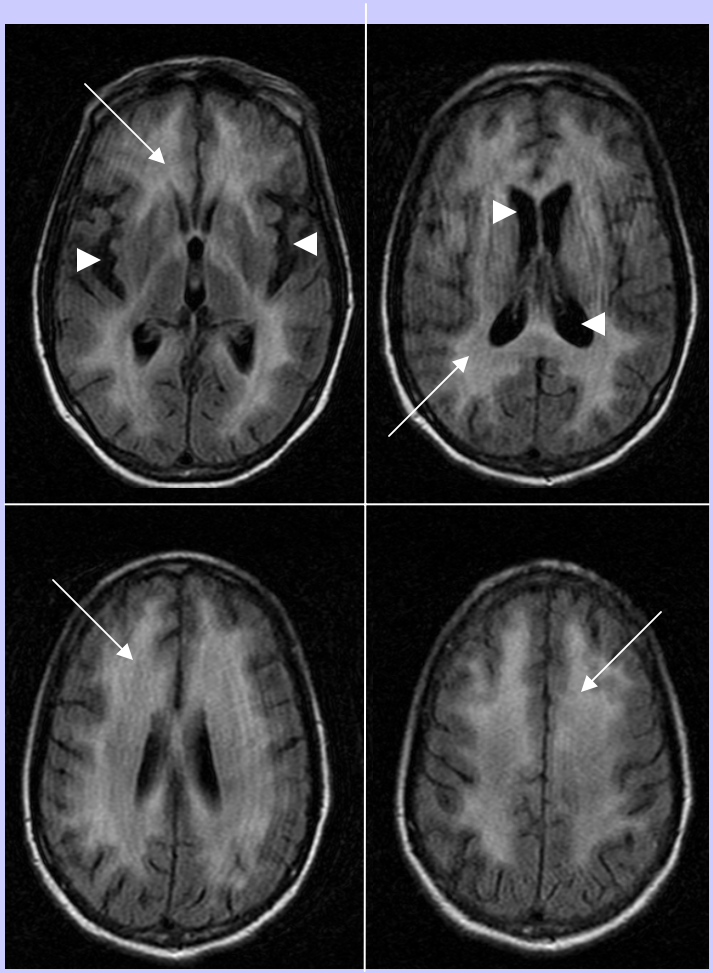
Frascati	Normal	Asymptomatic Neurocog. Imp.	MCMD	Dementia
Clinical MSK				
0	6	0	0	0
0.5	1	19	9	0
1	0	0	0	10
2	0	0	0	1

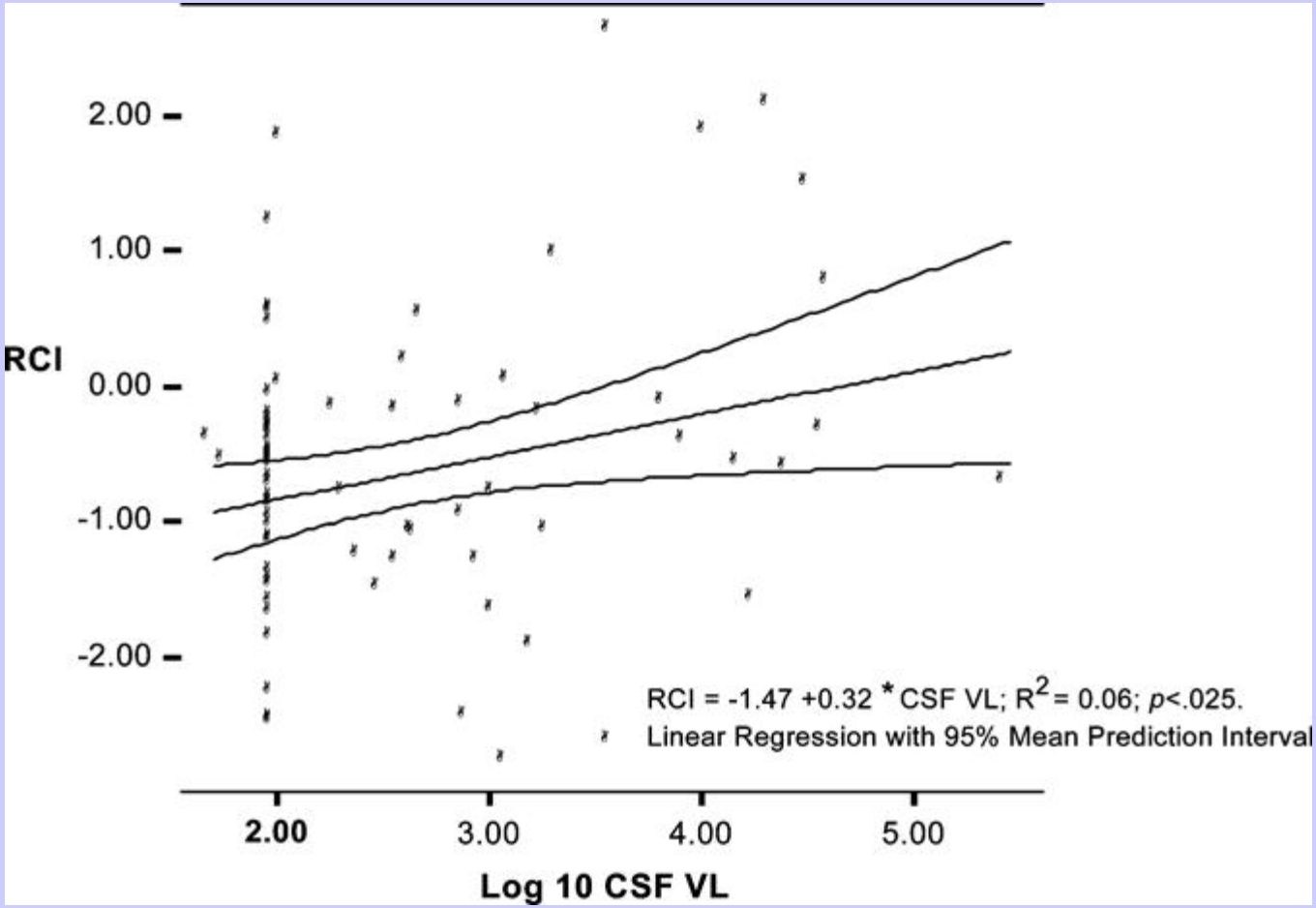

HAD
Mild neurocognitive Disorder
Asymptomatic Neurocognitive Impairment
HIV Associated Neurocognitive Disorders HAND
HIV Infection/AIDS

- previous studies demonstrated that the psychostimulant methamphetamine (MA) and the human immunodeficiency virus-1 (HIV-1) protein Tat interacted to cause enhanced dopaminergic neurotoxicity. The present study examined whether tumor necrosis factor-alpha (TNF-α) mediates the interaction between Tat and MA. In Sprague–Dawley rats, injections of Tat caused a small but significant increase in striatal TNF-α level, whereas MA resulted in no change. The increase in TNF-α induced by Tat + MA was not significantly different from that induced by Tat alone. Temporal analysis of TNF-α levels revealed a 50-fold increase 4 h after Tat administration. In C57BL/6 mice, Tat + MA induced a 50% decline in striatal dopamine levels, which was significantly attenuated in mice lacking both receptors for TNF-α. TNF-α synthesis inhibitors significantly attenuated Tat + MA neurotoxicity in hippocampal neuronal culture. The results suggest that Tat-induced elevation of TNF-α may predispose the dopaminergic terminals to subsequent damage by MA.

  Theodore S, et al: Neurobiology of Disease, September 2006, Pages 663-668


Cell Survival (% Control)
105
100
95
90
85
80
75
*
*
*
**
Media
Tat
MA
Tat+MA
Ptx
Thal
Tat+MA+Ptx
Tat+MA+Thal
Treatment




2.00
1.00
0.00
-1.00
-2.00
RCI
2.00
3.00
4.00
5.00
Log 10 CSF VL
RCI = -1.47 +0.32 * CSF VL; R2 = 0.06; p<.025.
Linear Regression with 95% Mean Prediction Interval

Lessons 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

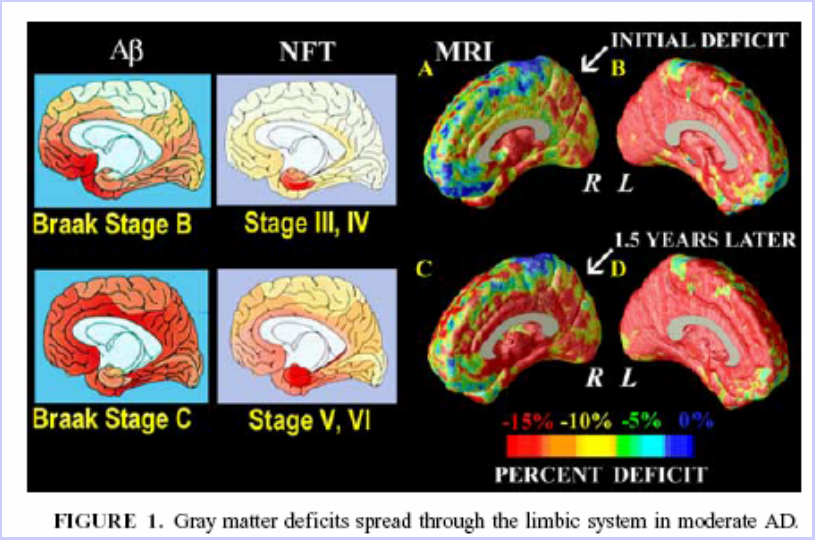


FIGURE 1. Gray matter deficits spread through the limbic system in moderate AD.

Table 1. Subclassification of mild cognitive impairment

Amnestic or single memory MCI	Usually progresses to AD
Multi-domains MCI (multiple domains slightly impaired)	Progresses to: AD, vascular dementia, might represent normal ageing
Single non-memory MCI	Progresses to: fronto-temporal dementia, Lewy body dementia, vascular dementia, primary progressive aphasia, Parkinson's disease, AD

AD, Alzheimer's disease; MCI, mild cognitive impairment.

Voisin T Curr. Opinion Neurol. 2003

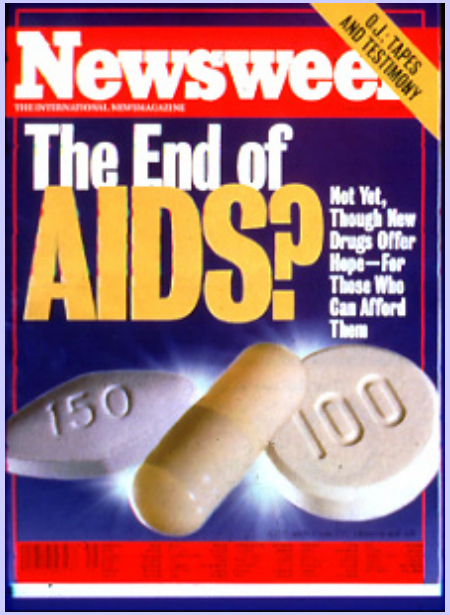
Recognition that there is a spectrum of HIV-associated neurocognitive disturbances

- Asymptomatic neurocognitive impairment (ANI)
- Minor neurocognitive disorder
- HIV-associated dementia

In HAART recipients, approx. 40-60% have measurable neurocognitive deficits !

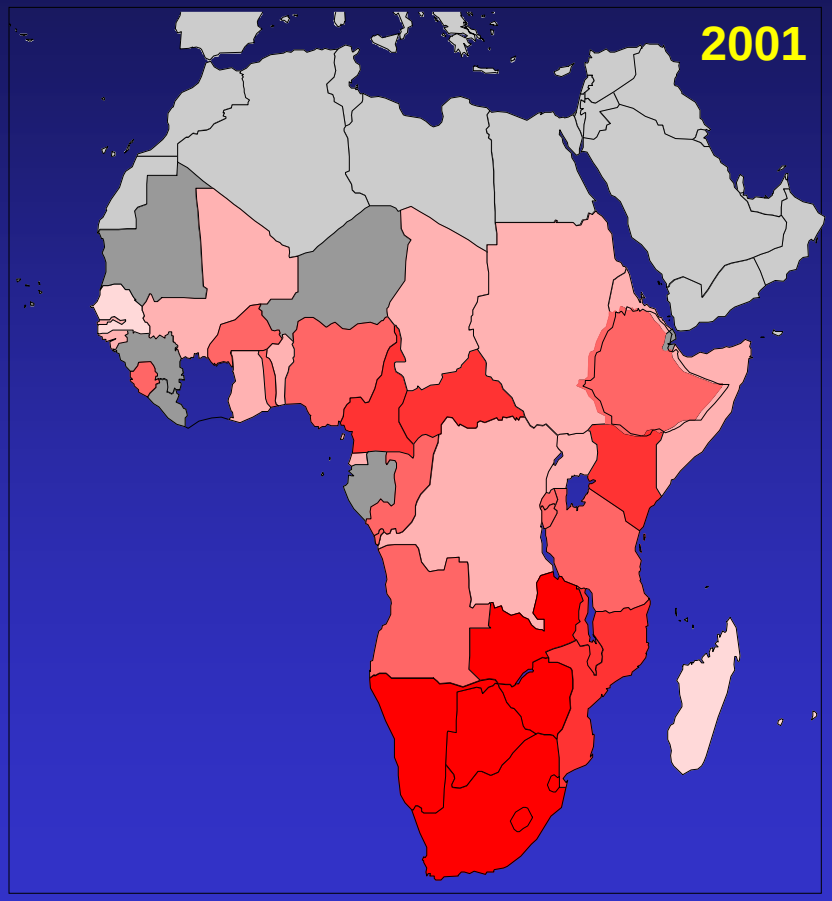
HIV and the AIDS Epidemic: 2007

- **Global 2005: 64m living with HIV/AIDS, 11m deaths, and *5.3 million new infections***
- ***HAART* introduced 1996 ~ ⬆ survival, but only reaching 5% of world's HIV+. Global AIDS initiative: 3m by 2005 thru' PEPFAR and other initiatives**
- **In 8 African countries, >20% adults are HIV+ decimating society**
- **In USA, HIV has become a chronic disease disproportionately affecting urban poor, African-Americans and Latinos.**
- **Concern that as OI's come under control, so HAND may become common cause of neurological disability globally**



HIV prevalence in adults in sub-Saharan Africa, 2001

- 20 – 39%
- 10 – 20%
- 5 – 10%
- 1 – 5%
- 0 – 1%
- trend data unavailable
- outside region

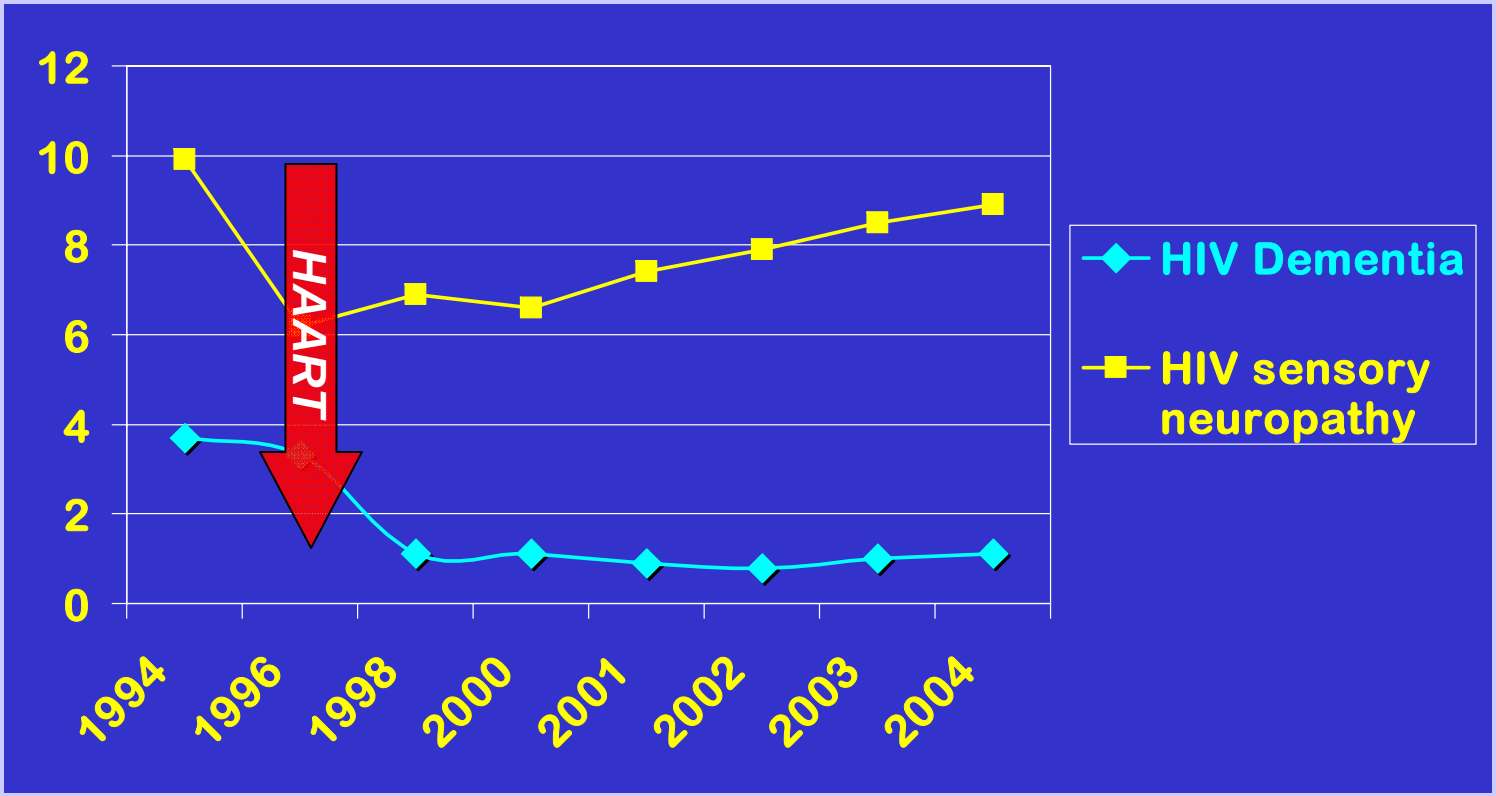


World Health Organization

Joint United Nations Programme on HIV/AIDS
UNAIDS
UNICEF • UNDP • UNFPA • UNDCP
ILO • UNESCO • WHO • WORLD BANK

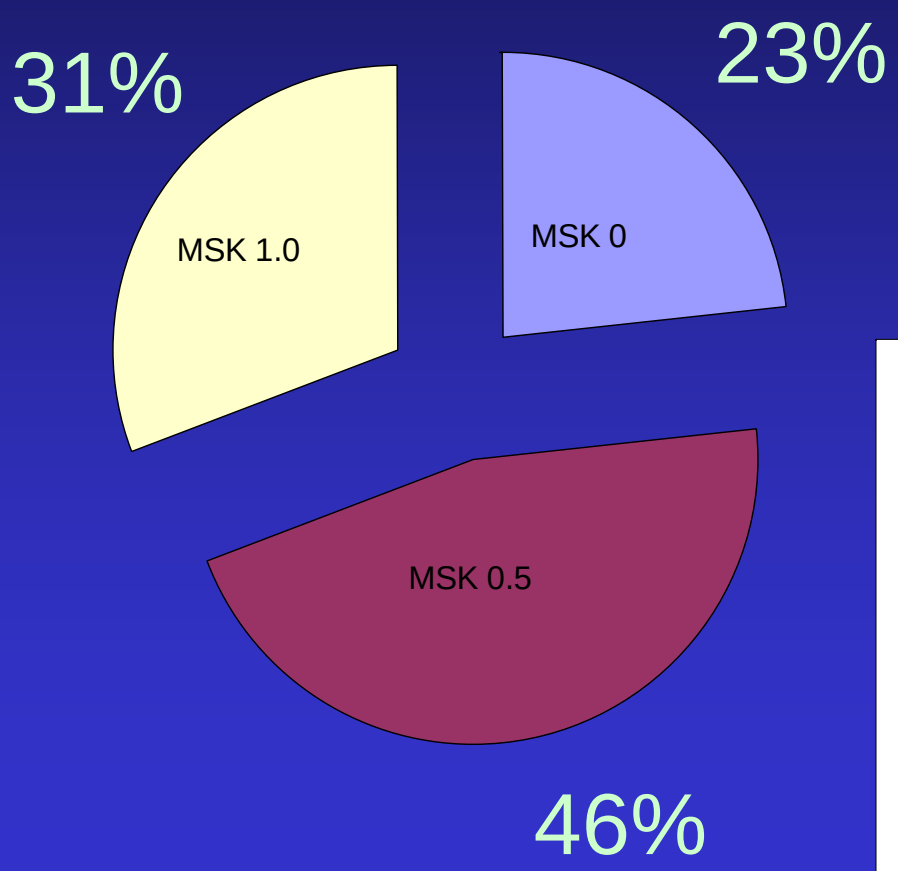
Incidence of HIV-associated Neurological Conditions Johns Hopkins HIV Clinical Cohort

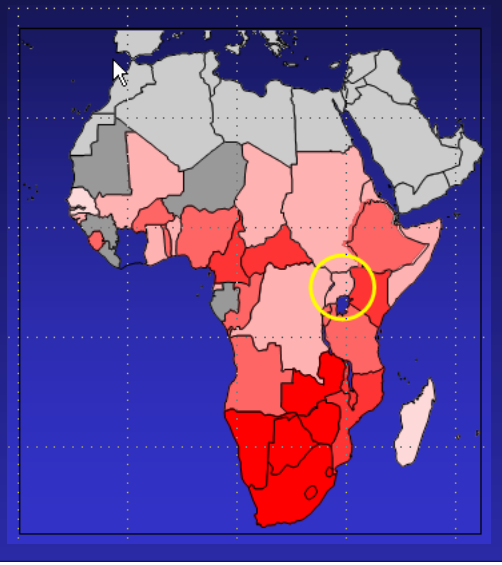
per 100 person years



Frequency of Dementia in Uganda cohort

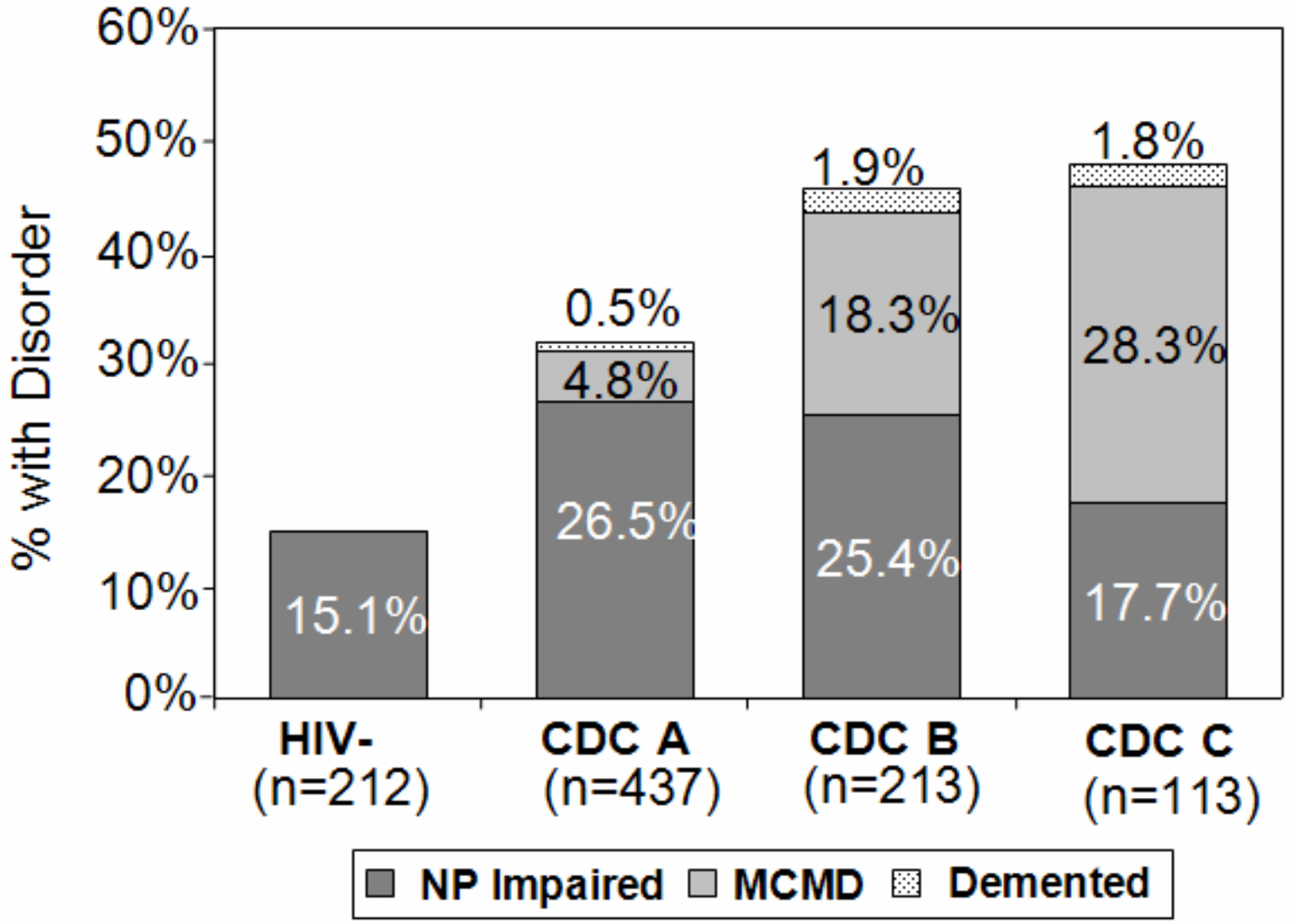
Wong, M: AAN 2004





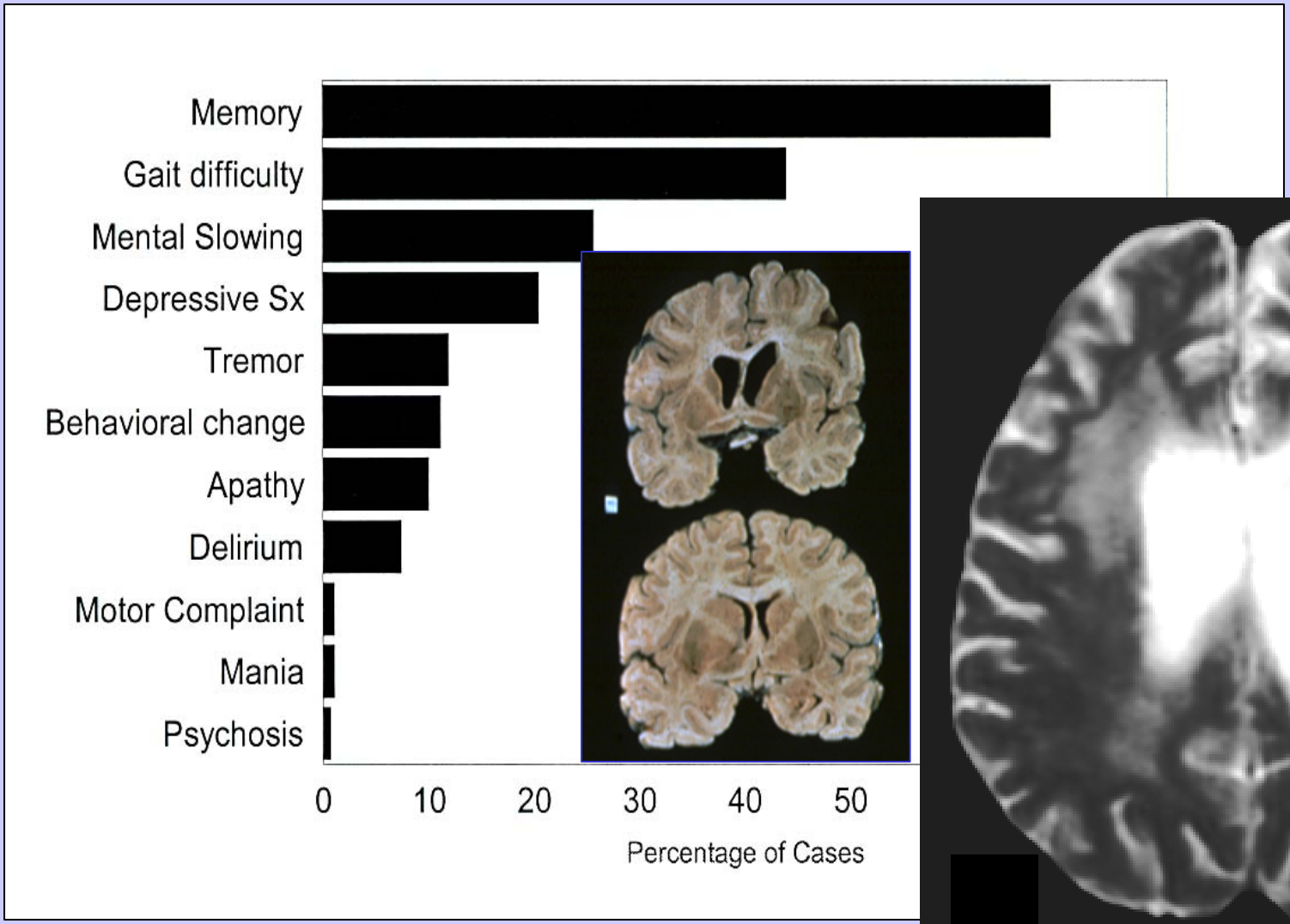
- MSK 0 (no impairment)
- MSK 0.5 (equivocal/subclinical impairment)
- MSK 1.0 (mild dementia)

Prevalence of Neurocognitive Disorders by Stage of HIV Disease



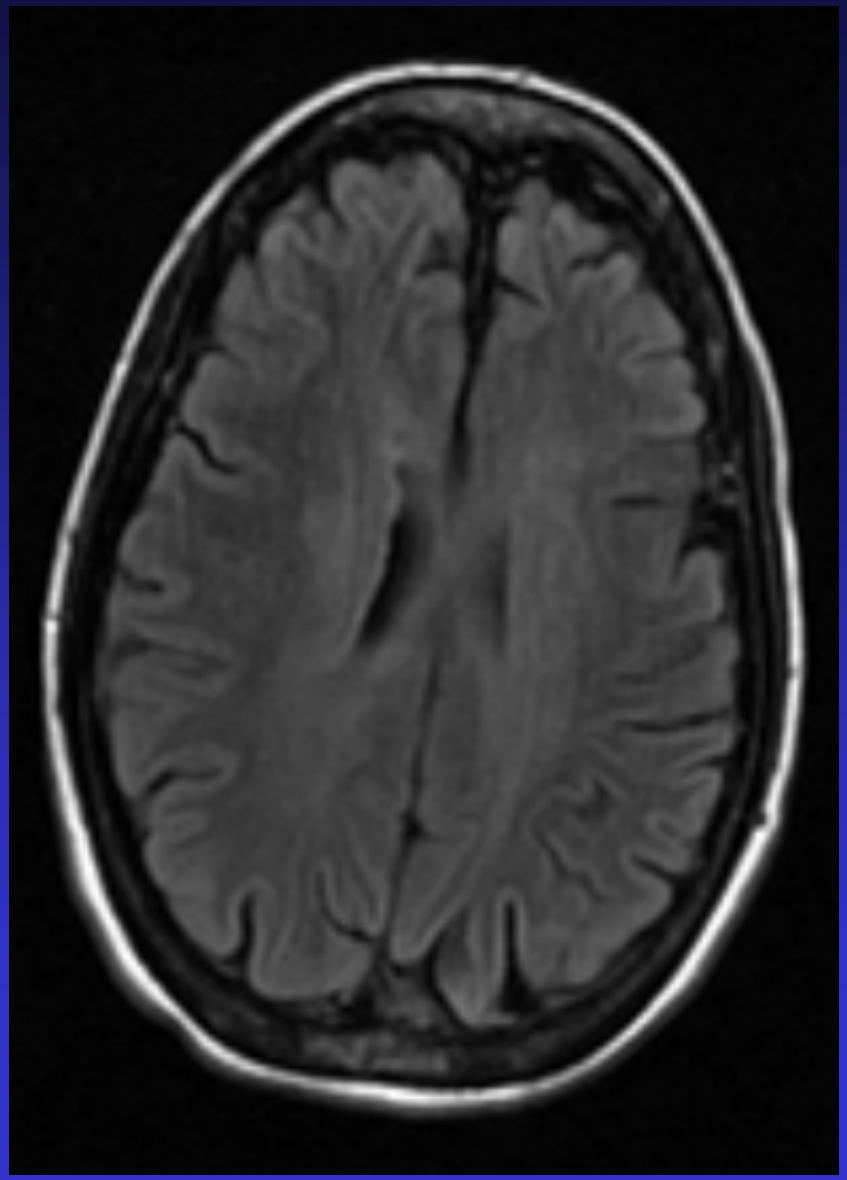
Courtesy of I Grant and R Heaton, HNRC, UCSD

Frequency of clinical features in JHU HIV-D cases (n=300)

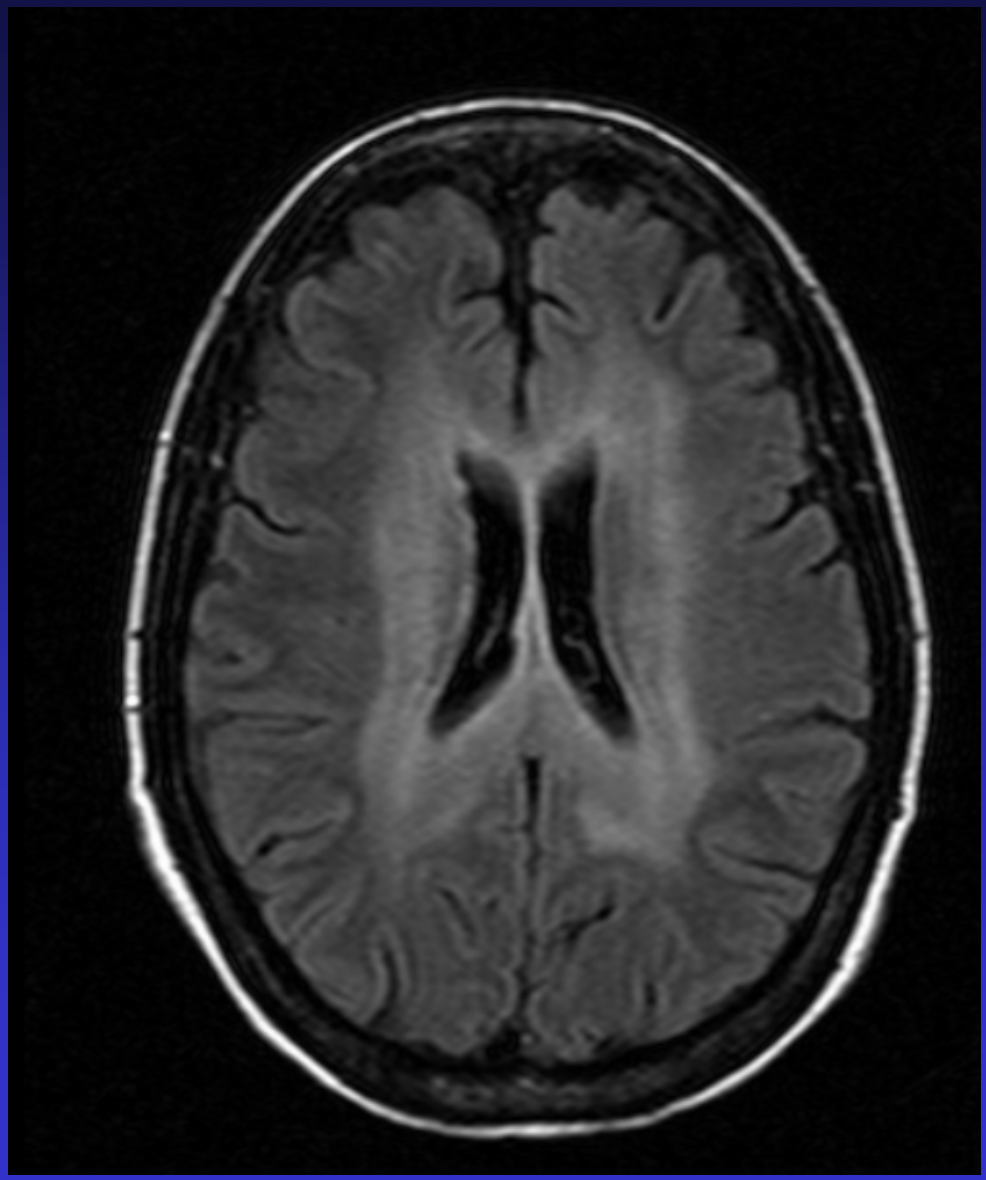


HIV-dementia: severe psychomotor slowing

12/2004



2/2005



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 or MCMD. Frequent transitions and reversals. Synaptodendritic injury with much less CNS infection.

HIV-associated cognitive impairment is prevalent….

Prevalence and patterns of neurocognitive disorders pre- and post-HAART

- Prevalence of neurocognitive impairment was similar pre- and post-HAART (41% and 38%). Patterns were different with more effects post-HAART on learning efficiency and complex attention, and fewer effects on attention, verbal fluency, and visuo-constructional deficits. *Cysique LA J Neurovirol, 2004*
- Prevalence of HAND possibly even increased pre- and post-HAART. *Sacktor N, 2002*

1994~monoRx 1998 72% HAART

AAN Classification			
Normal	25.0	30.4	
MCMD	47.7	33.9	**0.002**
HIV-D	27.3	35.8	

Pattern of pre-HAART cognitive deficits. *Cysique LA, J Intnl. Neurpsych. Soc, 2006*

- Symptomatic HIV+: global mild cognitive impairment, with moderate impairment in attention, psychomotor speed, motor coordination and learning
- AIDS: global moderate cognitive impairment with

t Neuropsychol Soc. 2006 May;12(3):368-82.

uropsychological profile of symptomatic AIDS and ADC patients in the pre-HAART era: a meta-analysis.

e LA, Maruff P, Brew BJ.

of Medicine, St. Vincent's Clinical School, University of New South Wales, Sydney, Australia. lcysique@ucsd.edu

ins essential to document the neuropsychological profile of acquired immunodeficiency syndrome (AIDS) dementia complex (ADC) and m immunodeficiency virus (HIV)-associated neurocognitive impairment by quantifying the magnitude of impairment across eras of treatmer e introduction of the highly active antiretroviral therapy (HAART), there is evidence of changes in aspects of ADC. To allow quantitative a isons with the HAART era studies, we developed a summary of neuropsychological performance acquired in pre-HAART era studies in ad n and ADC. Using a meta-analytical procedure and a test nomenclature that accounts for task complexity, we found that individuals with matic infection (but no AIDS) demonstrated a global mild level of cognitive impairment, except for the domains complex attention/psych motor coordination, and learning, which showed moderate impairment. Individuals with AIDS demonstrated a global moderate level of co ent with a predominance of deficits in attention, complex attention/psychomotor speed, learning, motor coordination, with additional de nemory and reasoning. Individuals with ADC demonstrated the most severe cognitive disturbances in domains of learning, motor coordi al deficits in veibal fluency and verbal memory. Moderate impairment was evidenced in domains of complex attention/psychomotor spee and visuospatial functions were relatively preserved. The profile of deficits in ADC suggests that it may not be only interpreted as a wor mpairment that is seen in the AIDS and symptomatic stages of HIV disease but that there are also additional deficits suggestive of an al enetic process(es).

Patterns of pre-HAART cognitive deficits. *Cysique LA, J Intnl. Neurpsych. Soc, 2006*

- Symptomatic HIV+: global mild cognitive impairment, with moderate impairment in attention, psychomotor speed, motor coordination and learning
- AIDS: global moderate cognitive impairment with predominant deficits inattention, complex attention/psychomotor speed, learning, motor coordination, verbal memory and reasoning
- HIV-D: most severe deficits in complex attention/psychomotor speed, and additional deficits in verbal fluency and verbal memory. Relative preservation of naming and visuospatial function
- *Suggests that HIV-D deficits are a worse form of the milder impairment that is seen in AIDS and symptomatic HIV infection, but that there are also additional deficits*

HIV-associated cognitive impairment is dynamic….

Transitions from NEAD I (1998) to NEAD II (2005)

	.	NEAD2 Normal	NEAD2 MCMD	NEAD 2 Mild HAD	NEAD 2 Moderate	NEAD 2 Severe
.		0	4	1	1	Worse
NEAD I Normal		0	5	0	1	0
NEAD I MCMD		*8*	24	13	3	3
NEAD I Mild		*2*	*10*	1	1	0
NEAD I Moderate		*1*	*5*	*0*	2	1
NEAD I Severe		*1*	*6*	*3*	*0*	0

Better

…and persistent

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*

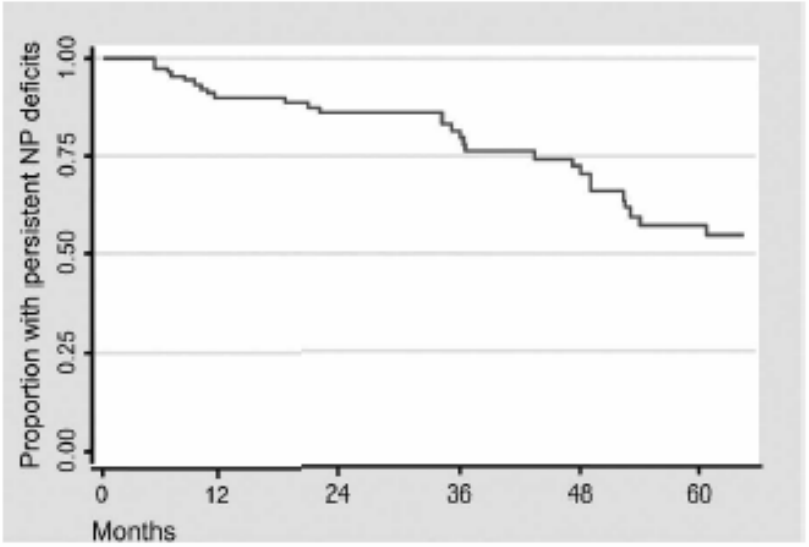


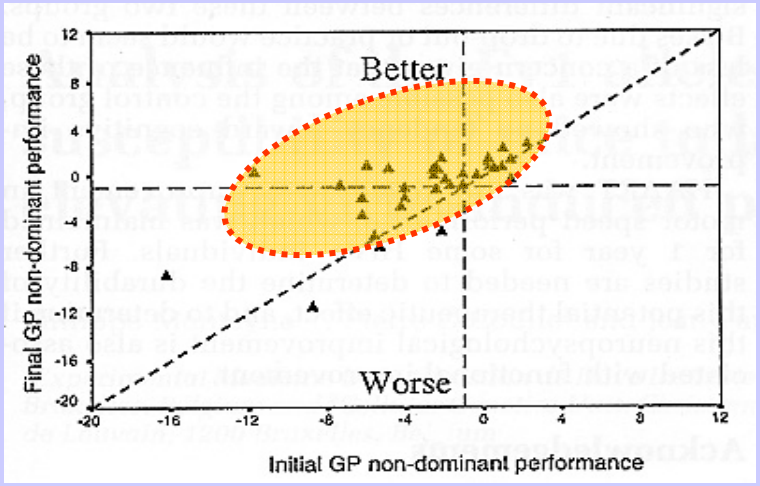
FIGURE 1. Kaplan-Meyer plot of the probability of showing persistent NP deficits by month of follow-up in the 94 study patients with HIV-related NCI treated with HAART.

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.

Patterns of HIV-dementia in HAART era



- ***"Progressive" HAD*** (equivalent to "subacute" or "chronic active")
- ***"Stable HAD"*** (fixed neurological deficits; previously called "chronic inactive")
- ***"Improving HAD"*** (improving or regressing neurological deficits)
- ***"Fluctuating HAD"*** (fluctuating neurological deficits)

Other 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

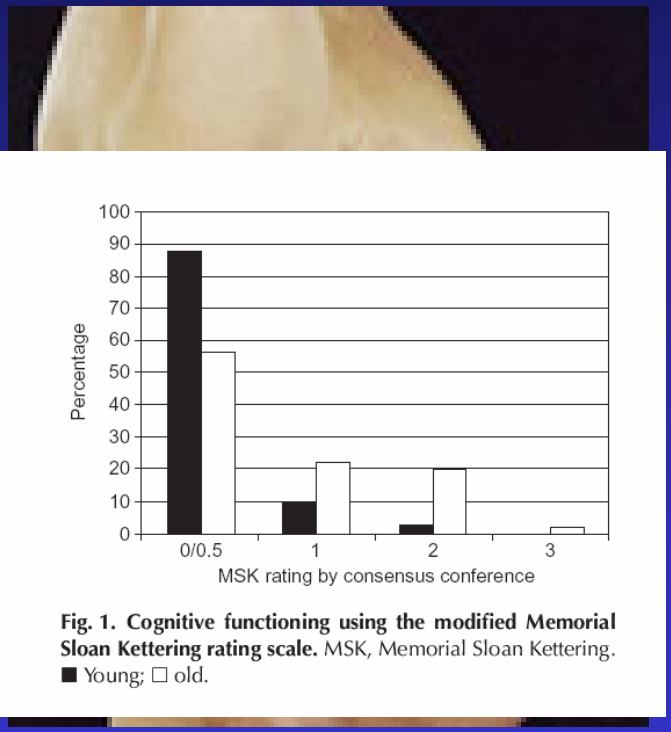
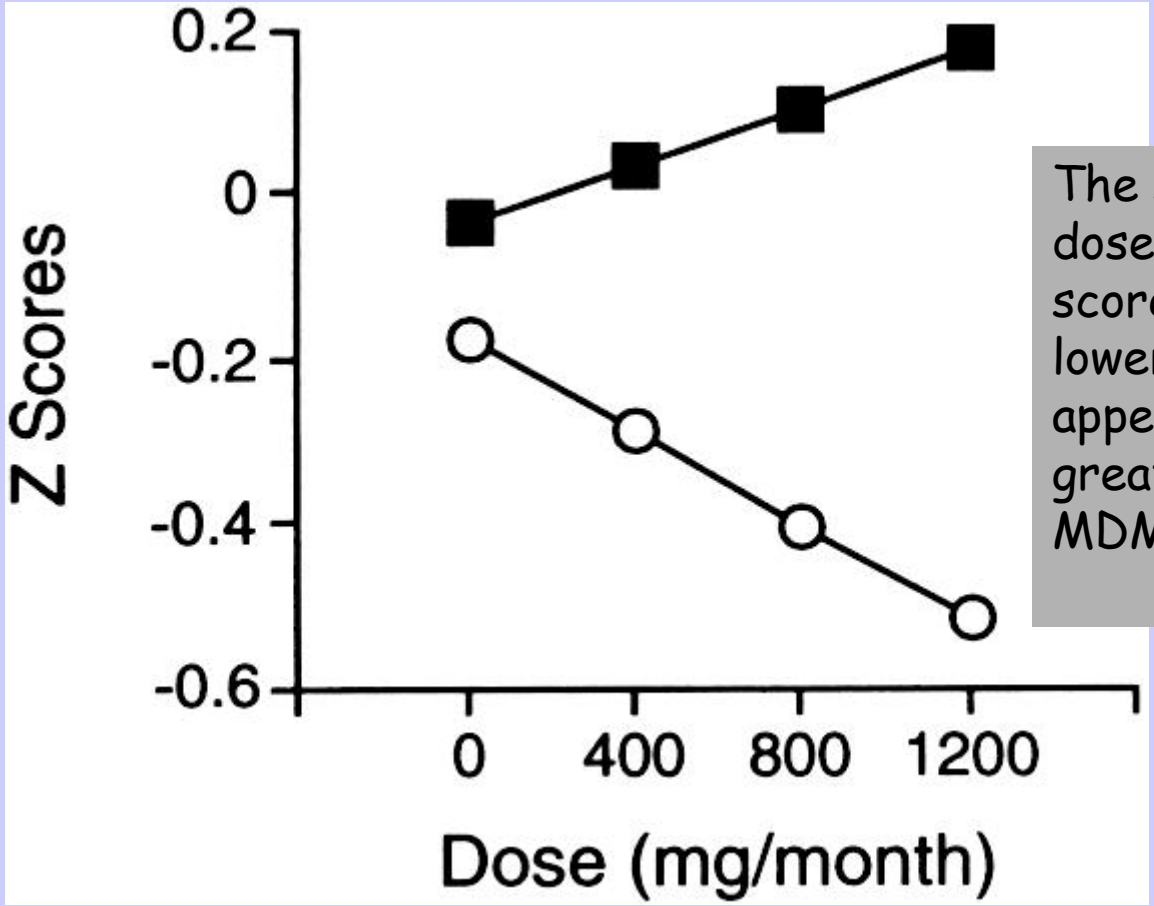


Fig. 1. Cognitive functioning using the modified Memorial Sloan Kettering rating scale. MSK, Memorial Sloan Kettering. ■ Young; □ old.

Memory impairment in abstinent MDMA ("Ecstasy") users

Bolla, Karen I. PhD; McCann, U. MD; Ricaurte, G. A. MD, PhD

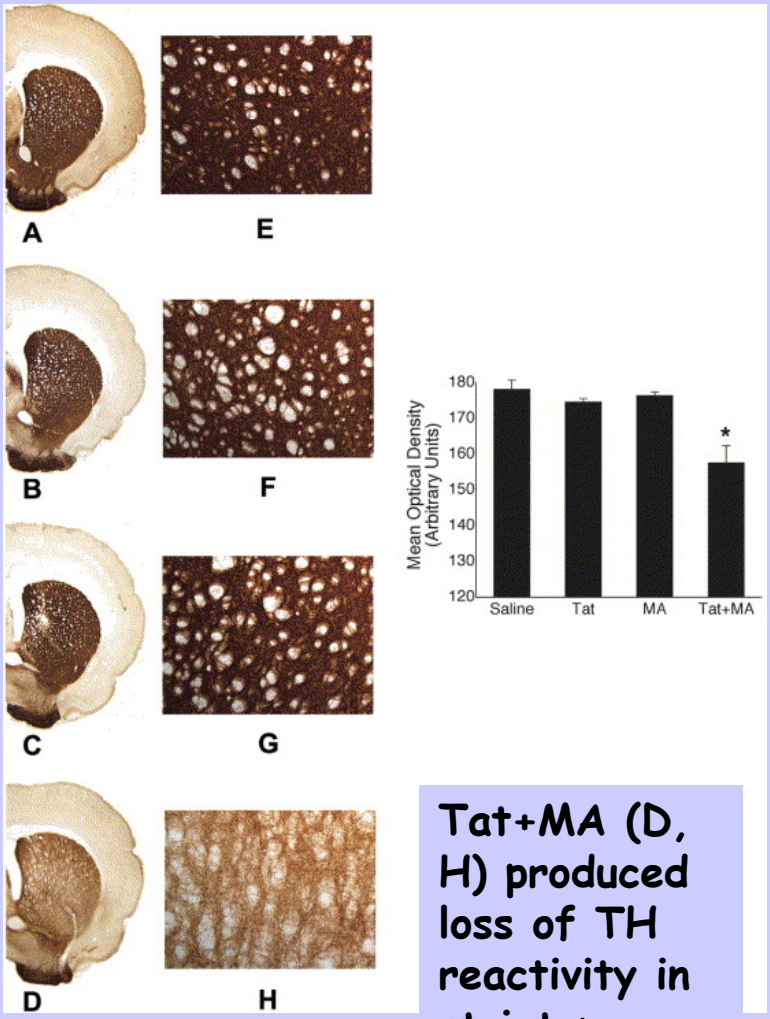


The study reveals a dose × vocabulary score interaction, ie lower vocabulary appeared to have a greater impact from MDMA.

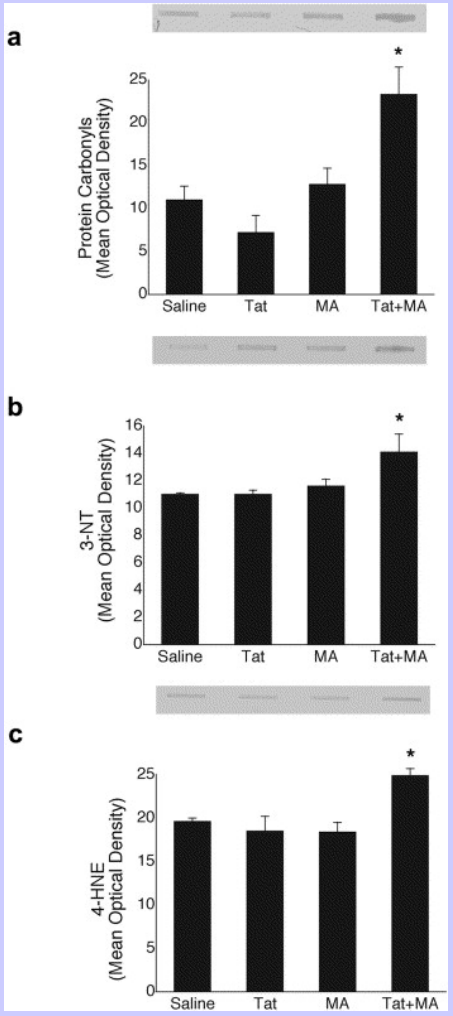
Neurology. 1998 Dec;51(6):1532-7

Effect of Tat+Methamphetamine treatment on striatal TH immunoreactivity

Theodore S. et al, 2006



Tat+MA (D, H) produced loss of TH reactivity in striatum



Effect of Tat+MA treatment on markers of oxidative stress in the striatum. Striatal synaptosomes were analyzed by a slot-blot method for the presence of protein carbonyls (a), 3-NT (b) and 4-HNE (c).

1997)

ns in the hippocampus of adult rats during chronic ethanol treatment and correlations to behavioral impairments

stin Wirkner [a] and Jörg Schramek [a]

v/v) ethanol over a period of 4, 12, and 36 weeks produced distinct alterations of the glial fibrillary acidic protein immunoreactivity (GFAP-IR) of dorsal hippocampal astr
of the astrocytes. Down-regulation of the total GFAP-IR was measured in all examined brain regions after 36 weeks of ethanol treatment. Prolonged ethanol treatment i
e cells. Regional differences in the vulnerability to the neurotoxic effects of chronic ethanol intake over 36 weeks were found: CA3 > CA1 + CA2 ⊐ CA4 > GD. In agreen
nd. The acquisition of maze performance using a complex elevated labyrinth was deteriorated after 36 weeks of ethanol treatment, suggesting a deficit in learning and m
uctural and functional changes produced by chronic ethanol treatment.

Time course of fluctuations in different dementias

Dementia of Lewy body type ~ hours

HIV-dementia ~ weeks/months

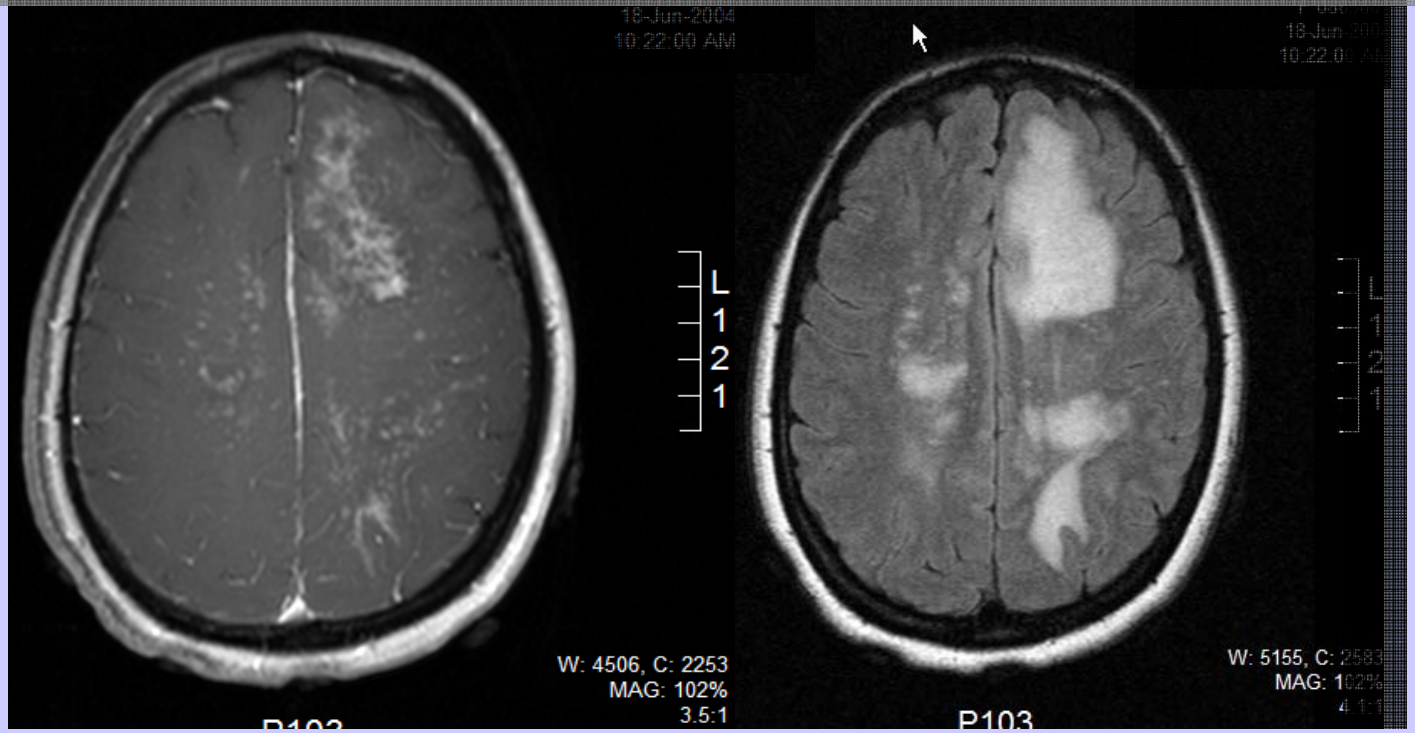
Alzheimer ~ months/years

Causes of fluctuations in HIV dementia

- Substance abuse
- Depression and fatigue
- ART effects/adverse effects
- Immune reconstitution syndrome (IRIS)
- Non-IRIS cytokine effects
- CNS ‘escape’
- Mitochondrial effects/oxidative stress
- Astrocyte and symaptodendritic effects

CNS immune restoration syndrome

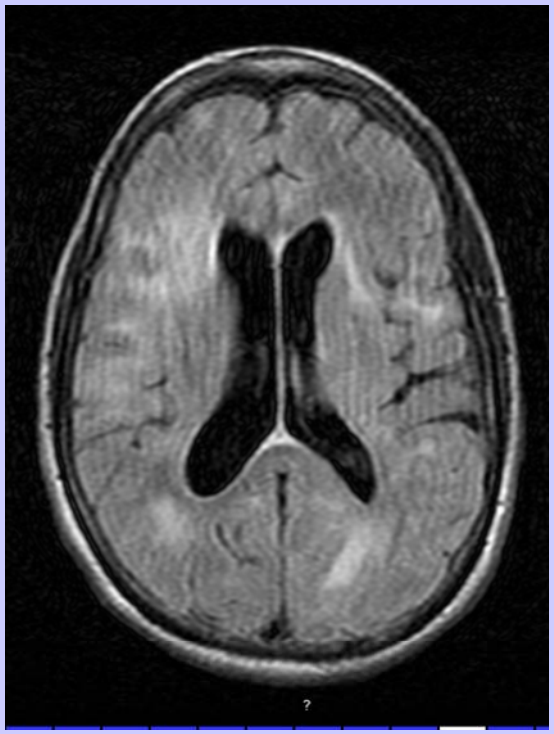
subacute onset of a left hemiparesis; no fever or h/a; CSF JCV +



CD4 count: 9 rising to 157
pHIV: 4.7logs dropping to undetectable

CNS “escape”

- Acute neurological syndrome: usually encephalopathy with no CNS OI
- Plasma HIV RNA levels << CSF
- Differential includes CMV encephalitis, HSV encephalitis, IRS
- Usual causes: non-CNS penetrant ART’s or poor adherence



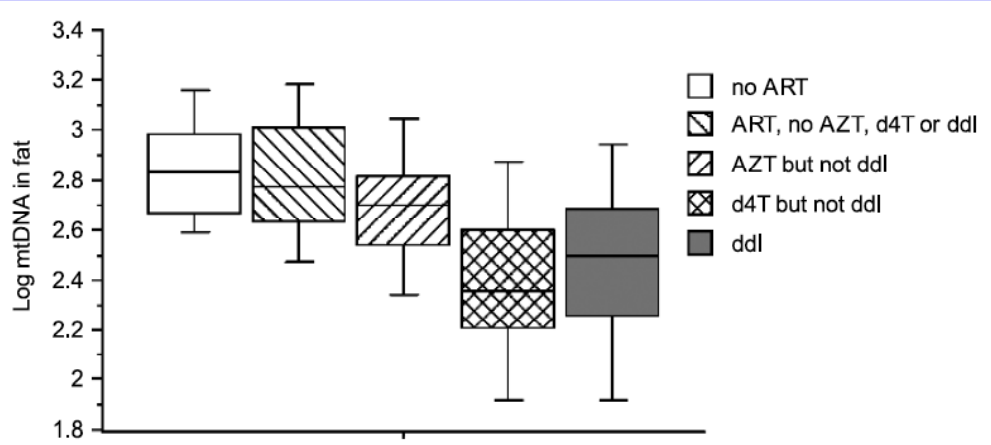
Wendell K, McArthur JC, CID 2003

Case KE: *reflecting poor CNS penetration ?*

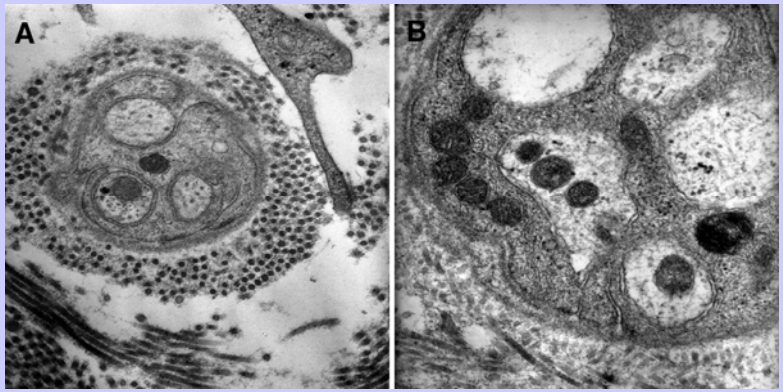
- 47 man with 6 months history of progressive dementia, gait imbalance, and reduced verbal output.
- CD4 42, started Kaletra+Truvada 3 months before LP
- CSF: 2 wbc, protein 62,
  - CSF HIV 76k
  - plasma HIV 481

CNS escape

Mitochondria effects from ART exposure ~ *? CNS relevance*



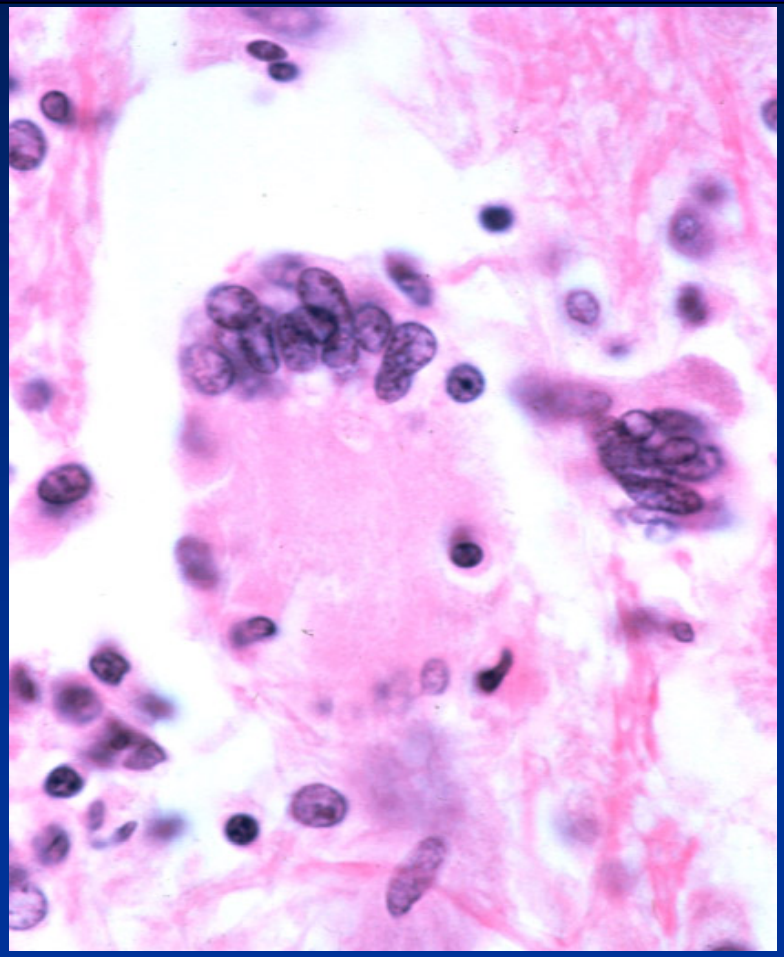
Log copy number of mtDNA per cell in subcutaneous limb fat by current NRTI exposure status. ART indicates antiretroviral therapy
(from Cherry C, JAIDS 2006 42(4):435-40).

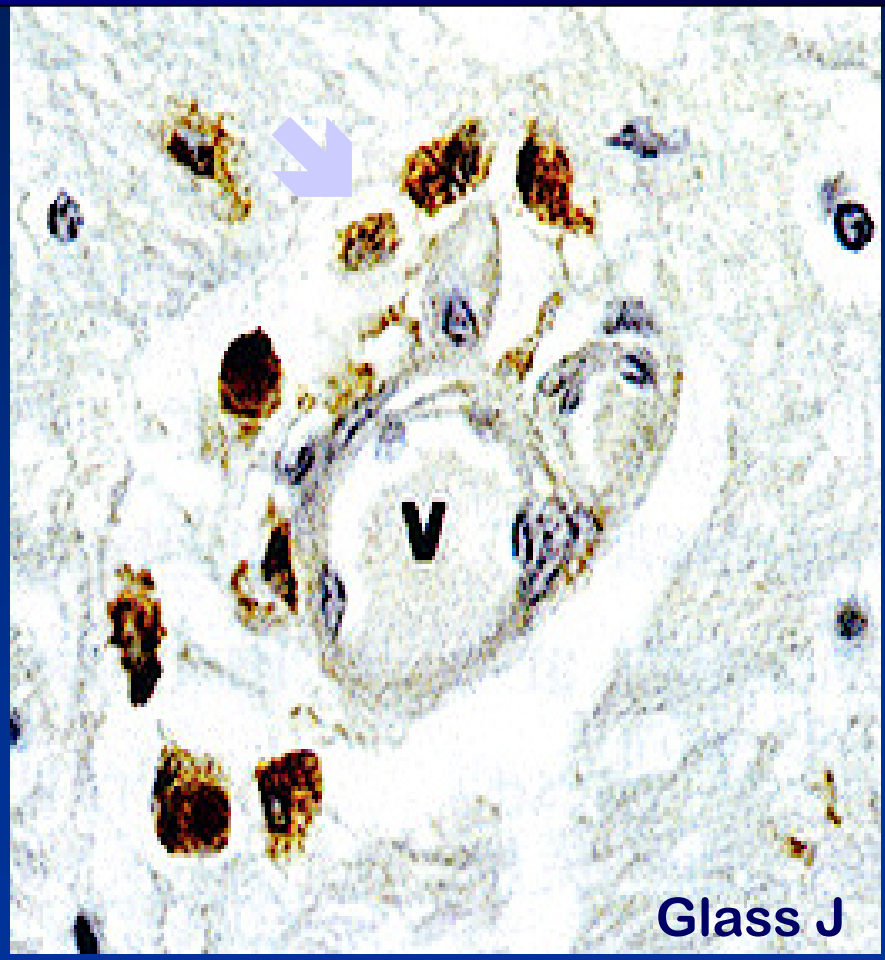


(A) A healthy Remak bundle at the papillary dermis containing 3 axons surrounded by collagen. (x25K); (B): HIV-associated sensory neuropathy. Remak bundle with dilated unmyelinated axons showing watery axoplasm and granular debris.
From Ebenezer G. submitted Brain 2007

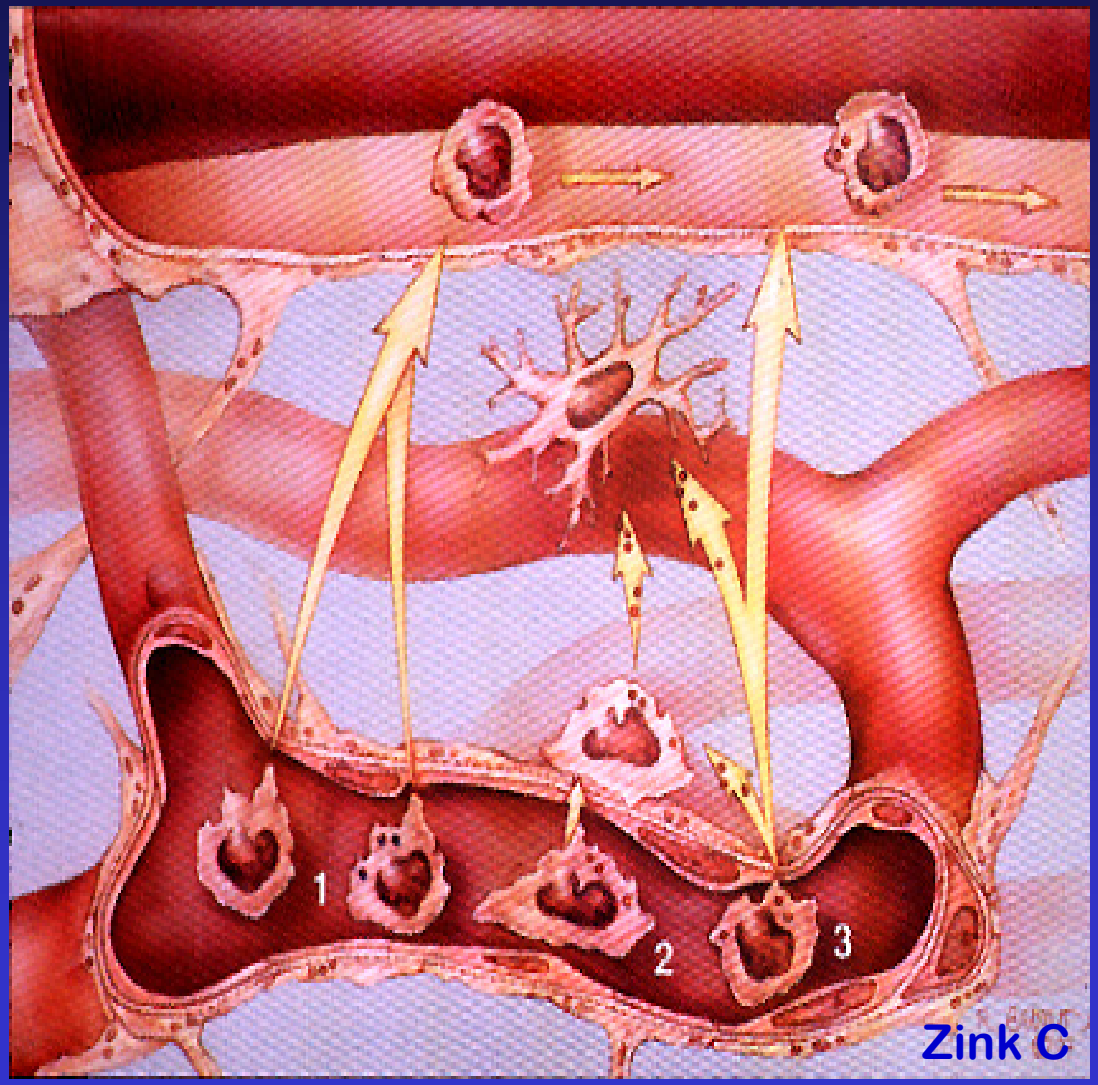
Perivascular macrophages are the principal CNS targets of productive SIV and HIV infection:

Takahashi K, 1996; Williams K, 2001; Gartner S, 2001



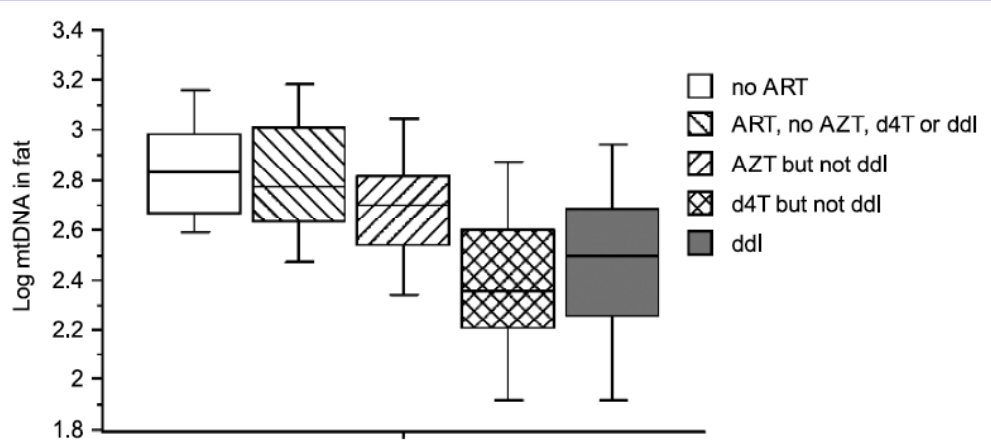


Pathogenesis of HIV-associated dementia

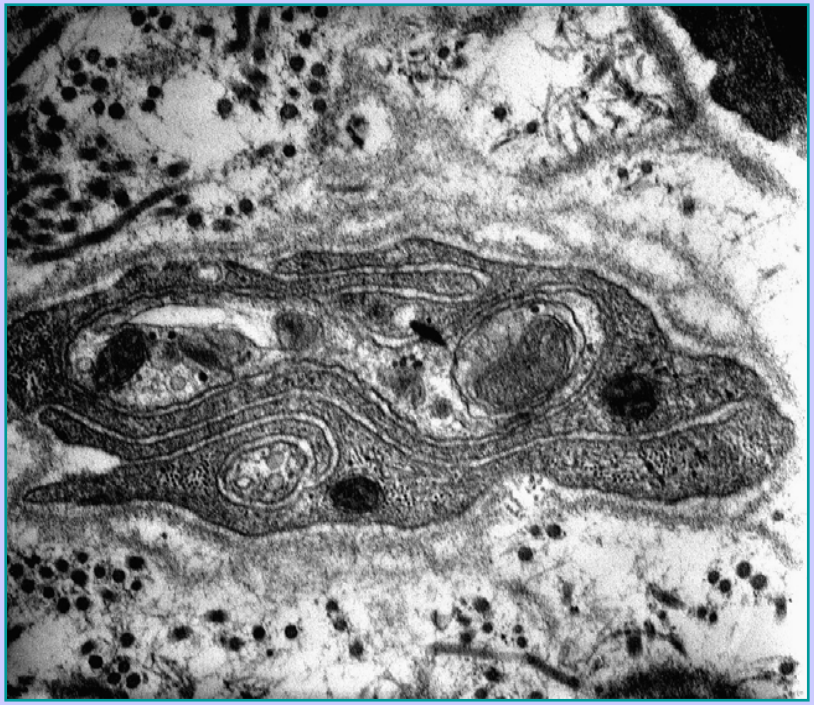


- Circulation and ingress of activated monocytes
- Productive CNS infection established, with reservoir in macrophages and astrocytes
- Release of inflammatory mediators and toxic HIV proteins (tat, gp120)
- Astrocytosis, BBB dysfunction and neuronal dysfunction, synaptic simplification

Mitochondria effects from ART exposure ~ *? CNS relevance*



Log copy number of mtDNA per cell in subcutaneous limb fat by current NRTI exposure status. ART indicates antiretroviral therapy
(from Cherry C, JAIDS 2006 42(4):435-40).

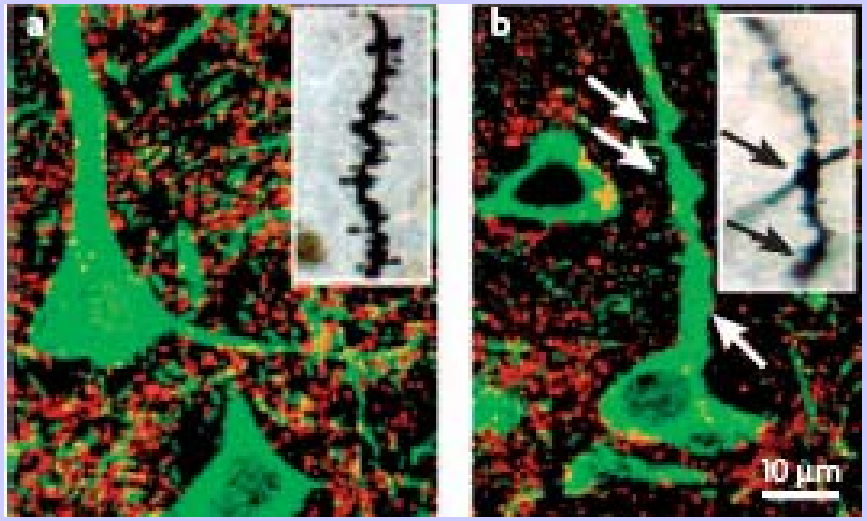


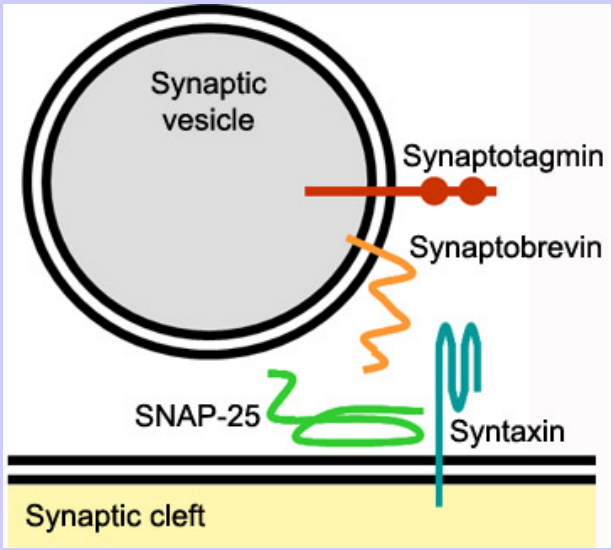
Abnormal mitochondria in dermal Remak bundle.
From Ebenezer G. submitted Brain 2007

Synaptodendritic injury in HIV dementia may be less permanent

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

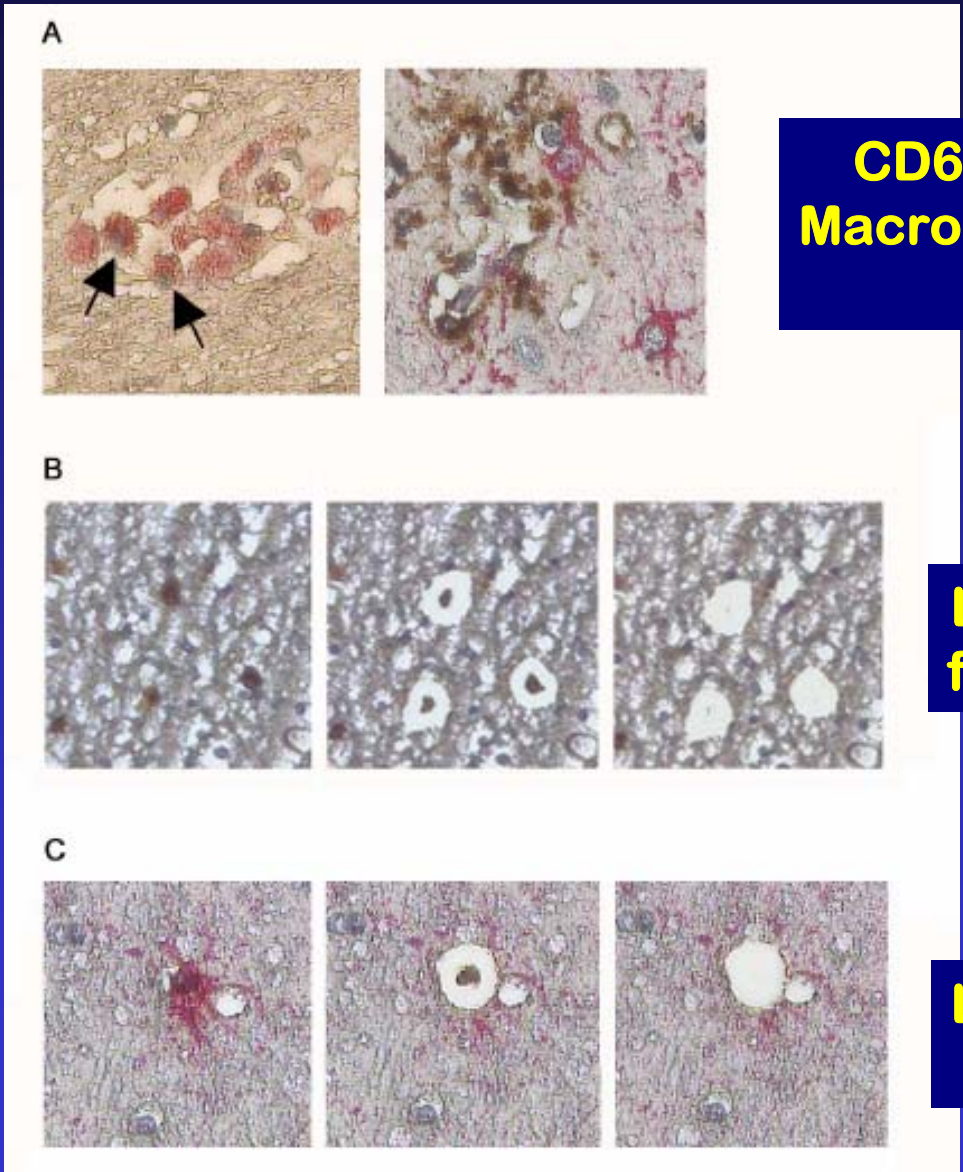
Arek Szklarczyk, JHU





Excess proteolysis
of SYNAPTIC PROTEINS by MMP-7

Detection of integrated HIV-1 DNA in astrocytes and macrophages: ? permanent reservoirs of HIV



CD68 and p24 antigen in Macrophages and astrocytes

Laser capture microdissection from macrophage lineage cells

Laser capture microdissection from astrocytes

Churchill M., JNV, 2006

Neuropathologic Features of Cases Initially With an Isolated Amnestic Syndrome vs Those With Cognitive Impairment Involving Multiple Domains

Table 5. Neuropathologic Features of Cases Initially With an Isolated Amnestic Syndrome vs Those With Cognitive Impairment Involving Multiple Domains

Neuropathologic Feature	Amnestic MCI Cases, No. (%) (n = 24)	Multiple-Domain MCI, No. (%) (n = 10)	*P* Value (Fisher Exact Test)
Consensus pathologic diagnosis of AD	18 (75.0)	6 (60.0)	.43
Khachaturian criteria for AD	20 (83.0)	7 (70.0)	.39
CERAD criteria for AD*	15 (62.5)	3 (30.0)	.13
NIA-Reagan criteria for AD†	18 (75.0)	5 (50.0)	.23
Braak staging criteria for NFTs‡	20 (83.0)	8 (80.0)	>.99
Vascular lesions present§	8 (33.3)	4 (40.0)	.71
AGD present	12 (50.0)	6 (60.0)	.72
Lewy bodies present	6 (25.0)	3 (30.0)	>.99

Abbreviations: AD, Alzheimer disease; AGD, argyrophilic grain disease; CERAD, Consortium to Establish a Registry for Alzheimer Disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangle; NIA-Reagan, National Institutes of Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease.

*According to the CERAD scoring system, "no" refers to not AD or possible AD, and "yes" refers to probable or definite AD.

†According to the NIA-Reagan scoring system, no refers to not AD or low probability of AD and yes refers to moderate or high probability of AD.

‡According to Braak staging criteria, no refers to a Braak stage of I or II, and yes refers to a Braak stage of III, IV, V, or VI.

§Presence of vascular lesions determined to have contributed to the diagnosis of dementia.

Jicha, G. A. et al. Arch Neurol 2006;63:674-681.

ARCHIVES OF NEUROLOGY

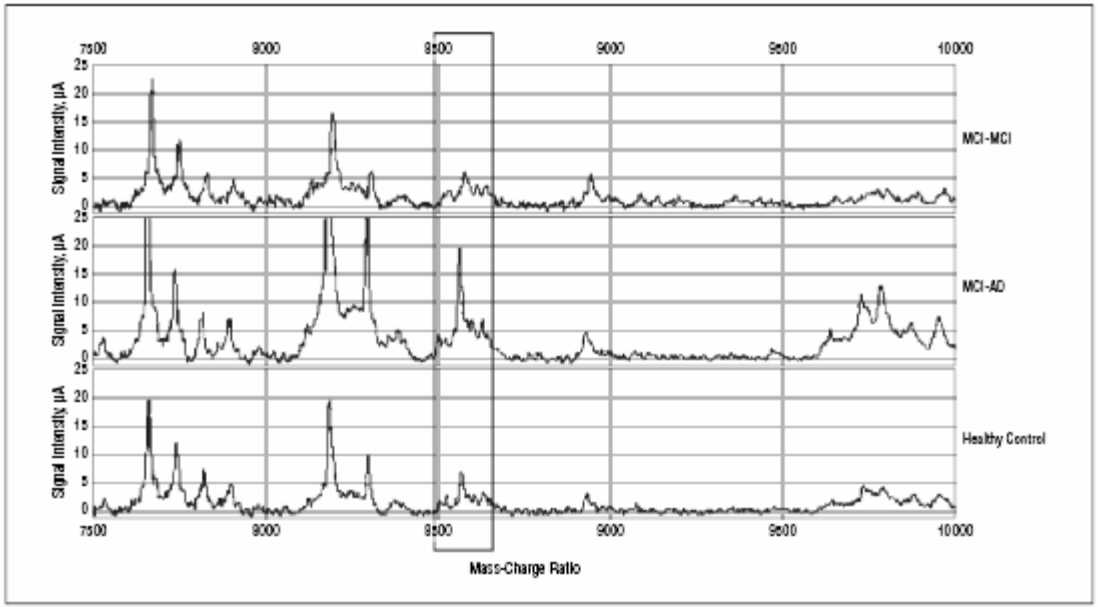


Figure 2. Representative spectra for a patient with stable mild cognitive impairment (MCI-MCI), a patient with MCI who progressed to Alzheimer disease (MCI-AD), and a healthy control for ubiquitin (highlighted in box).

Comparison of Dana cohort (1994-7) and NEAD (1998-present): initially DANA on monotherapy (76%), but NEAD 72% on HAART			
	Dana (n=272)	**NEAD (n=376)**	**P value**
Recruitment Years	1994-1995	1998-2002	
Age, years mean (SD)	39.7 (7.5)	41.7(7.2)	**0.0006**
Male gender (%)	77.9	70.5	**0.03**
(% White/Black /Hispanic/other)	50/40/7/3	23/65/10/2	**0.001**
Education : yrs, mean (SD)	13.5 (2.9)	12.5 (2.3)	**0.001**
AIDS defining illness (%)	37.9	49.5	**0.003**
CD4+ count, mean (SD)*	177.9 (182.2)	136.0 (87.4)	0.30
AAN Classification **Normal** **MCMD** **HIV-D**	 25.0 47.7 27.3	 30.4 33.9 35.8	**0.002**
* P value from t test comparing log-transformed CD4 counts			

Dec;10(6):350-7.

of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) d post-highly active antiretroviral therapy eras: a combined study of two cohorts.

, **Brew BJ**.

incent's Clinical School, University of New South Wales, Sydney, Australia. l.cysique@student.unsw.edu.au

udy was to assess the prevalence and pattern of neuropsychological impairment in cohorts of human immunodeficiency virus (HIV)-ss pre- and post-HAART (highly active antiretroviral therapy) eras. Two cohorts of HIV-infected individuals attending tertiary referral cs were studied. The cohorts represented two eras of antiretroviral medication: monotherapy (n = 51) and HAART (n = 90). Each europsychological domains in regard to the prevalence as well as pattern of neuropsychological impairment. Because the authors e the prevalence and pattern of neuropsychological deficits in nondemented advanced HIV-infected individuals, patients with a current mmunodeficiency syndrome (AIDS) dementia complex were not included. The prevalence of impairment was not significantly different HAART eras using a standard criterion to define impairment: -2 SD in two neuropsychological measures (41.1%/38.8%). Prevalence ficantly reduced in patients with undetectable plasma viral load. The pattern of neuropsychological impairment was different across eras, with an improvement in attention, verbal fluency, visuoconstruction deficits, but a deterioration in learning efficiency and change remained even in patients with an undetectable plasma viral load, although the severity was partially diminished. cits remain common in the HAART era, essentially uninfluenced by HAART. The finding that some neuropsychological functions are re deteriorating indicates that these deficits do not reflect "burnt out" damage but rather that there is an active intracerebral process f which is still to be determined.

efficiency and complex attention, and relatively less on attention, verbal fluency, and visuoconstructional deficits. *Cysique LA J Neurovirol, 2004*

rovirol. 2006 Apr;12(2):100-7.

hip of antiretroviral treatment to postmortem brain tissue viral load in human immunodeficiency virus-infected patients.

l D, **Marquie-Beck J**, **de Almeida S**, **Lazzaretto D**, **Letendre S**, **Grant I**, **McCutchan JA**, **Masliah E**, **Ellis RJ**.

t of Pathology, University of California, San Diego, La Jolla, California 92093, USA. tdlangford@ucsd.edu

mmunodeficiency virus (HIV)-1 invades the central nervous system (CNS) soon after infection and is partially protected there from host i
etroviral drugs (ARVs). Sanctuary from highly active antiretroviral therapy (HAART) in the CNS could result in ongoing viral replication, p
opment of drug resistance and neurological disease. Despite the importance of these risks, no previous study has directly assessed HA
brain tissue viral load (VL). The authors evaluated 61 HIV-infected individuals for whom both histories of HAART treatment and postm
measurements were available. Two groups were defined based on HAART use in the 3 months prior to death: HAART(+) subjects had
nd HAART(-) subjects had not received HAART. HIV RNA was quantified in postmortem brain tissue (log10 copies/10 microg total tissue
em plasma (log10 copies/ml) by reverse transcriptase-polymerase chain reaction (RT-PCR). Brain tissue VLs were significantly lower amo
cts compared to HAART(-) subjects (median 2.6 versus 4.1; P= .0007). These findings suggest that despite the limited CNS penetratio
iral medications, HAART is at least partially effective in suppressing CNS viral replication. Because some HAART regimens may be better
this regard, regimen selection strategies could be used to impede CNS viral activity, limit neuronal dysfunction, and prevent or treat clini
nitive disorders in HIV-infected patients. Furthermore, such strategies might help to prevent the development of ARV resistance.

798671 [PubMed - indexed for MEDLINE]

So what is everyday impact of HAND ?

Impact of HIV dementia

- Survival: 3-fold higher risk of death
- Driving ability
- Work performance
- Medication adherence
- *Less compliant with medical care ?*
- *Less compliant with drug cessation ?*
- *Less compliant with protective sex measures ?*

The impact of HIV-associated neuropsychological impairment on everyday functioning.

J Int Neuropsychol Soc. 2004 May;10(3):317-31.
Heaton RK et al

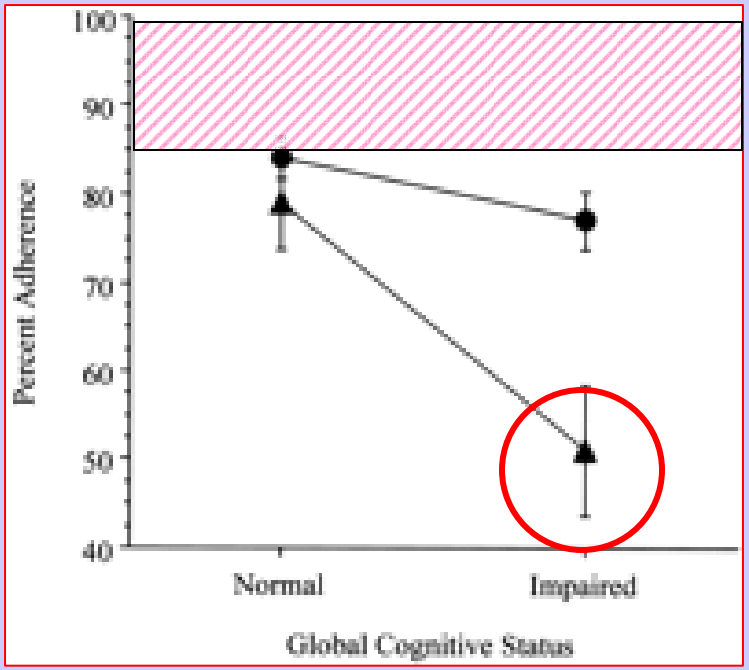
To evaluate the functional, or "real-world" impact of HIV-associated NP impairment in 267 HIV-infected participants. All received comprehensive NP, neuromedical, and standardized functional evaluations that included laboratory measures of everyday functioning

Compared to NP-normal participants, those with NP impairment performed significantly worse on all laboratory measures of everyday functioning

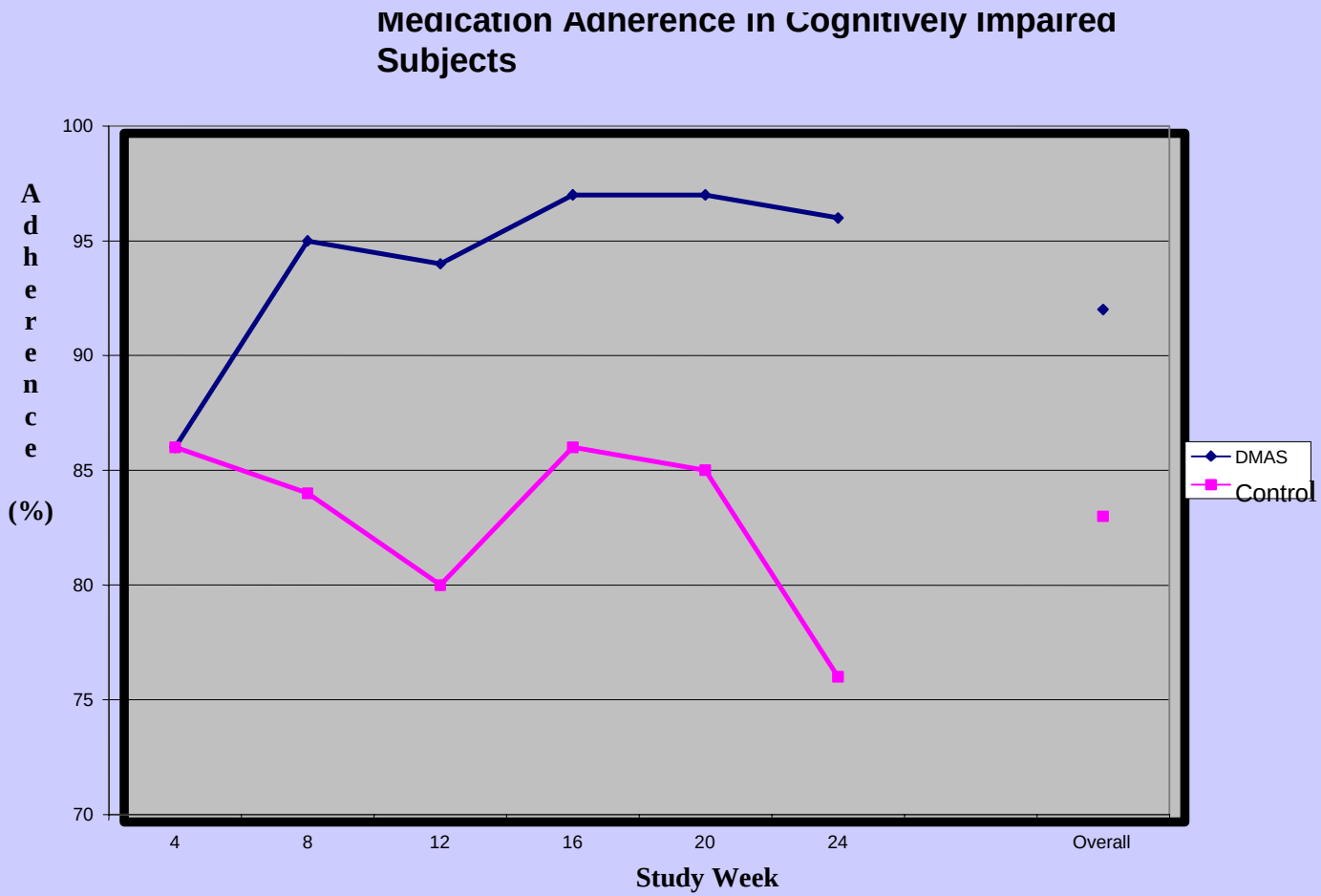
Impact of HIV-D or MCMD on medication adherence

- *Hinkin C Neurology, 2002*

  Neurocognitive compromise and complex medication regimens are associated with significantly lower adherence rates in OLDER subjects. Cognitively compromised participants on more complex regimens had the greatest difficulty with adherence.

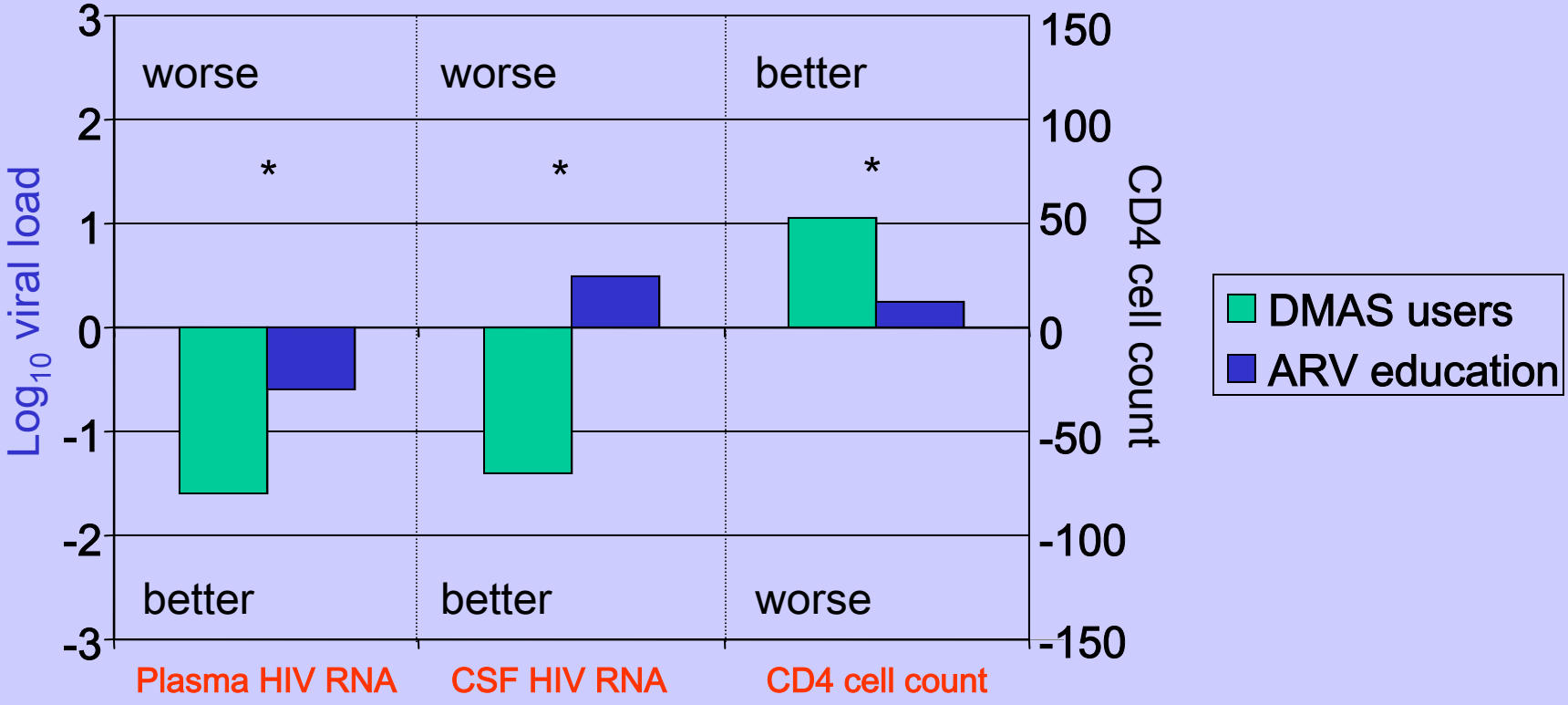


Improving adherence to HAART in cognitively impaired HIV+ subjects: intervention study using a verbal prompting device *Andrade A 2005*



Change in HIV-1 Markers in intervention adherence study

Andrade A. J AIDS 2005



* p<.05 relative to ARV education group

Surrogate markers in HIV-dementia

- **ART Adherence**
- **MRS**
- **Functional MRI/PET**
- **Computerized motor testing**
- **CSF HIV RNA**
- **CSF immune activation markers**
- **CSF cellular injury markers**
- **Plasma immune activation markers**
- **Plasma proteomics**
- **Genetic markers of susceptibility or progression**

Most of these have not been fully assessed or validated in the HAART era

Research biomarkers for HIV dementia or encephalitis (associative or predictive)

A • CSF Fractalkine. *Erichsen D, J Neuroimmunol. 2003 May;138(1-2):144-55*

A • CSF sFas: Towfighi A, Neurology 2004 Feb 24;62(4):654-6.

A • CSF markers of oxidative stress: *Haughey N, Ann Neurol, 2004*

P • HIV RNA: plasma and CSF levels predict subsequent NP impairment *Ellis R, Arch Neurol 2002; Marcotte T, Arch Neurol 2003*

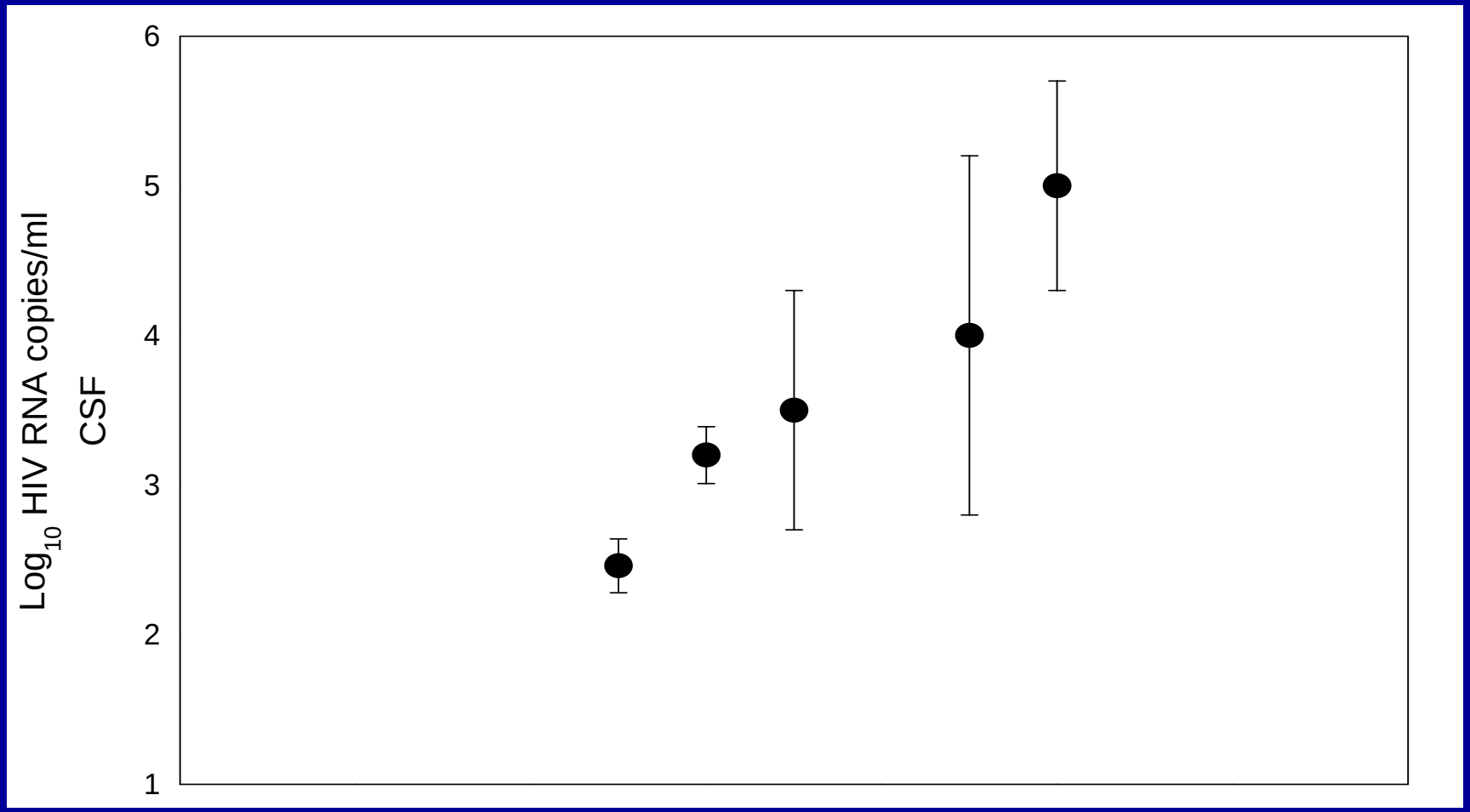
A • OTK18 expression in brain monocytes is a signature for advanced HIV-1 encephalitis.
Carlson KA J Neuroimmunol. 2004 May;150(1-2):186-98.

A • Plasma proteomic markers: 4348 Da protein distinguishes HIV-D from non-demented (sensitivity 100%, specificity 75%) *Luo X, Neurology. 2003 Jun 24;60:1931-7*

P • MCP1 promoter polymorphisms predict HAD *Gonzales E. PNAS, 2002; Copy number of a segmental duplication for CCL3L1 (MIP-1alpha) affects disease susceptibility*
Gonzales E. Science. 2005

NEAD CSF HIV RNA compared to other studies

Mcarthur JC, Arch Neurol, 2004



All

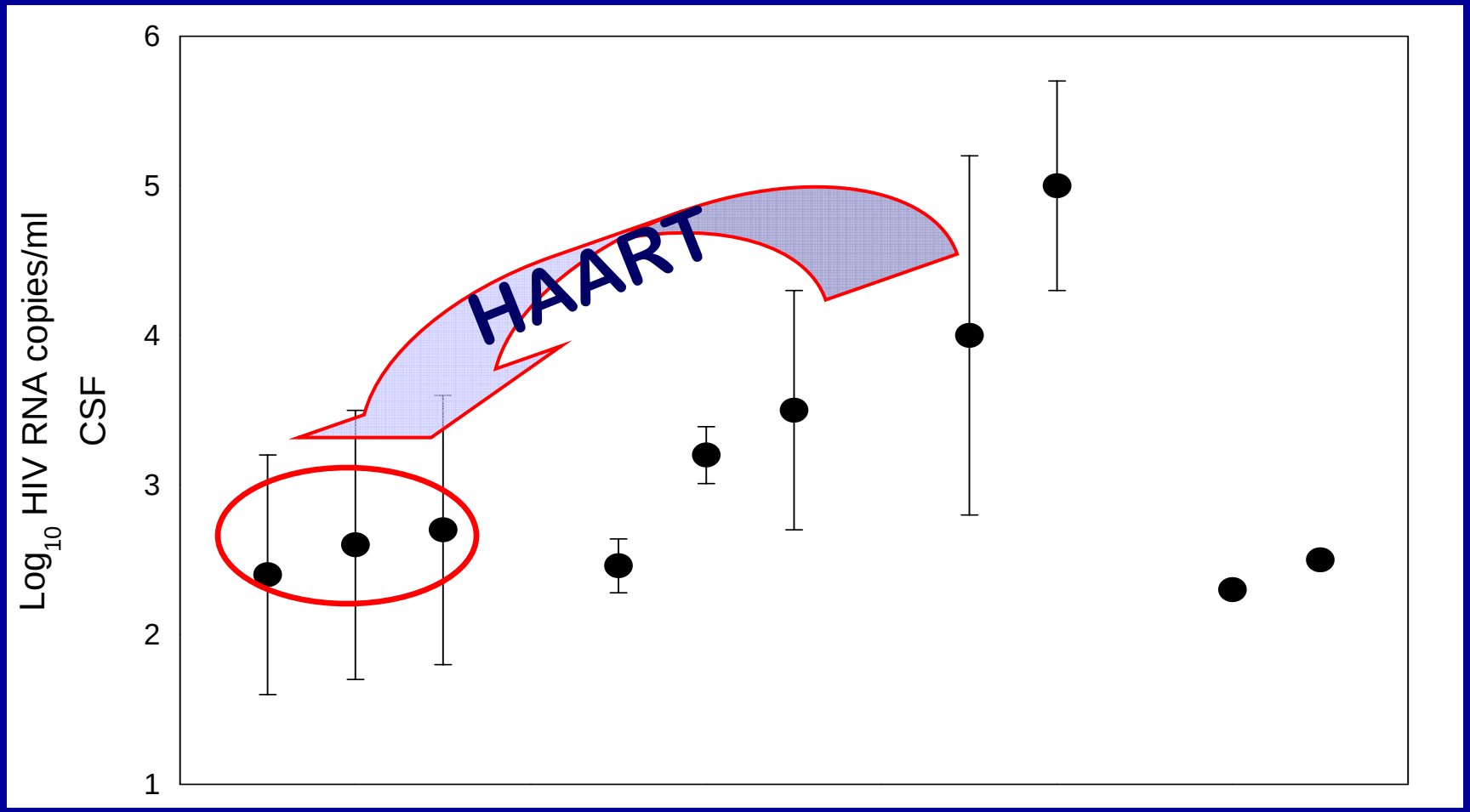
MCMD N=29 | **HIV-D N=37** | **Severe N=8** | **MSK 2 N=6** | **MSK 3 N=5**

McArthur | Brew

Historical Comparison
Pre-HAART

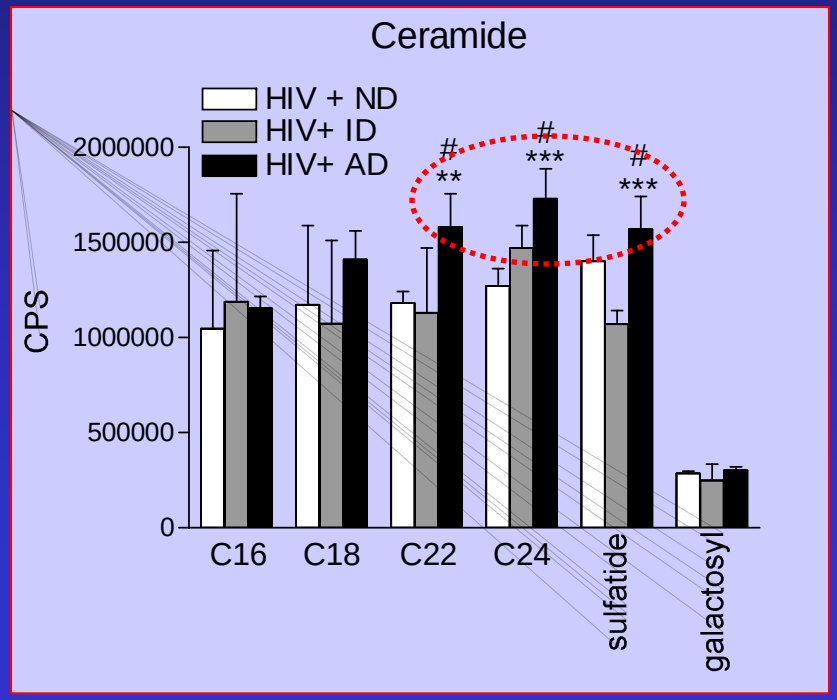
NEAD CSF HIV RNA compared to other studies

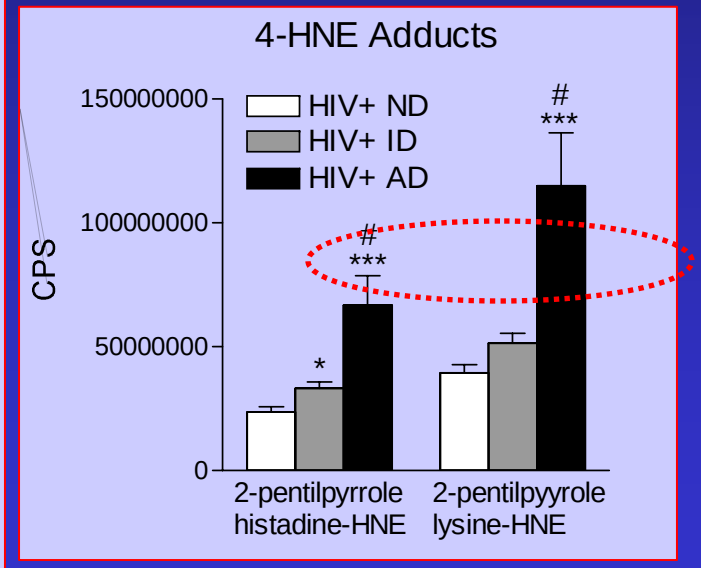
Mcarthur JC, Arch Neurol, 2004



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

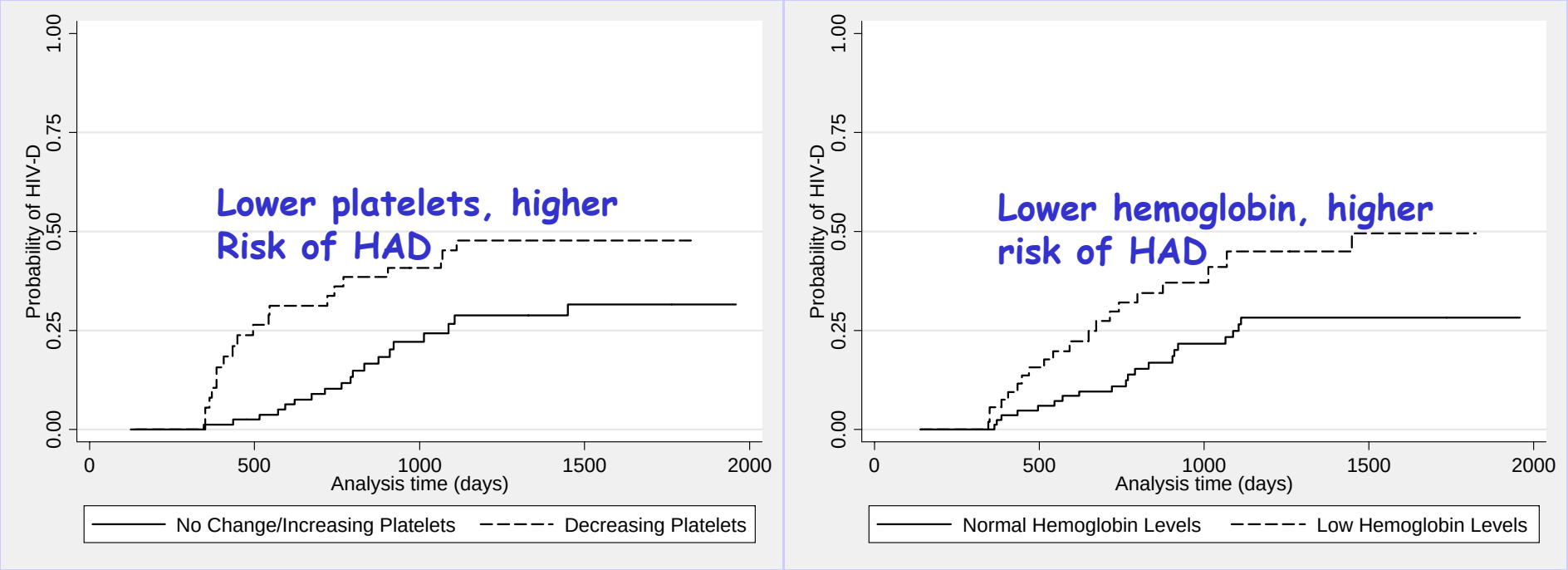
ND = not demented
ID = stable dementia (*MSK 1 or 2: no change)*
AD = progressive dementia (*MSK 1 or 2: new transition)*





Platelet and hemoglobin as markers of incident dementia

Wachtmann L NEAD-2 study



Kaplan-Meier curves of the cumulative incidence of HIV-associated dementia by change from baseline platelet count and by hemoglobin levels in the North-East AIDS Dementia (NEAD) cohort.

The HIV+ adult cohort was stratified into four mutually exclusive genetic risk groups (GRGs) based on possession of a population-specific low or high number of *CCL3L1* copies (*CCL3L1low* or *CCL3L1high*) and disease-accelerating, i.e., detrimental (det) or nondetrimental (non-det) *CCR5* genotypes (*CCR5det* or *CCR5non-det*)

AIDS-defining illness	*n*	$CCL3L1^{high}CCR5^{det}$			$CCL3L1^{low}CCR5^{non-det}$			$CCL3L1^{low}CCR5^{det}$		
		RH	95% CI	*P*	RH	95% CI	*P*	RH	95% CI	*P*
CMV infection	100	1.53	0.71-3.30	0.278	1.60	1.00-2.58	0.051	***6.21***	***3.63-10.63***	***2.7×10^{-11}***
Cryptococcosis	33	3.27	0.98-10.87	0.053	***2.46***	***1.00-6.02***	***0.048***	***8.11***	***2.93-22.46***	***5.6×10^{-5}***
Cryptosporidiosis	24	1.21	0.27-5.47	0.802	1.21	0.49-3.00	0.686	1.63	0.36-7.37	0.526
HAD	54	2.05	0.82-5.13	0.126	1.65	0.87-3.11	0.124	*3.18*	*1.33-7.60*	*0.009*
Herpes simplex	26	1.78	0.50-6.41	0.375	1.22	0.49-3.04	0.668	1.66	0.36-7.53	0.513
Histoplasmosis	20	3.32	0.83-13.30	0.090	***2.81***	***1.02-7.74***	***0.045***	1.56	0.19-13.01	0.682
Kaposi sarcoma	74	1.76	0.76-4.05	0.186	1.66	0.96-2.86	0.069	***3.86***	***1.90-7.83***	***2.0×10^{-4}***
Lymphoma	37	***2.87***	***1.10-7.48***	***0.031***	1.42	0.66-3.08	0.369	***3.38***	***1.21-9.43***	***0.020***

Gonzales E…
…Ahuja S. et al
Science, 2005

Research markers for HIV dementia or encephalitis (associative or predictive)

A
- CSF Fractalkine. *Erichsen D, J Neuroimmunol. 2003 May;138 (1-2):144-55.*

A
- CSF sFas: Towfighi A, Neurology 2004 Feb 24;62(4):654-6.

A
- CSF markers of oxidative stress: *Haughey N, Ann Neurol, 2004.*

P
- HIV RNA: plasma and CSF levels predict subsequent NP impairment, *Ellis R, Arch Neurol 2002; Marcotte T, Arch Neurol 2003*

A
- OTK18 expression in brain monocytes is a signature for advanced HIV-1 encephalitis. *Carlson KA J Neuroimmunol. 2004 May;150 (1-2):186-98.*

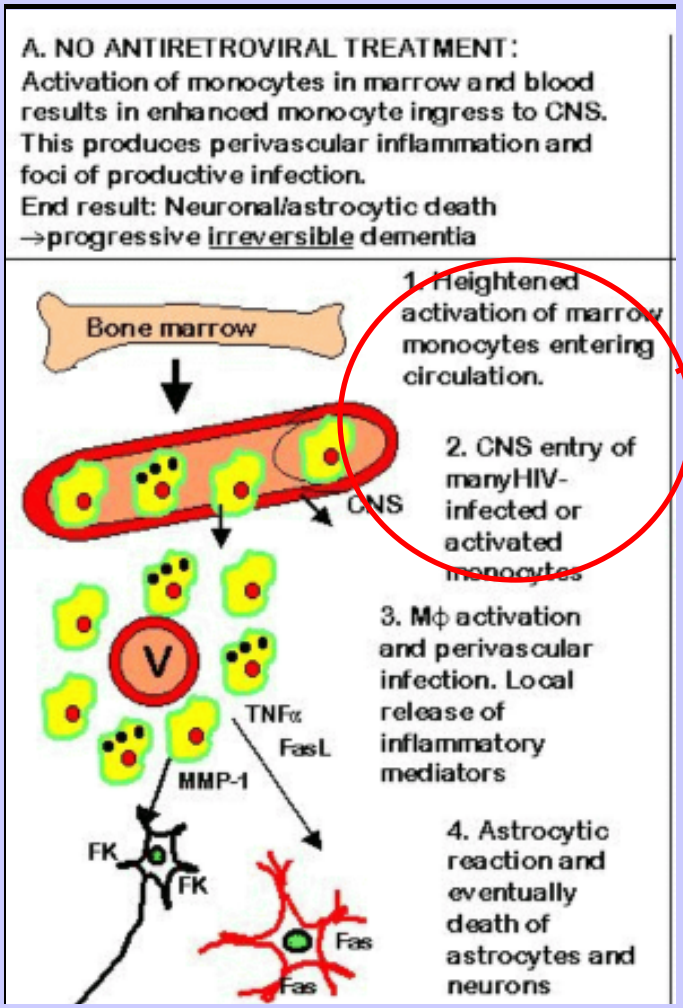
A
- Plasma proteomic markers: 4348 Da protein distinguishes HIV-D from non-demented (sensitivity 100%, specificity 75%) *Luo X, Neurology. 2003 Jun 24;60:1931-7*

P
- Genetic markers: MCP1 promoter polymorphisms *Gonzales E. PNAS, 2002; 99(21):13795-13800*

HIV-D therapeutic strategies

- CNS penetration
- Compartmentalization of HIV gentotypes
- HIV-dementia trials ~ HAART
- HIV-dementia trials ~ adjunctive therapies
- Questions for new trials
- Timing of initiation of HAART when HAND is detected ?

Cartoon of pathological phases in HAND



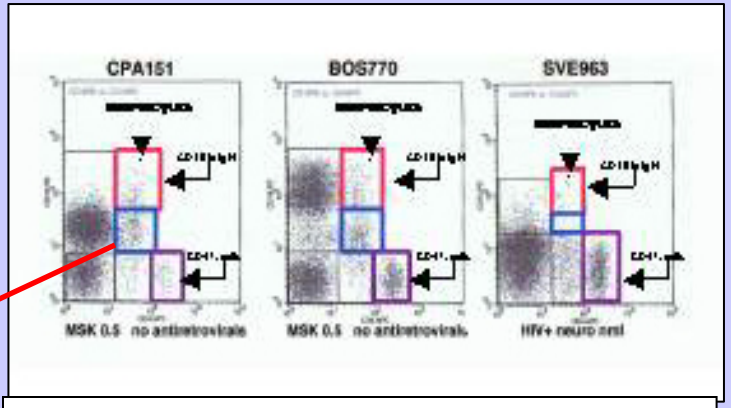
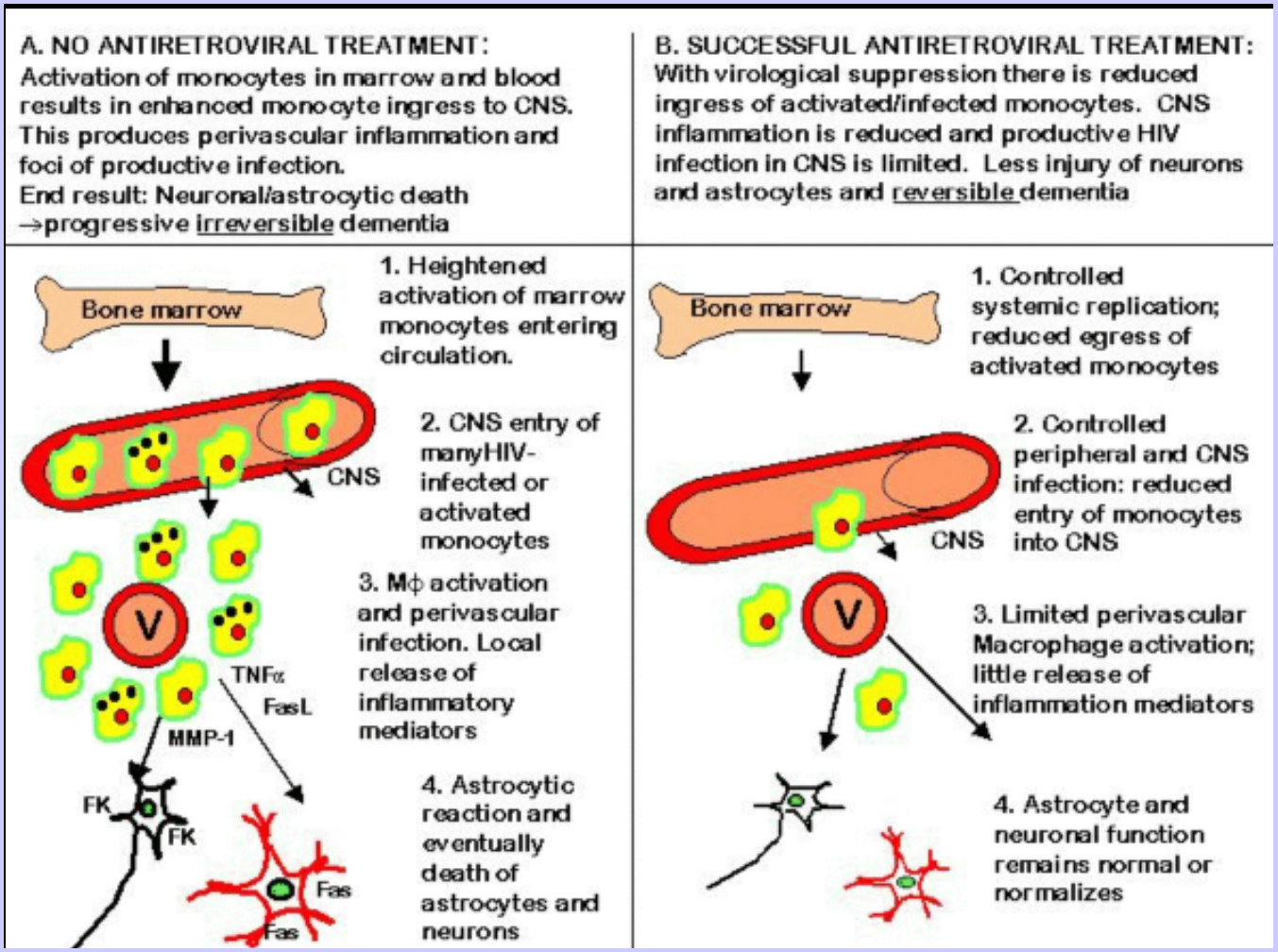


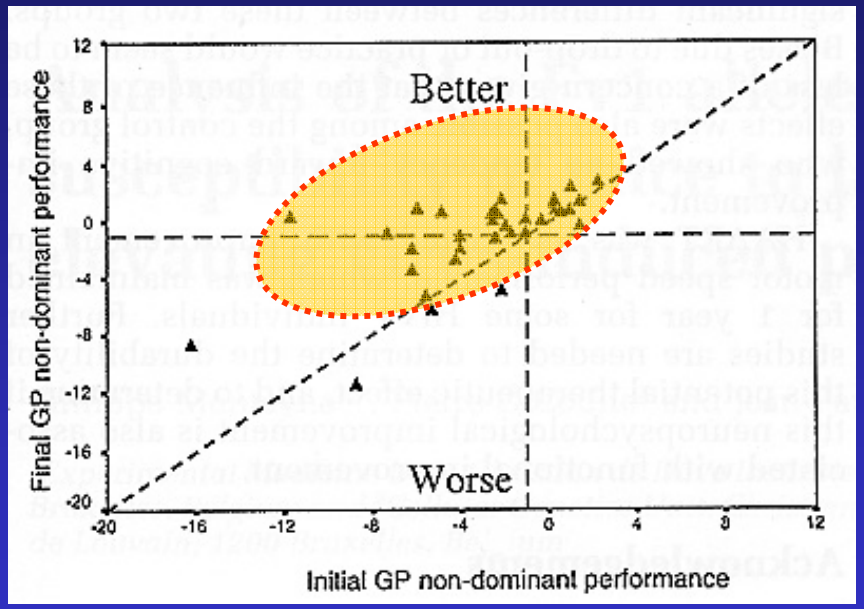
Figure 3. CD4/CD16 dot plots of patient leukocytes. Staining performed using the whole blood lysis method. T-cells are CD4-bright, monocytes (middle panels) are CD4-dim.

Frequency of CD16+ blood monocytes in NEAD subjects				
		Percent CD16+ monocytes		
Clinical Diagnosis	N	mean	std. dev.	range
HIV+ MCMD/HIV-D	54	51.5	21.0	5-18
HIV+ neuro nml	9	25.6	6.7	14-36
HIV- controls	6	11.5	4.3	16-86
Three-color immunophenotyping was performed using the whole blood lysis method and antibodies from BD Biosciences. Monocytes were defined as CD14+/CD4dim cells.				

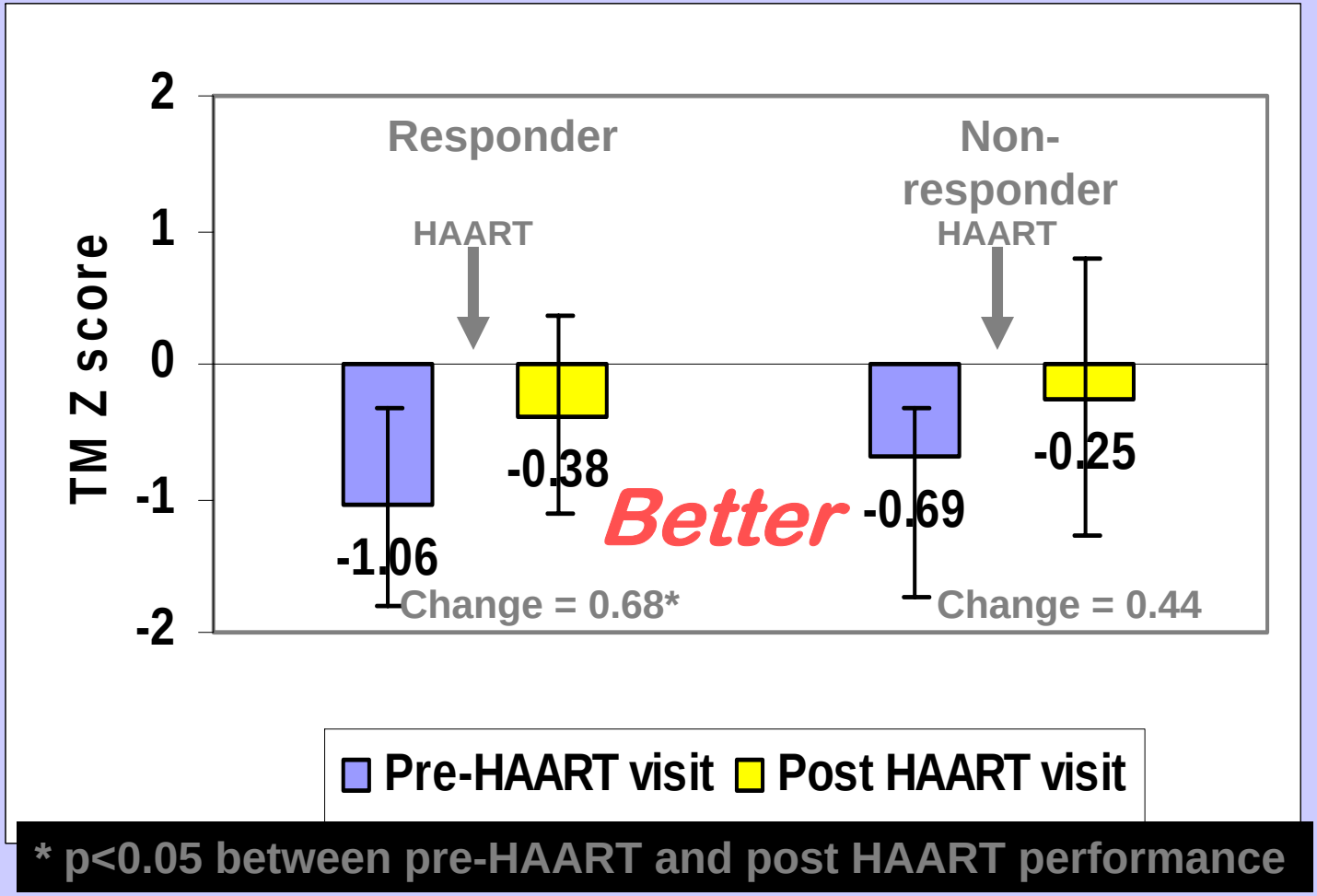
Cartoon of pathological phases in HAND



HIV-dementia: severe psychomotor slowing improving *after* antiretroviral therapy.



MACS study: Trail Making Test, Part B (TM) performance partial correlation with virological response *Sacktor N, 2002*



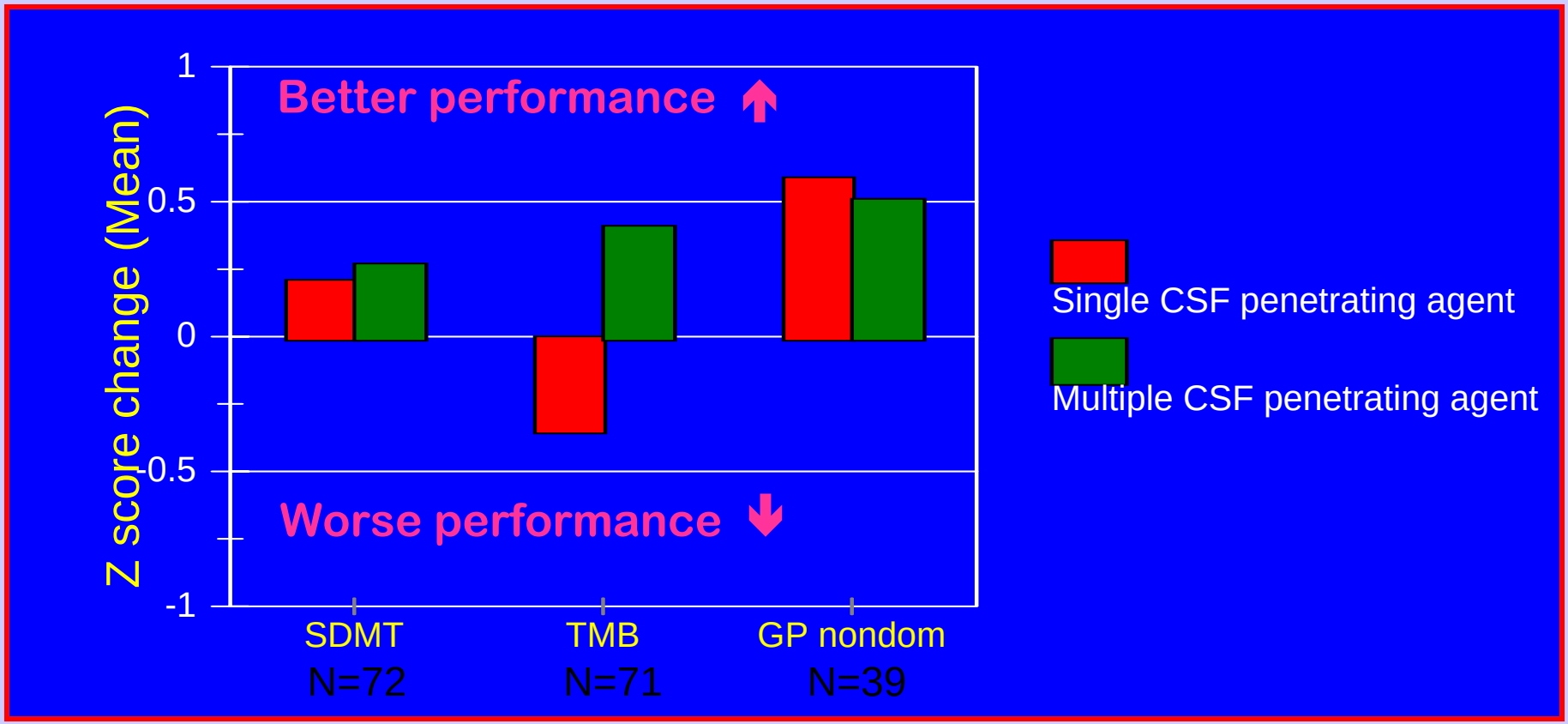
This may be analogous with observation by S Deeks ~ CD4 response even in virological failures (NEJM 2001)

Choice of optimum HAART regimen for HIV dementia

Does CNS penetration profile matter ?

- ***Sacktor N, 2001:*** **no effect on cognitive function**
- ***Cysique L, 2004:*** **effect only in cognitively impaired**
- ***Letendre S., 2006*** **~ new index of penetration**

Psychomotor Speed improvements with HAART does NOT depend on HAART regimen.



Subjects on regimens containing *multiple* CNS-penetrating agents showed no significant differences on any tests of psychomotor speed, compared to those receiving regimens with only a *single* CNS-penetrating agent.

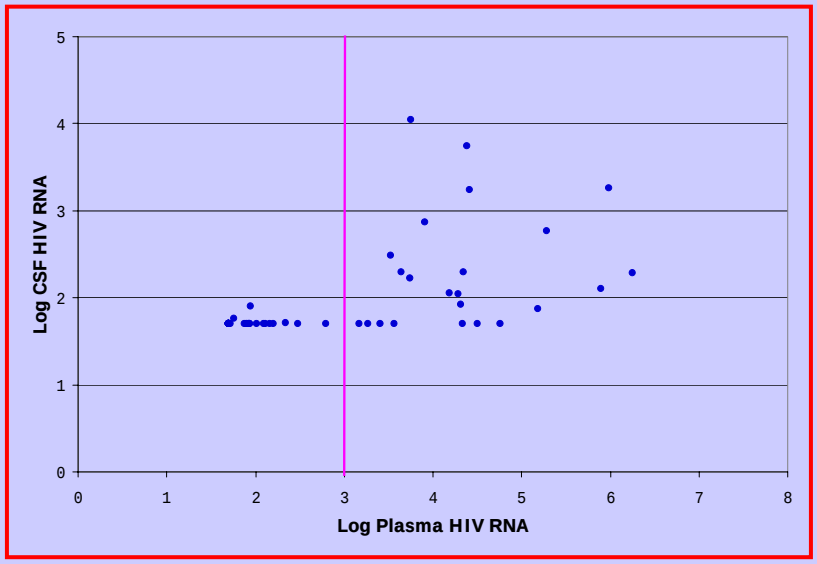
Sacktor N, Neurology, 2001

Suppression of HIV Replication in Plasma Requires Suppression of HIV Replication in CSF
C. Marra et, al. ACTG 736

CROI 2007

Conclusions

- CSF RNA was rarely detectable when plasma HIV RNA was <1000.
- Subjects with plasma HIV RNA ≥1000, were 5X more likely to achieve CSF suppression with an ART regimen with good CNS penetration
- Achievement of an undetectable HIV RNA in both CSF and plasma was 3X more likely with an ART regimen with good CNS penetration.
- These results suggest that an antiretroviral regimen with good CNS penetration is important in achieving suppression of HIV RNA ***both in CSF and plasma***

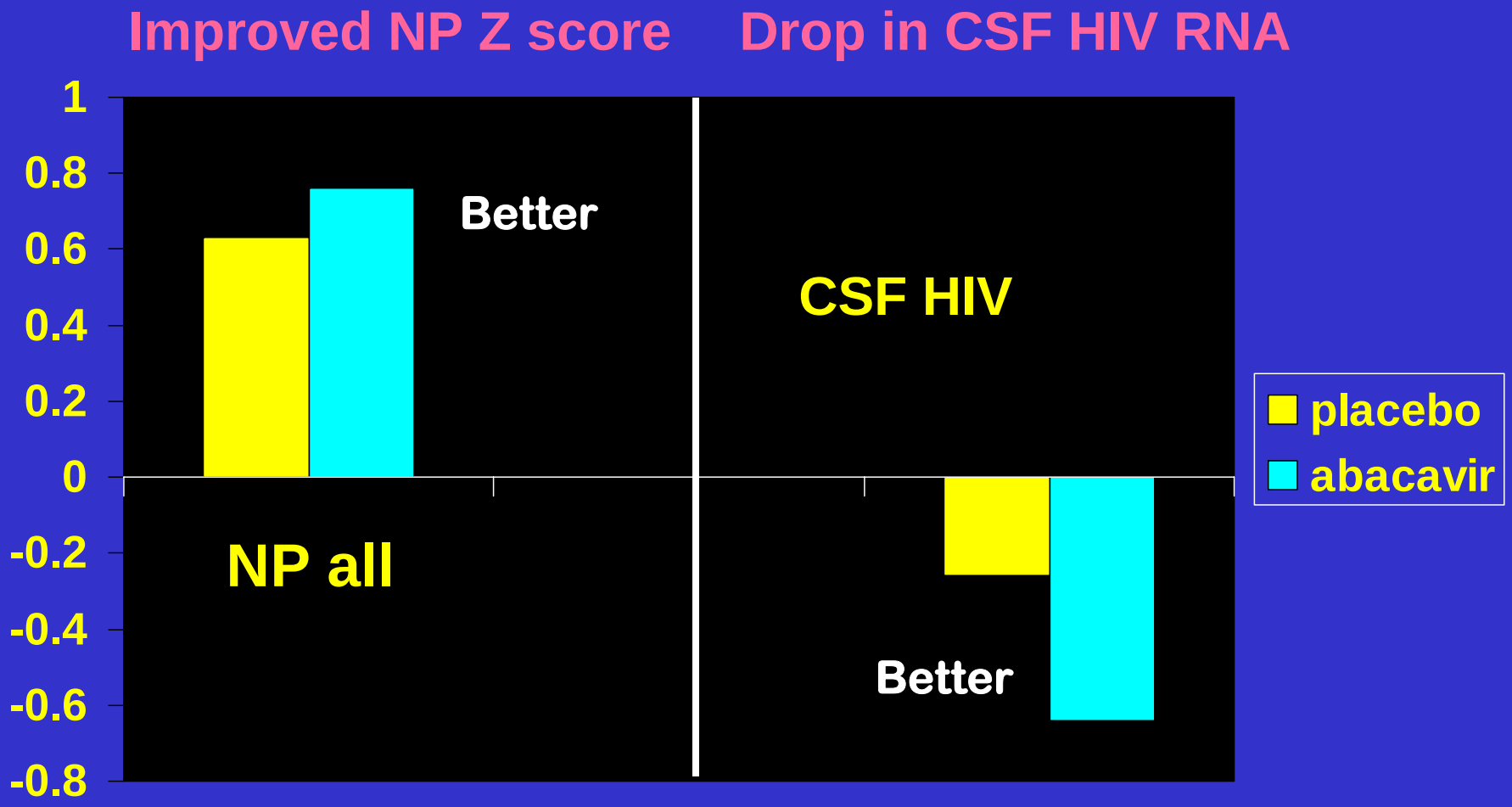


ART trials for HIV-dementia

Agent	*Outcome*	*Comments*
Zidovudine	Positive effect on NP	High dose ZDV monotherapy *Price RW Ann Neurol 1993*
Abacavir add on	No difference from background	Majority had RT resistance mutations. Run-in effect of background ART. *Brew BJ, under review*
ZDV alternating ddI v. ZDV+ddI v. ZDV+ddC v. ZDV+ddI+NVP	Triple therapy or ZDV/ddI improved NP impairment	Not solely a trial of HIV-D; no protease inhibitors; all had CD4 <50. *Price RW, AIDS 1999*
HAART in Uganda	Positive effect on NP	First demonstration of reversal of HIV-D in RLC *Sacktor N. 2006*

Abacavir 3001 HIV-D trial: abacavir or placebo added to stable HAART (n=105)

Brew BJ PLOS, 2007



Conclusions:

Four factors compromised the study:

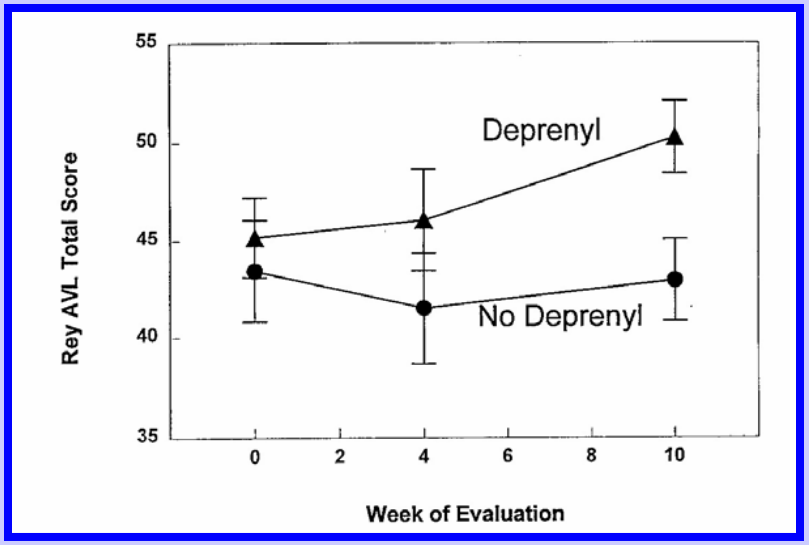
- **pre-existing ABC resistance**
- **the unexpected continuing, prolonged and beneficial effect of HAART upon HAND**
- **The variability of the NP data was much greater than expected reducing the likelihood of detecting treatment differences**
- **HAD may have been 'burnt out', eg immune activation markes were normal in >80%**

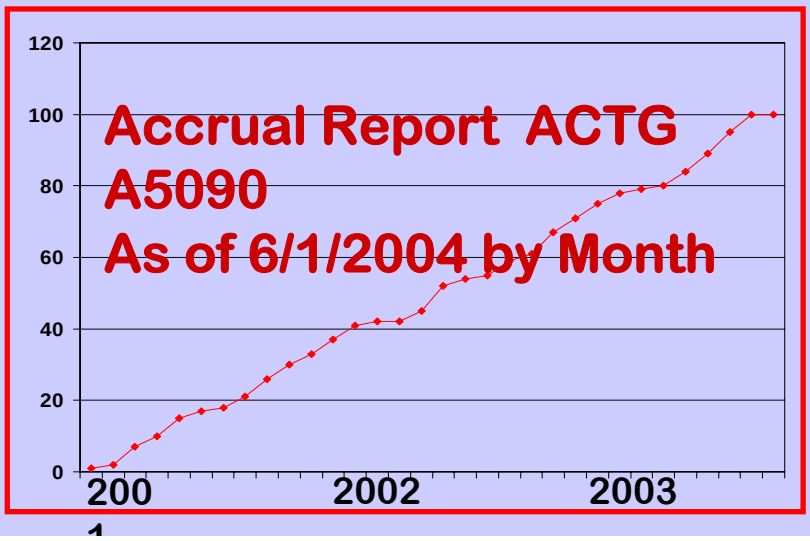
Placebo Controlled Trials of Adjunctive Agents for HIV Dementia

Agent	Action	Conclusions
Nimodipine	Calcium channel	NP trend
Selegiline	Anti-oxidant	*+ NP effect*
OPC14117	Anti-oxidant	NP trend
Thioctic acid v selegiline	Anti-oxidants	*+ NP effect for selegeline.*
Lexipafant	PAF antagonist	*+ NP effect*
Memantine	NMDA antagonist	*+ delayed NP effect*
CPI-1189	?TNF✂ antagonist	No effect
Peptide T	? Chemokine antag	No effect

So why have these trials not had more effect on clinical practice ?

- Modest effect
- Questionable functional impact
- Slow accrual
- Slow reporting with average delay of 2-3 years !
- Poor PR
- Limited community and Pharma 'buy in' for trials
- Not always the right question at the right time ~ eg augmentation with abacavir as one drug in resistant subjects





Addressing the therapeutic ‘gap’

Uncorrected Version. Published on March 16, 2007 as DOI:10.1189/jlb.1106711

Osteopontin prevents monocyte recirculation and apoptosis

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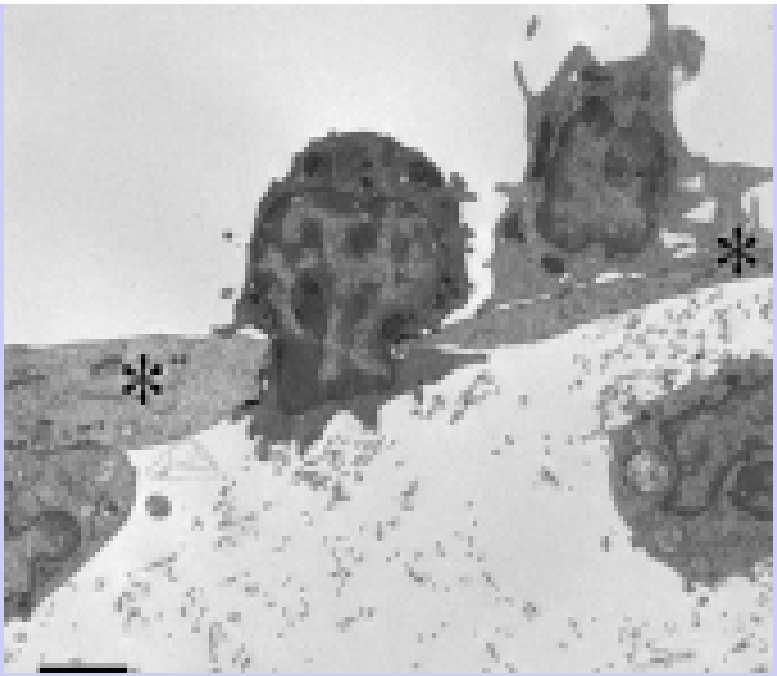
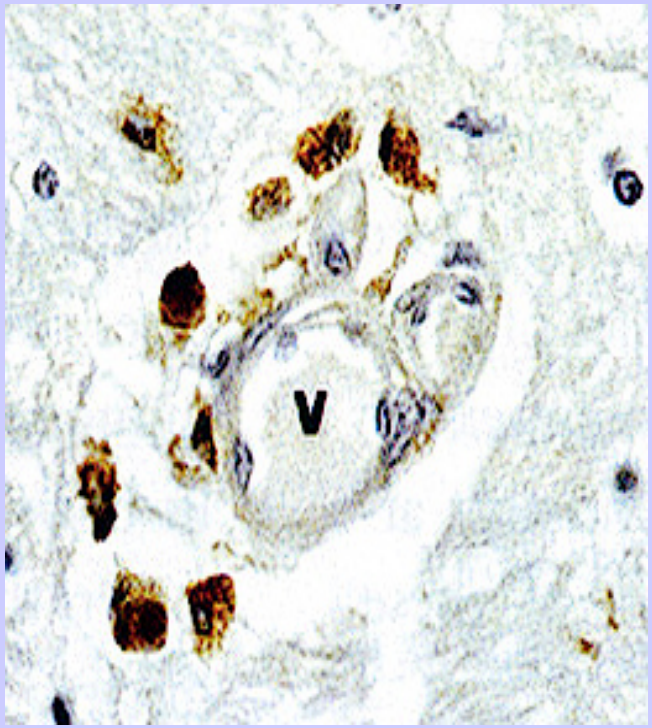
*Molecular and Integrative Neurosciences Department and †Core Microscopy Facility, The Scripps Research Institute, La Jolla, California, USA

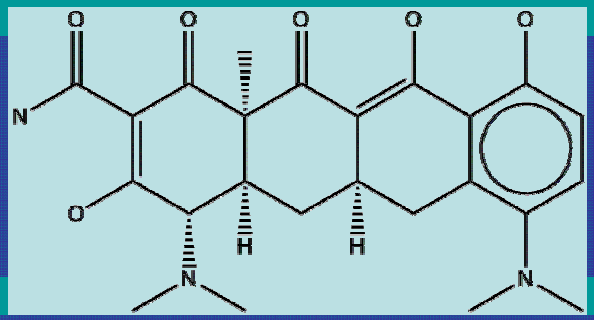




Potential novel therapies for HAND ?

- GF120918 (*MDR* modulator)
- maxi-HAART regimens
- Integrase inhibitors
- chemokine receptor blockers
- EPO
- MCP-1 blockers
- SSRIs
- Valproic acid
- neuroimmunophilin ligands
- cyclin-dependent kinase (cdk) inhibitors
- minocycline

Minocycline



- Second generation tetracycline with good CNS penetration and proven safety
- Effective in vitro at low viral doses even against R5 and X4R5 viruses, and in single-cycle reporter cell assays.
- Inhibits NF-kappa B in microglia. *Si Q., et al, JNV 10: 284, 2004*
- C Zink demonstrated significant effect on SIVE *JAMA, 2005*
- N Sacktor has now initiated an ACTG trial in USA, and proposed one in Uganda

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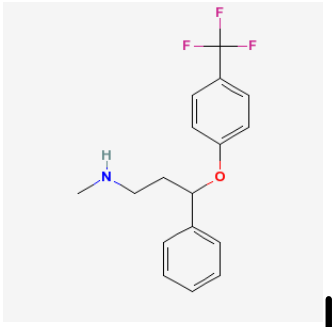
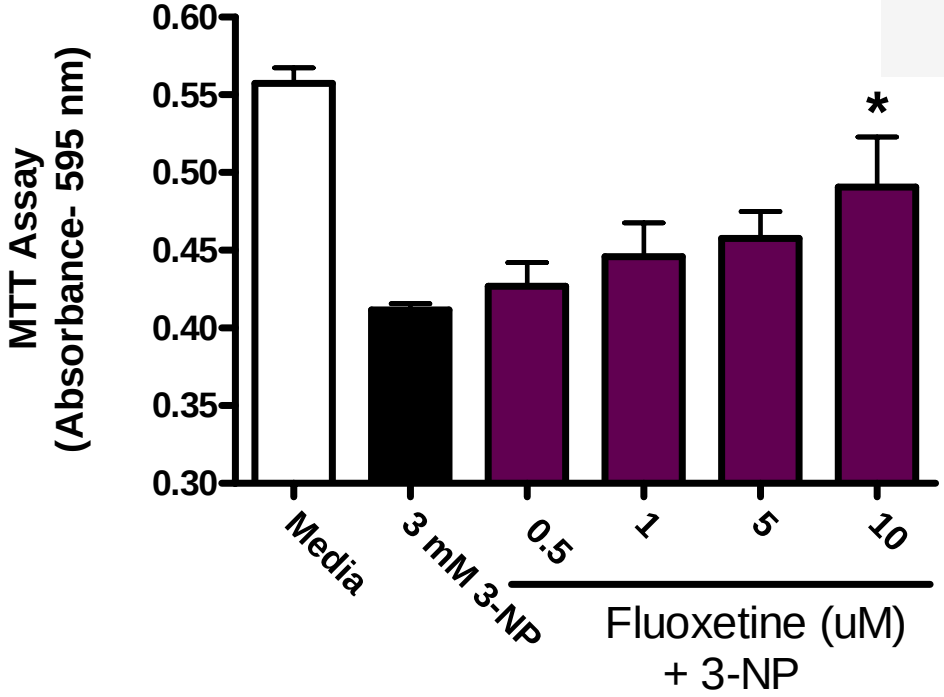
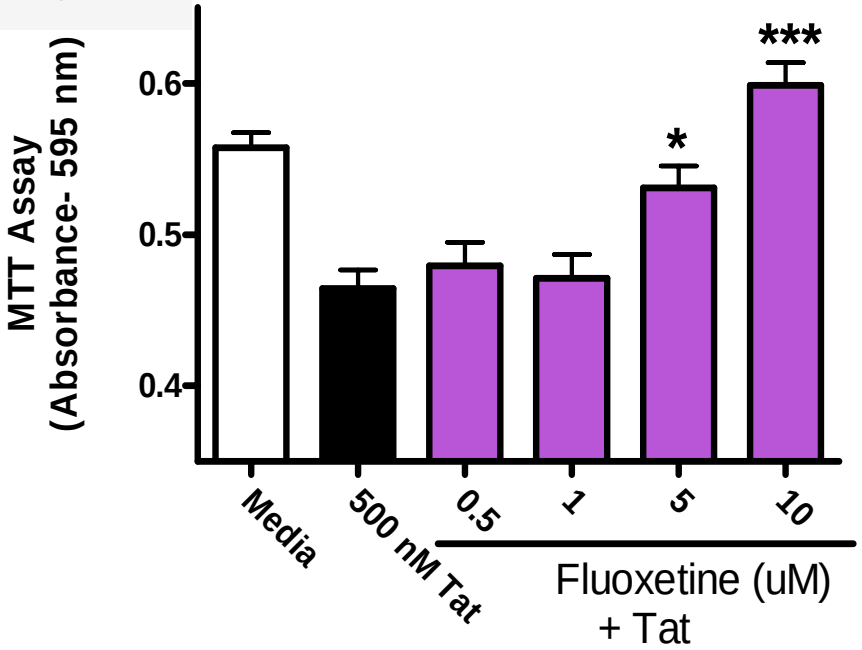
of HIV-associated cognitive disorders

Fluoxetine protects rat hippocampal cultures vs. 3-NP and Tat toxicities







Utility of measurement of CSF HIV RNA in HIV-D

- Not diagnostic of HIV dementia
- In established HIV dementia: *to assay CSF genotype and then follow CSF HIV RNA to assess CNS efficacy of a new regimen*
- Identification of occasional cases of “CNS escape” ~ where CNS replication >> systemic replication

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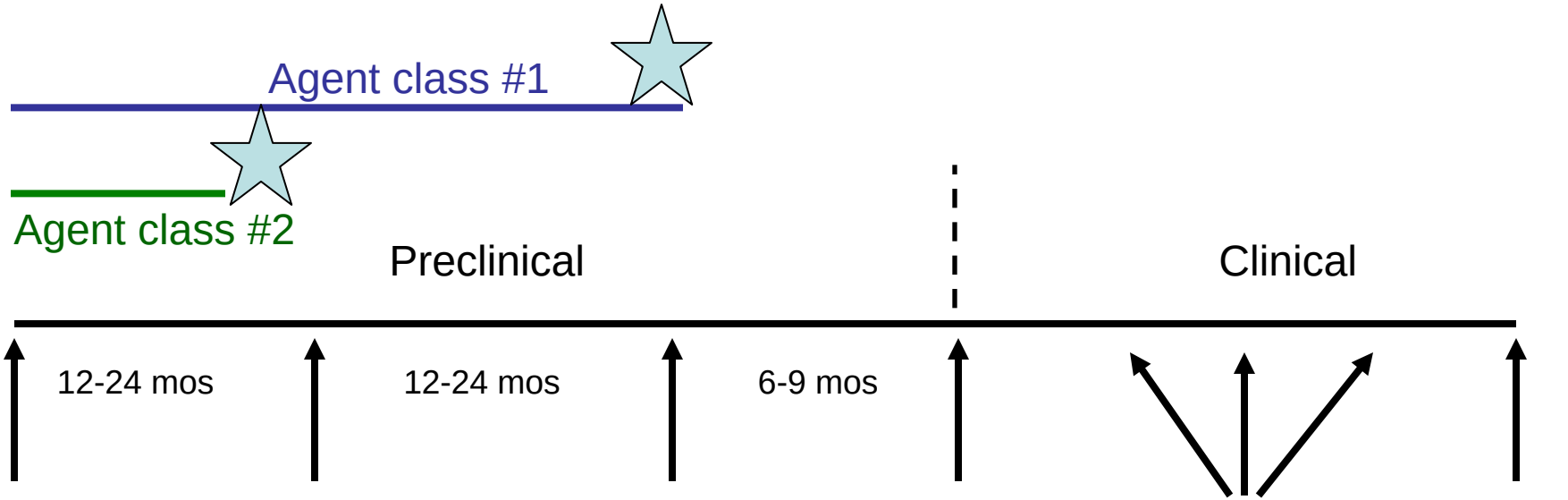
Drug Discovery Research Timeline



Exploratory Discovery Research (Compound Screening, D-R, molecular modeling and Chemical synthesis)

Lead Optimization Pharmaceutics Profiling, Toxicity, In vivo Proof-of-Concept

Clinical Candidate Identified (Pharmacology, GLP Tox, DMPK, Safety, Compound Manufacturing)

Clinical Trials
Ph I Safety &PK
Ph II Dose Range-Finding, P-O-C
Ph III Confirmatory

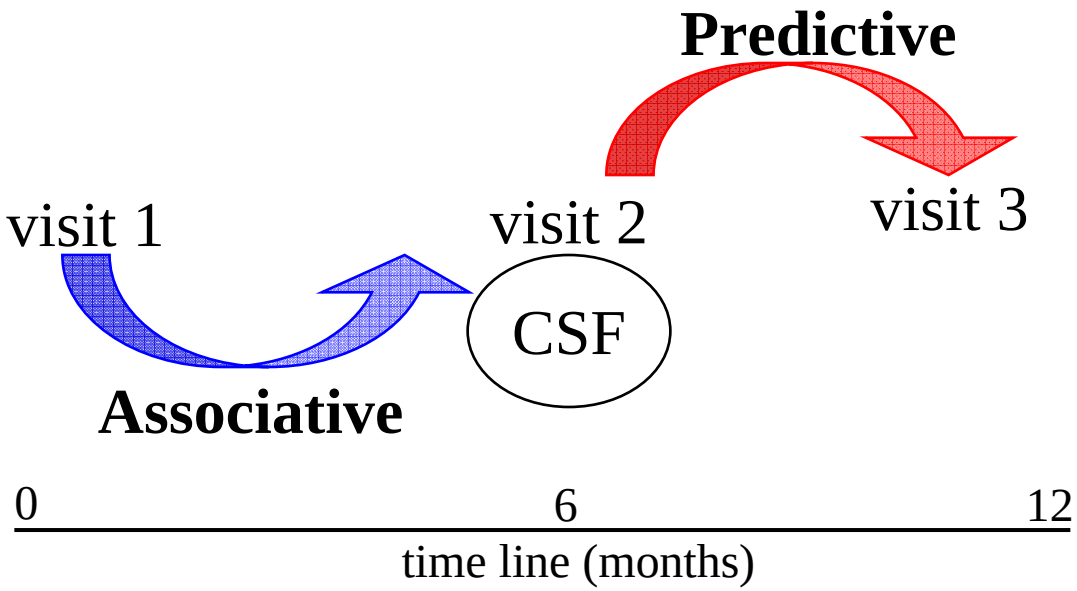
Post HAART patients were grouped based on changing cognitive status

Associative

HIV-not demented (HIV-ND)
HIV-inactive dementia (HIV-ID)
HIV-active dementia (HIV-AD)
(worse)

Predictive

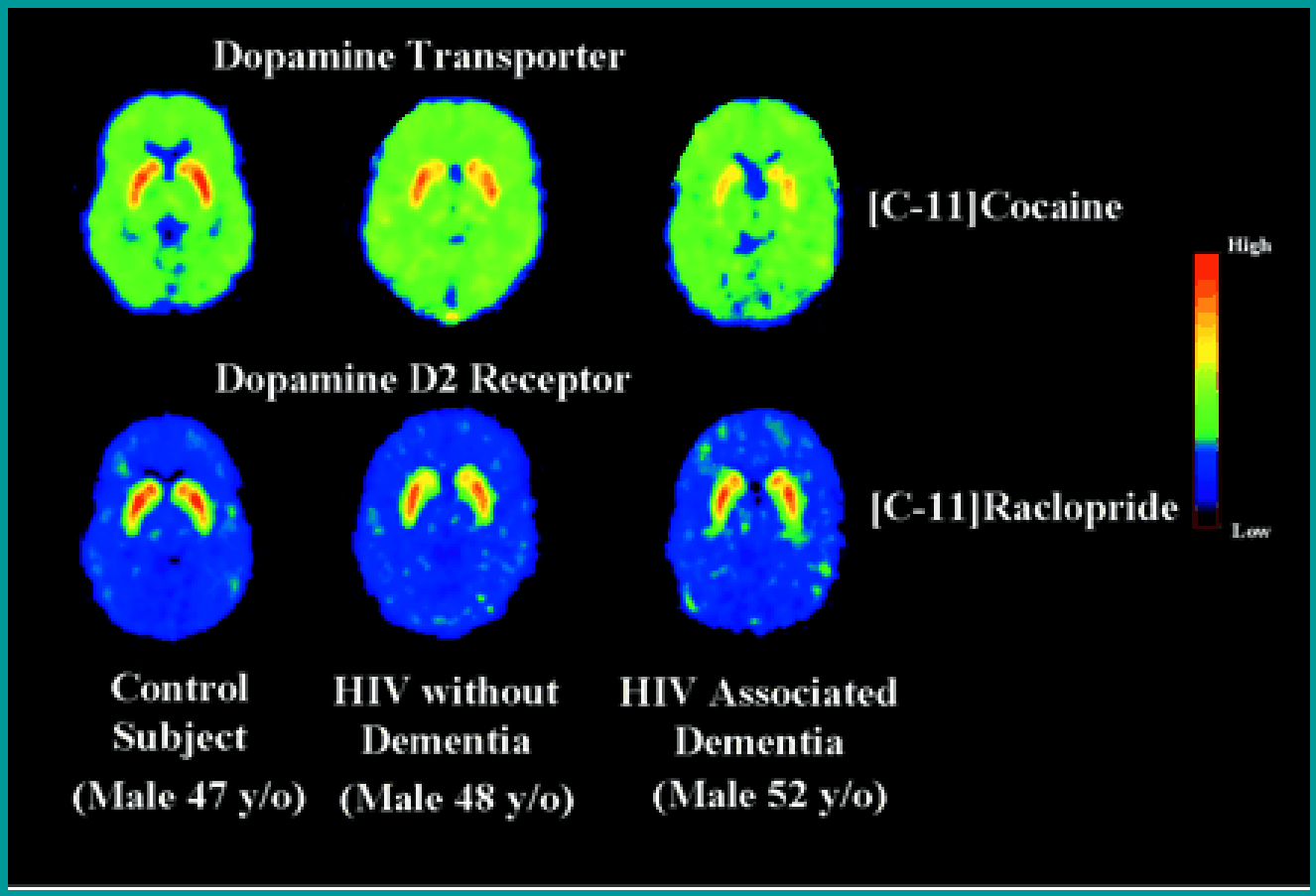
HIV-not demented (HIV-ND)
MSK-stable (MSK-stb)
MSK-improved (MSK-imp)
MSK-worse (MSK-wor)



MRS correlates in HIV-dementia

- ↓ NAA, ↑ CHO, ↑ MI on SV-MRS *(Barker P; Chang L; Navia B)*
- SV-MRS abnormalities in mild neurological dz *(Gonzales G; Chang L).*
- Correlates with NP testing, CSF HIV RNA levels *(Chang L)*; and immune activation markers (*Ryan, Gendelman)*
- Normalizes with HAART, but changes can take 9 months *(Chang L)*
- Not confirmed in other HIV+ groups

Novel measures for HIV-D ?: dopamine PET in HIV-D *Chang Brain 2004*



22. **Acute and early infection cases exhibit alterations in cerebral blood flow.**

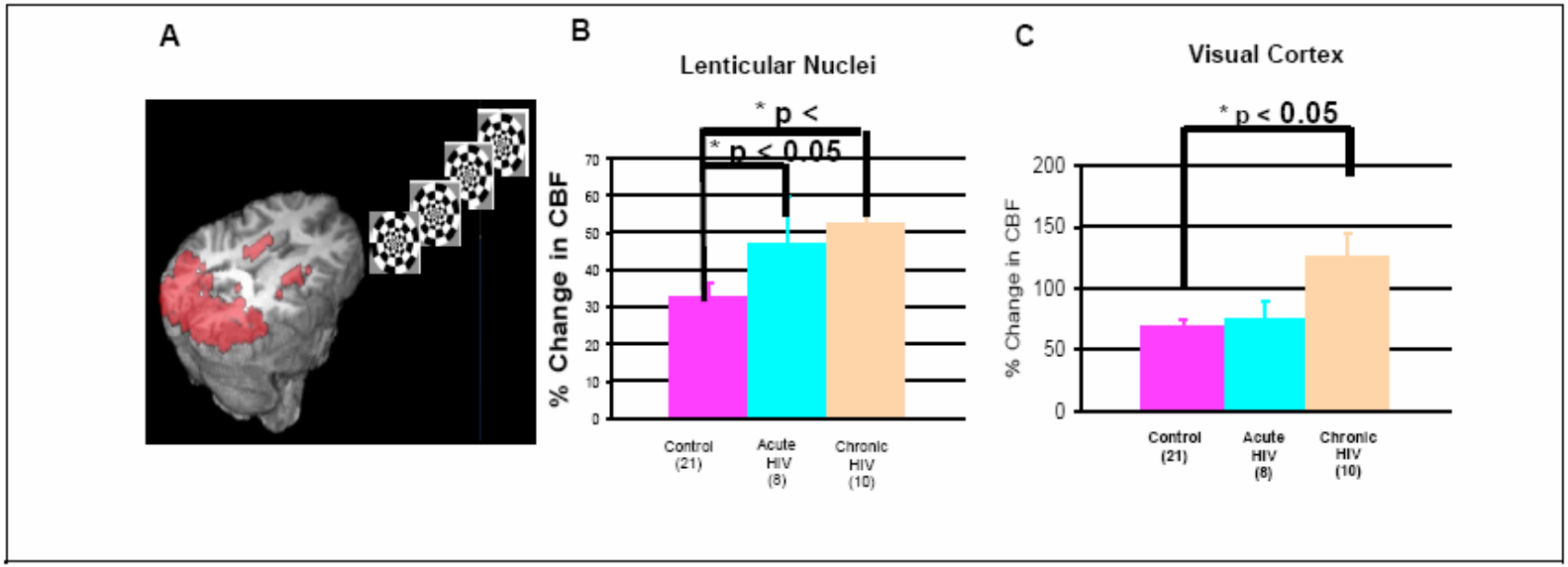


Figure 5. (A) In order to activate the visual cortex and lenticular nuclei, participants were to press keys on a keypad that corresponded to numbers presented in the center of a flickering checkerboard stimulus. Cerebral blood flow, determined via arterial spin labeling, is shown for (B) lenticular nuclei and (C) visual cortex of acute and early infection cases.

Is there a therapeutic 'gap' for HAND ?

- **Despite HAART's effect on incidence, prevalence of HAND remains high**
- **Neuronal loss is presumably permanent, even when CNS inflammation is 'burnt out'**
- **HAART can reverse neurocognitive deficits, but usually is only partial**

Design of ART and adjunctive trials for HIV-D ~ *clinically relevant questions*

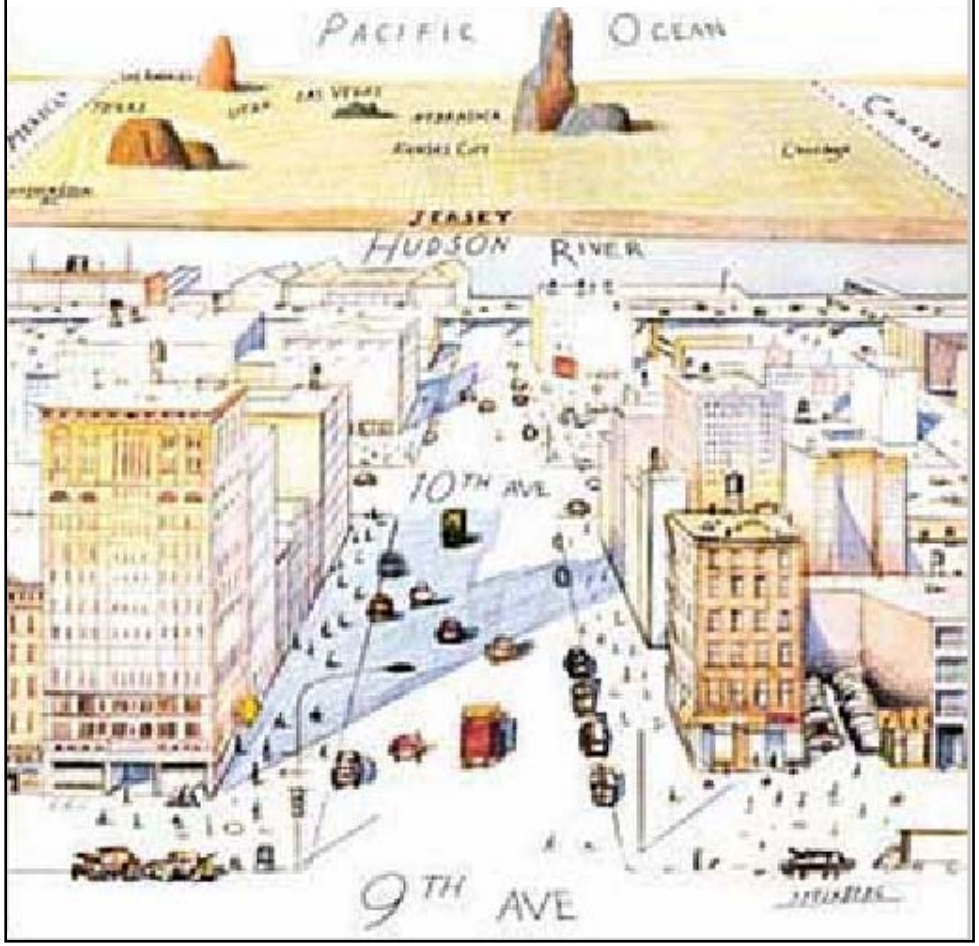
- How reversible is HAND, and when should treatment start ?
- If virological suppression is complete, will this protect against HAND ?
- What is needed to close treatment gap ?
- What are the determinants of treatment response ?
- How can we dissect comorbidities ?
- Can we improve outcome measures to reduce variability and sample size ?

Challenges for the NeuroAIDS community

- Identify neurological priorities for NIH, national AIDS organizations, and support NARC
- Emphasize prevalence and functional importance of HIV-D, MCMD, and ANI
- Develop clinically useful *predictive and surrogate* markers
- Design and conduct controlled clinical trials *rapidly and with large enough numbers to impact practice*
- Recognize limitations of current definitional criteria and of autopsy-based series
- Develop therapies and outcome measures that can be applied in resource-limited settings

The HIV Neurologist 2007

.....with apologies to The New Yorker



To date,
no therapies,
diagnostics,
or predictive
markers have
entered clinical
practice