

HIV & CNS

NAP Retrovirology - 2016

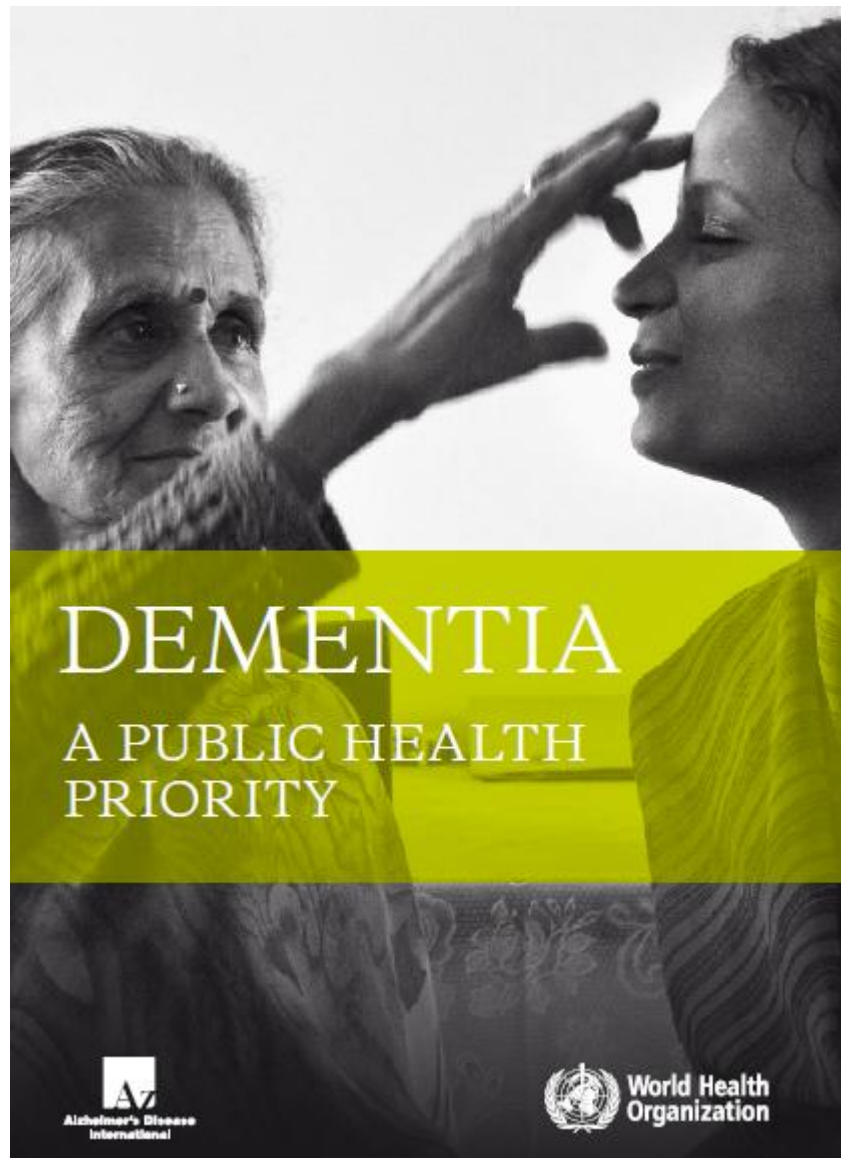
HAND

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http://www.who.int/mental_health/publications/dementia_report_2012/en/index.htm

DEMENTIA

A PUBLIC HEALTH PRIORITY

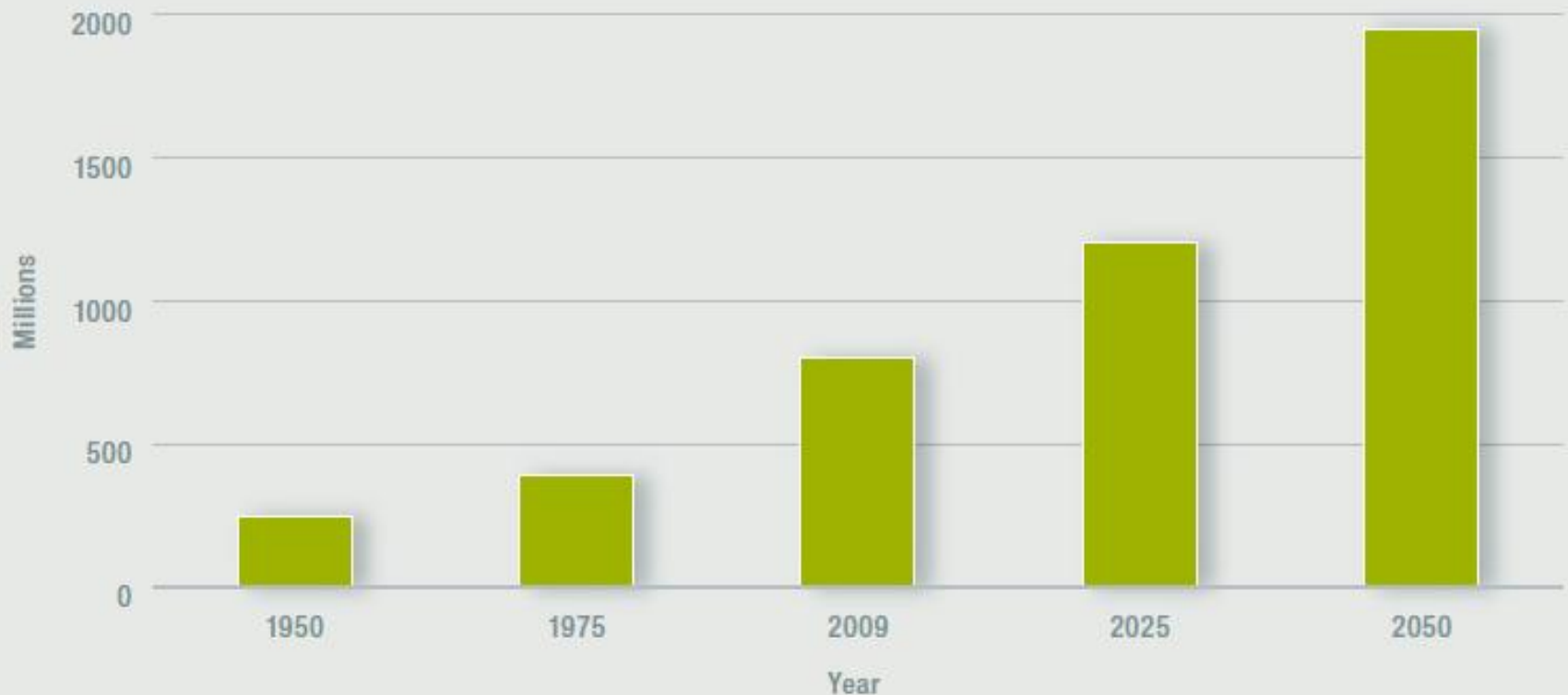


FIG 1.1 World population aged 60 years or over, 1950–2050 (5)

DEMENTIA

A PUBLIC HEALTH PRIORITY



FIG 2.2 Estimated prevalence of dementia for persons aged 60 and over, standardized to Western Europe population, by Global Burden of Disease region

GRID

(Horowitz SL, *et al.* Ann Neurol 12:80, 1982)

AIDS

(Snider WD, *et al.* Ann Neurol 14:403, 1983)

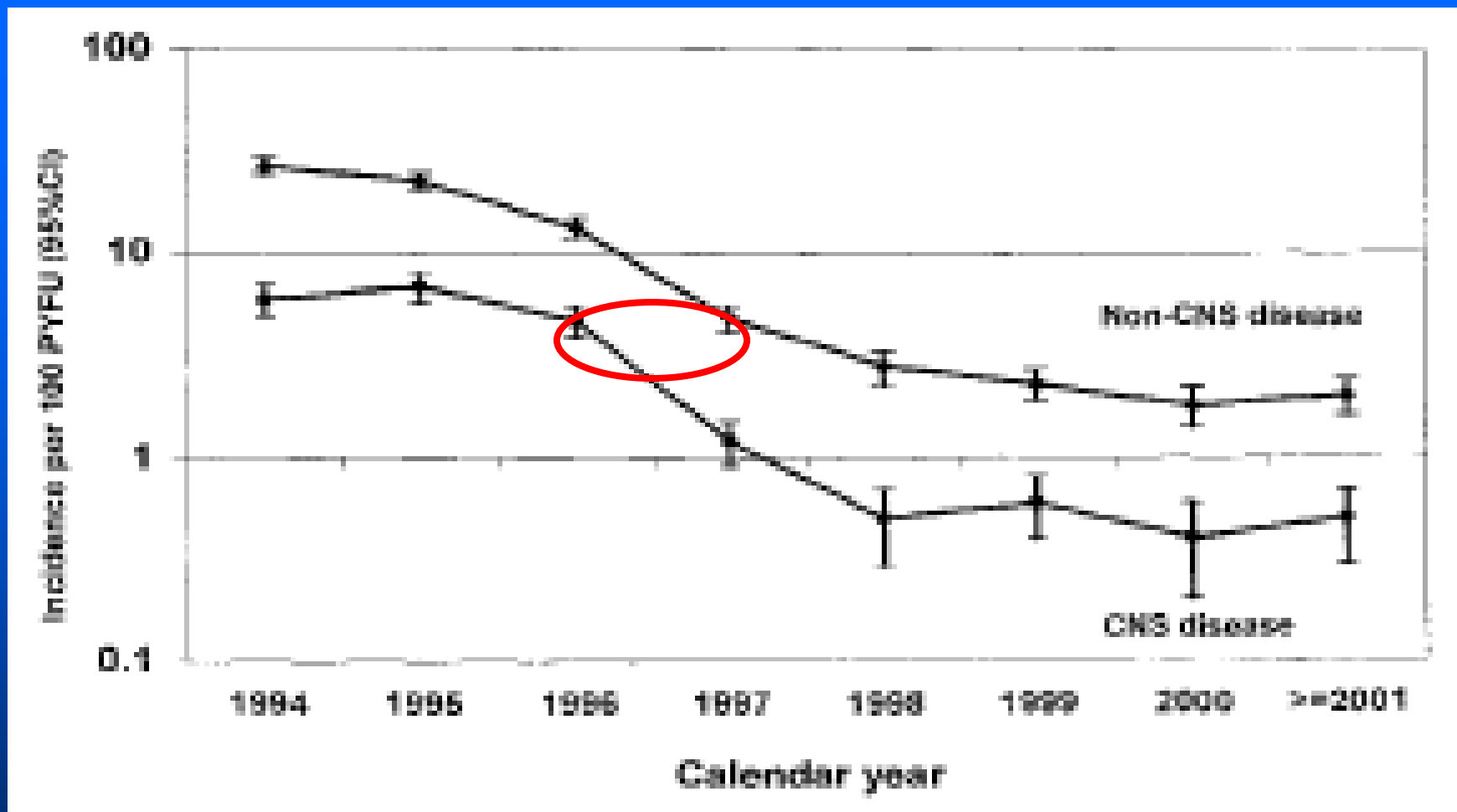


HAART ERA - DEVELOPED COUNTRIES

**Important reduction in morbidity and mortality
in patients with AIDS**

(Hogg RS et al., 1998)





d'Arminio Monforte *et al.* Ann Neurol 2004;55:320-8



NeuroAIDS in the HAART era - Italy

(January 2000 – March 2004)

(n = 1,136)

Disease	n (%)
CNS Toxoplasmosis	324 (28.5)
HIV Encephalopathy	231 (20.3)
PML	136 (12)
Neurocryptococcosis	111 (9.8)
EUO	85 (7)
PSNCL	40 (3.6)
Neurotuberculosis	26 (2.3)
CMV Encephalitis	11 (1)
HSV Encephalitis	6 (0.6)



HAART era - Neurology

Decrease in some opportunistic infections

Increase in inflammatory affections and
therapeutic adverse effects

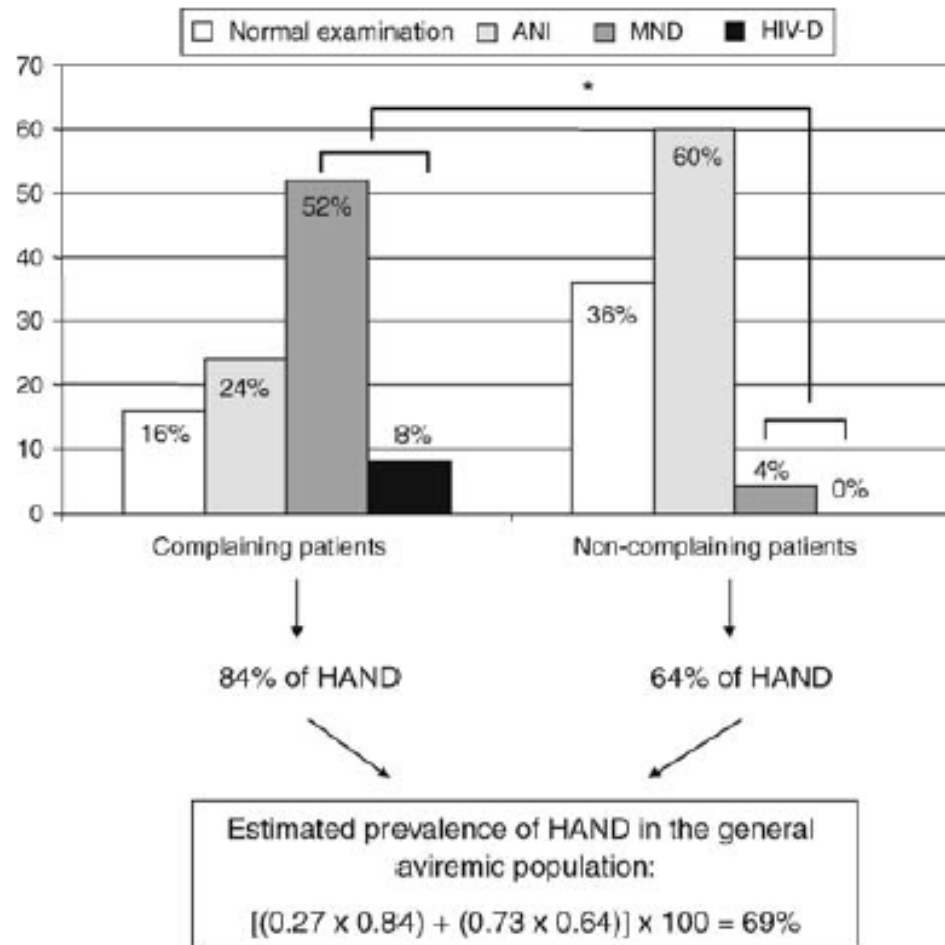
Primary HIV-CNS infection

(Dore G, *et al.* AIDS 13:1249, 1999)

HIV-related neurological diseases are
common despite HAART



Prevalence of HAND in cART-treated suppressed patients



MINISTÉRIO DA SAÚDE

SECRETARIA DE VIGILÂNCIA EM SAÚDE

1º ENCONTRO CIENTÍFICO DE PESQUISAS APLICADAS À VIGILÂNCIA EM SAÚDE

Prevalência e fatores associados as alterações neurocognitivas em pacientes com HIV-1

Coordenador: Maria Rita Polo Gascón

Instituição: Instituto de Infectologia Emílio Ribas

E-mail: mariaritapolo@yahoo.com.br

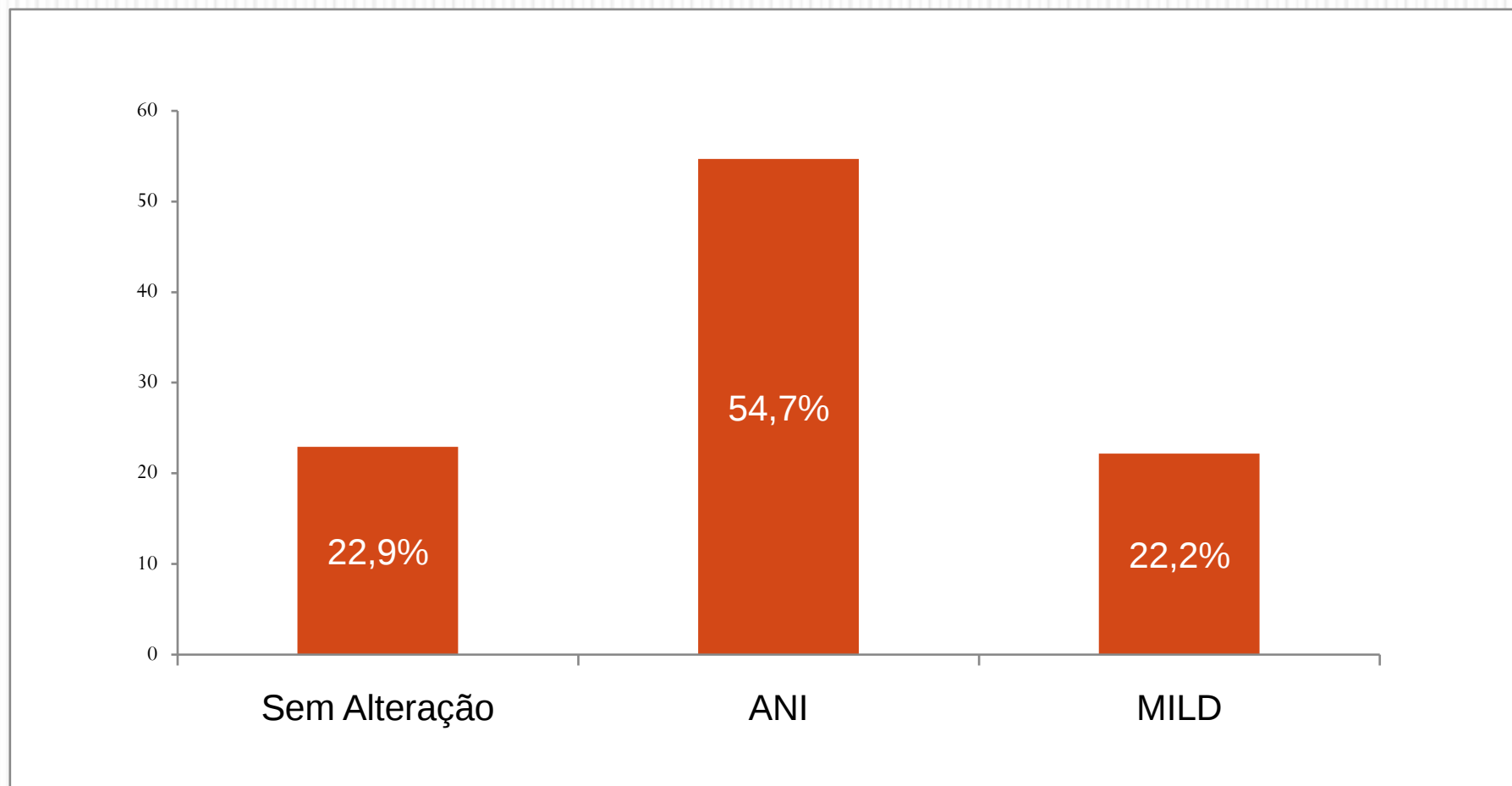


RESULTADOS

✓ 575 pacientes;

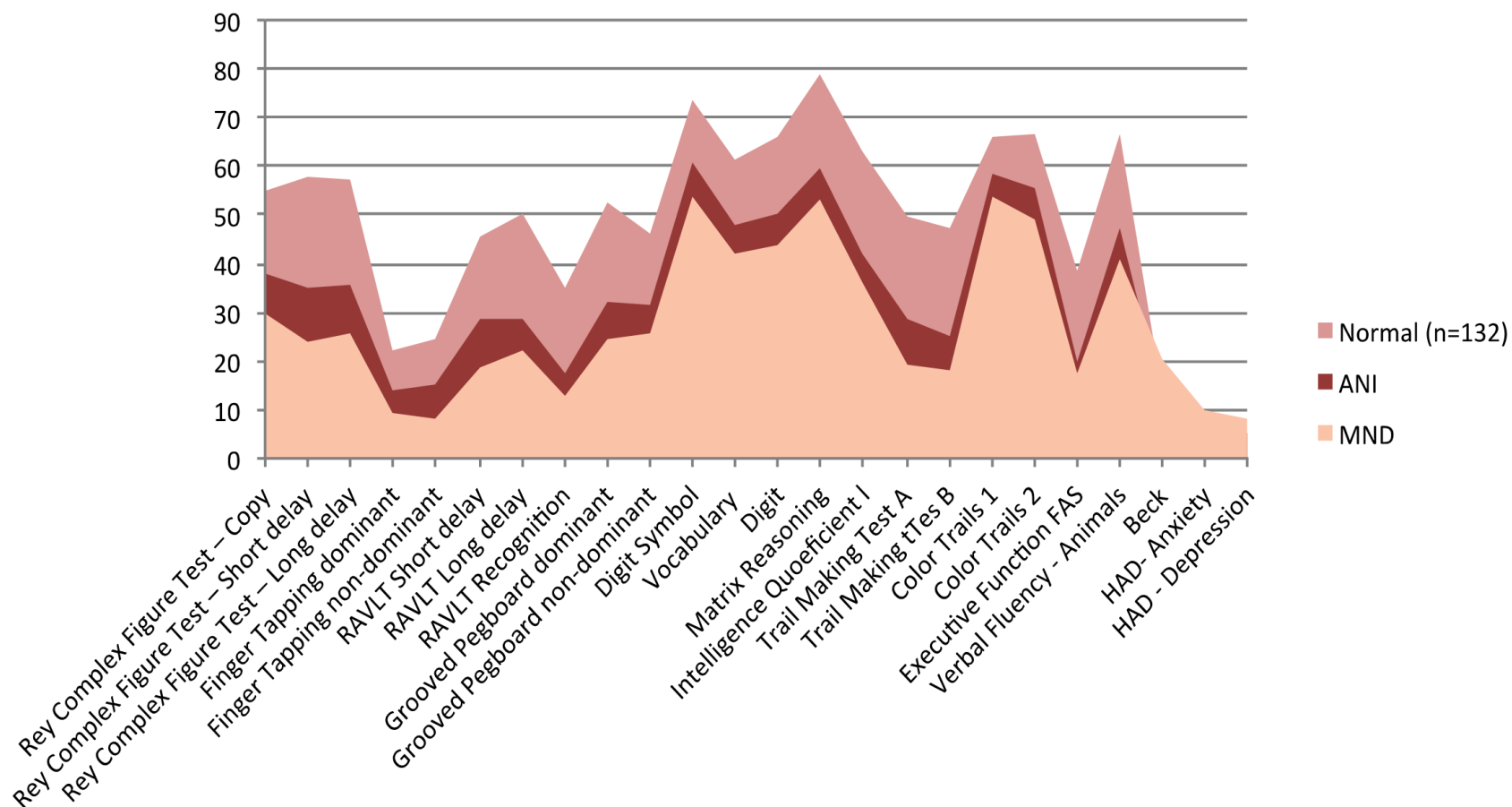
Characteristics	
Male, n(%)	377 (65.6)
Age, year mean(CI)	44.98 (44.1 – 45.9)
Education, year mean(CI)	11.92 (11.62- 12.22)
Time of infection diagnosis, year mean(CI)	13.13 (12,49 – 13.78)
CD4, mean(CI)	631 (604 – 658)
Viral load indetectable n(%)	427 (74.3)
No previous disease n(%)	456 (79.3)

Results: (HAND) – 575 patients – São Paulo, BRAZIL, 2015



RESULTADOS

Atenção – Memória – Speed – Função Visuo-espacial

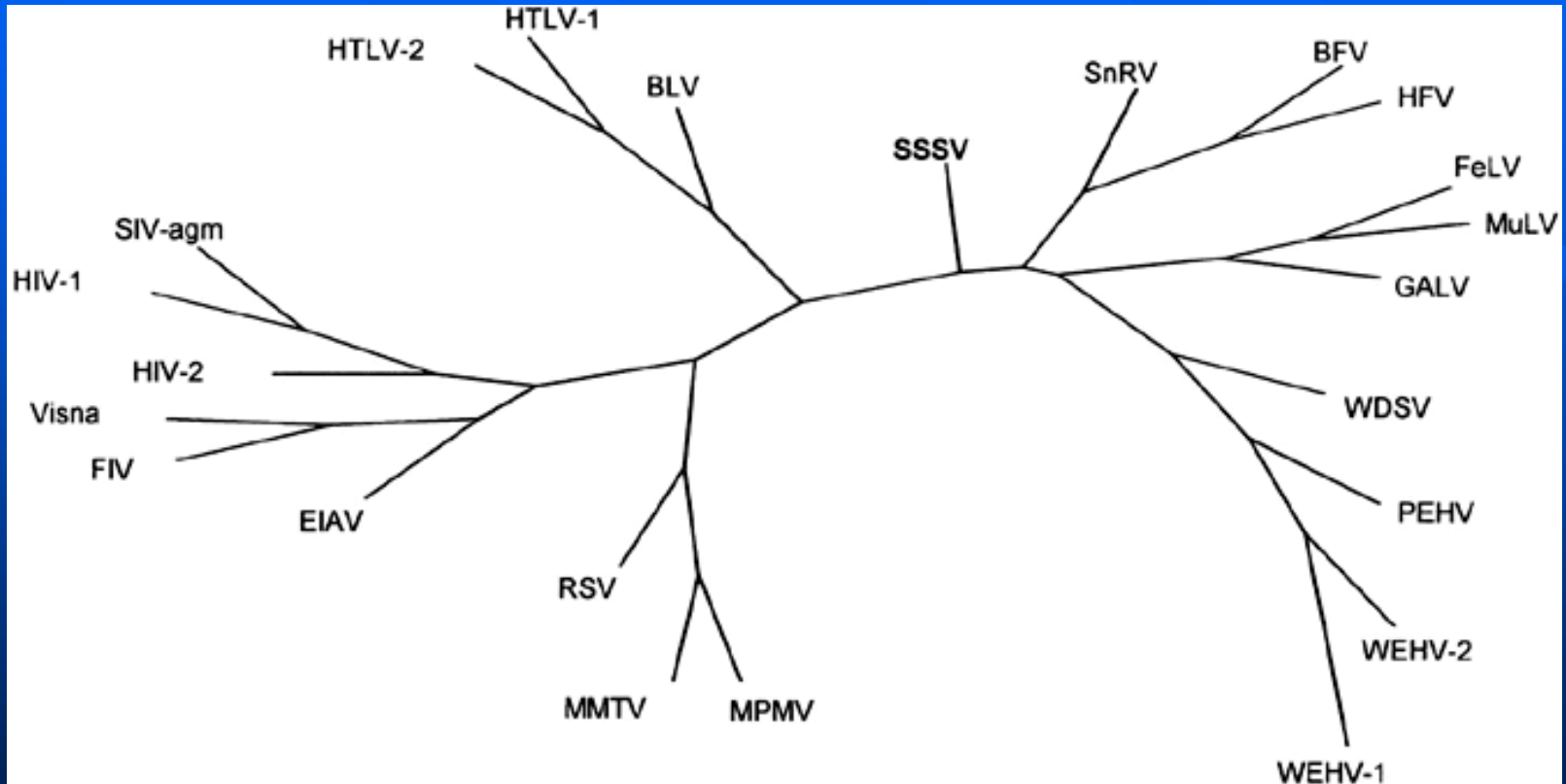


4. Resultados:

✓ Na comparação em função da HAND foram encontradas diferenças significativas entre os 3 grupos em:

Gênero M ($p < 0,001$)
Escolaridade ($p < 0,001$)
Carga viral ($p < 0,001$)
Doença prévia ($p < 0,001$)

ÁRVORE FILOGENÉTICA DA FAMÍLIA RETROVIRIDAE





HIV-1 X HTLV-I - HTLV-II

HIV-1

- Origem: ~100 anos
- Receptor: T CD4
- Infectividade: Alta
- Taxa Mutação: Alta
- 10 subtipos
- Recombinação: Sim
- **Replicação: Alta**
- **Evolução: 90% em 10-15 anos**
- **Apoptose: Alta**
- IL-2: Baixa

HTLV-I

- ~ 100.000 anos
- T CD4+
- Baixa
- Baixa
- 5 subtipos
- Não
- **Baixa**
- **<5% em 30-40 anos**
- **Diminuída**
- IL-2: Elevada



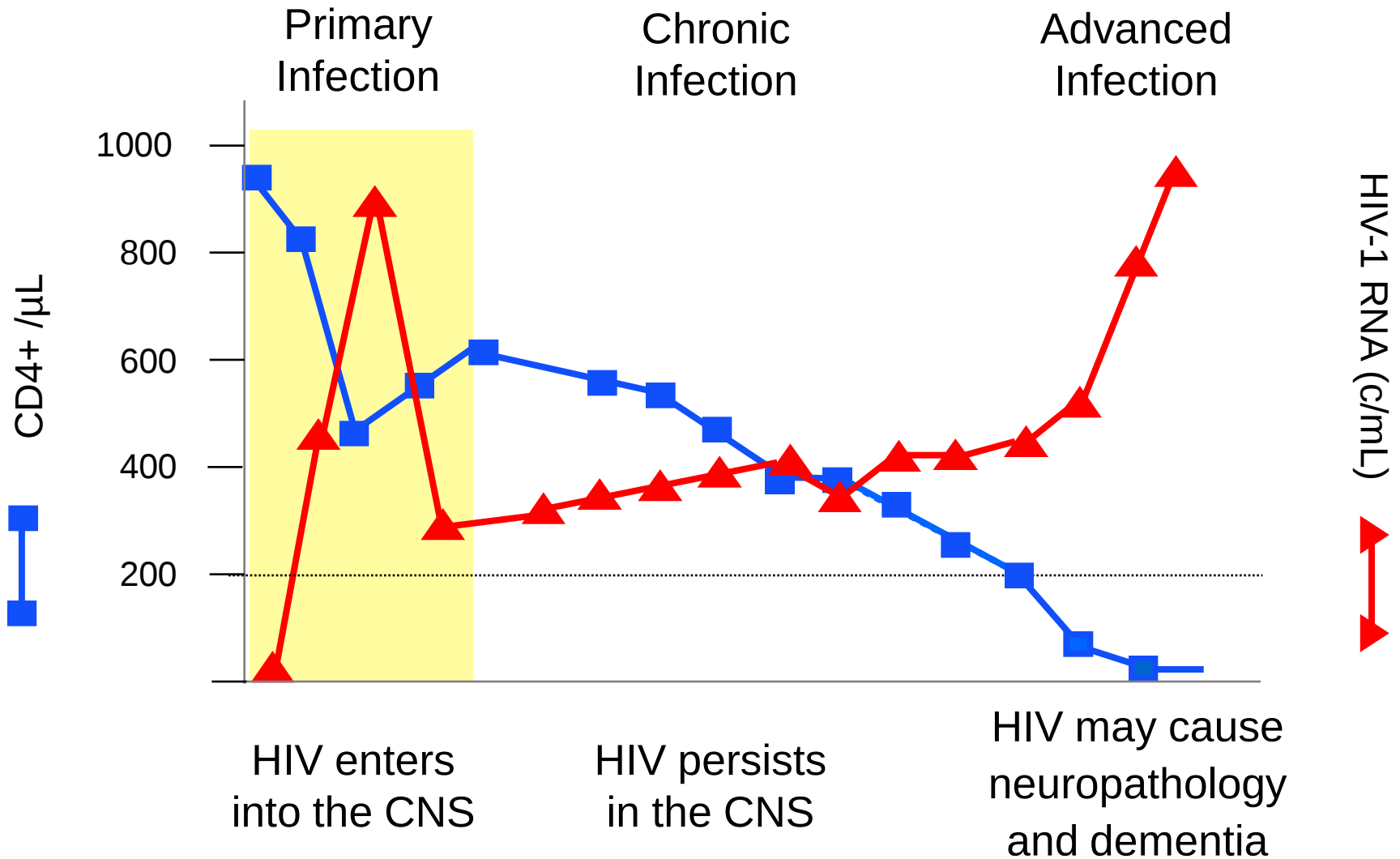
HAND

(HIV Associated Neurocognitive Disorder)

(Neurology, 2007)



HIV and the CNS



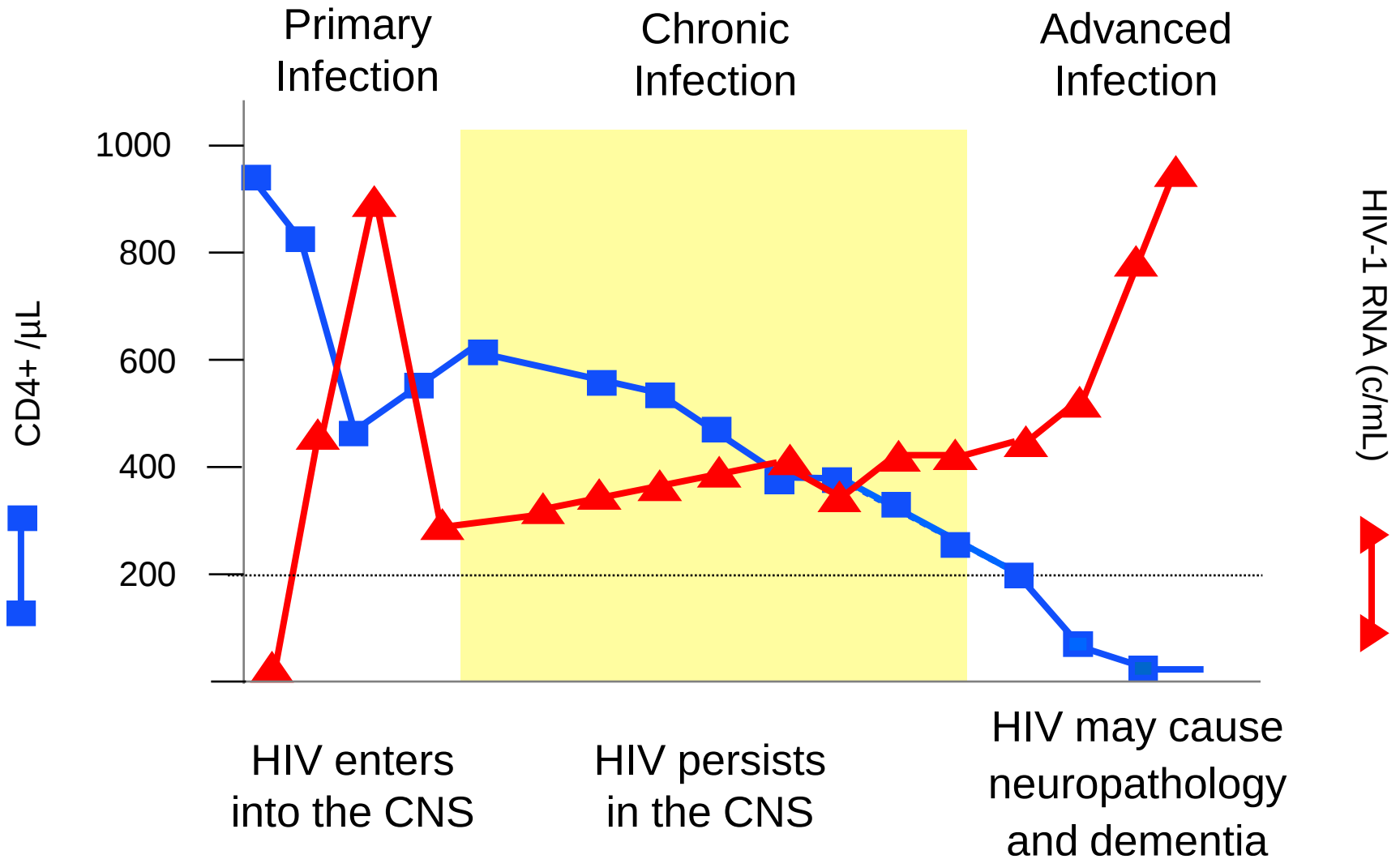
What clinical evidence indicates that HIV invades the CNS in early HIV?

ANSWER:

- In HIV seroconversion illness the CNS may be involved¹
 - Meningoencephalitis
 - Headaches
 - Seizures
 - Myelopathy
 - Cranial nerve palsies
 - Sensory polyneuropathy
 - Guillain Barre syndrome
 - **Natalizumab – M.C. – Encefalopatia aguda**

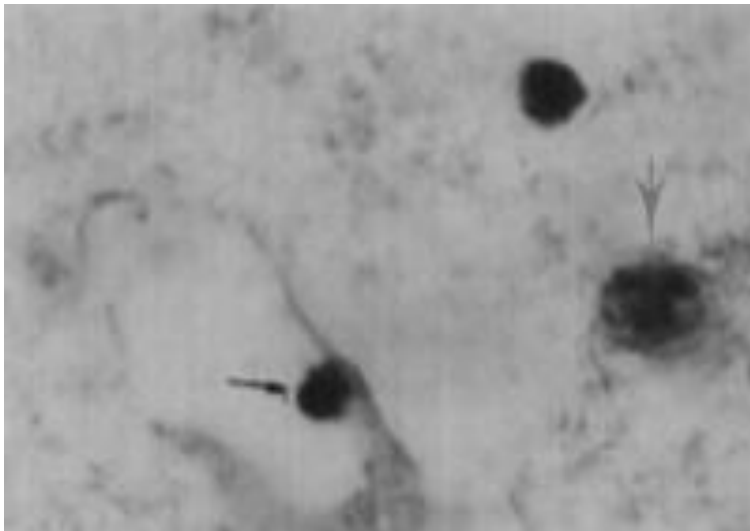


HIV and the CNS



HIV-1 DNA in the CNS in asymptomatic HIV infection: cell localization by in situ-PCR

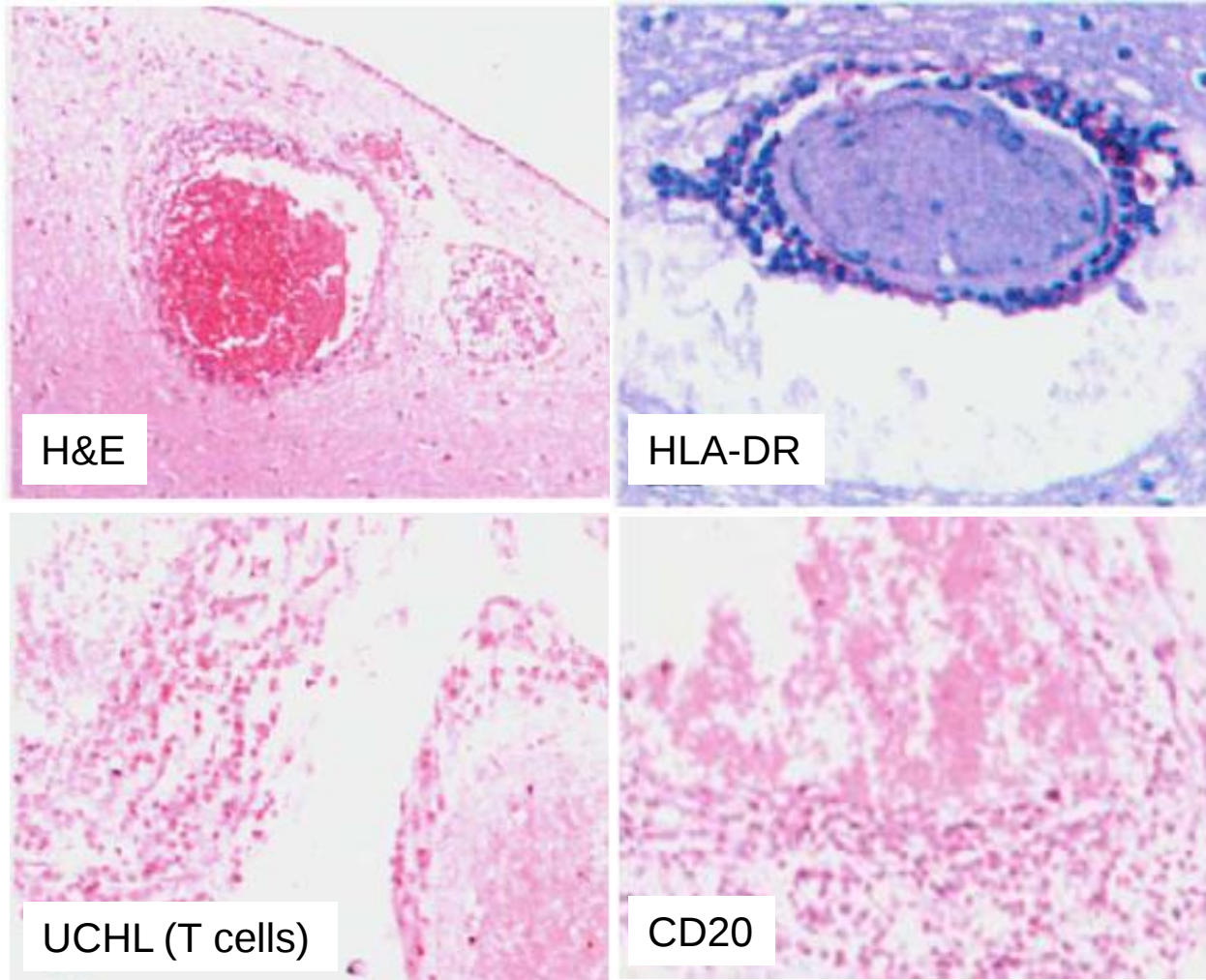
HIV DNA in microglial cells



HIV DNA in astrocytes and endothelial cells



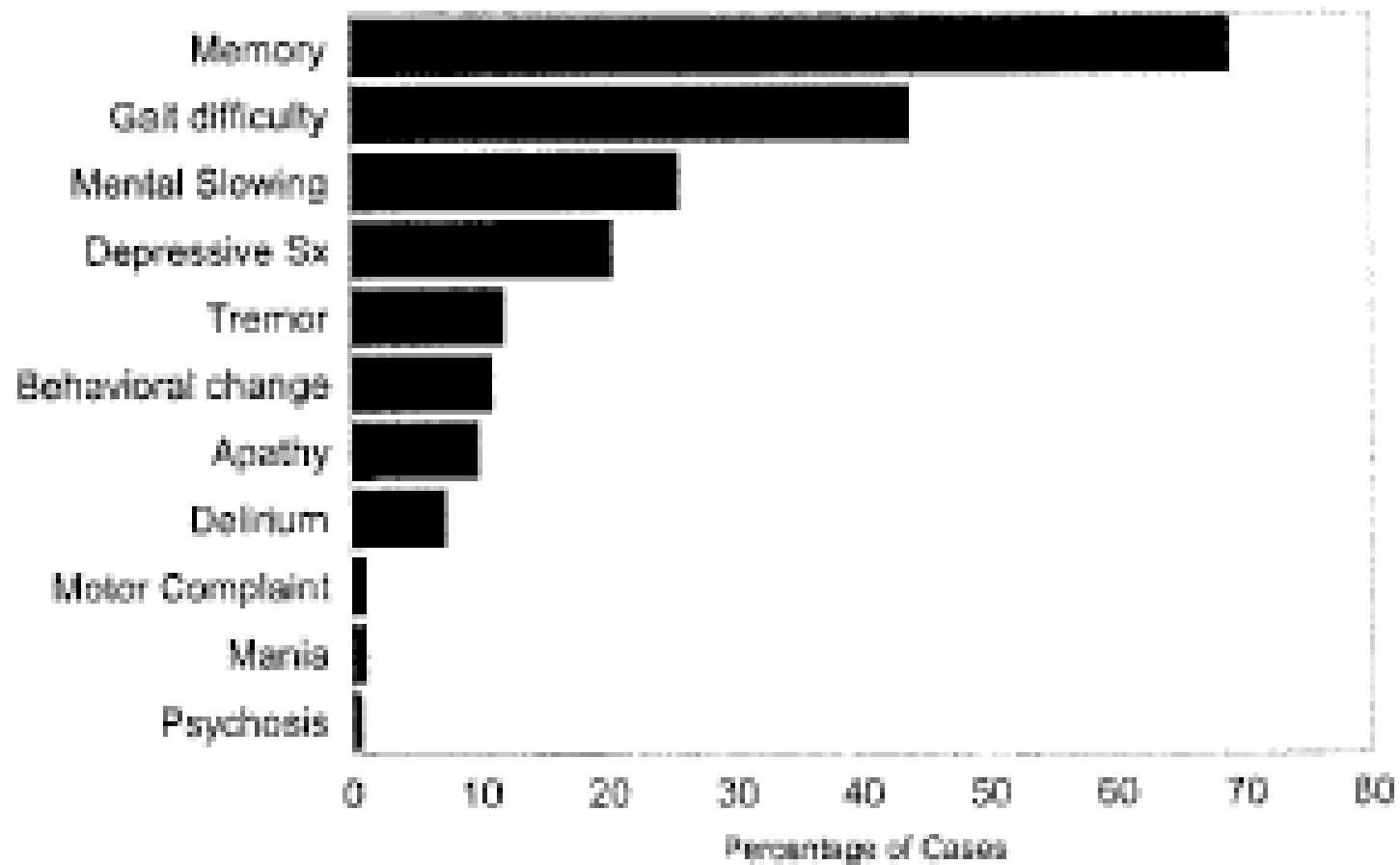
Inflammatory changes in the brain of early HIV-1 infection



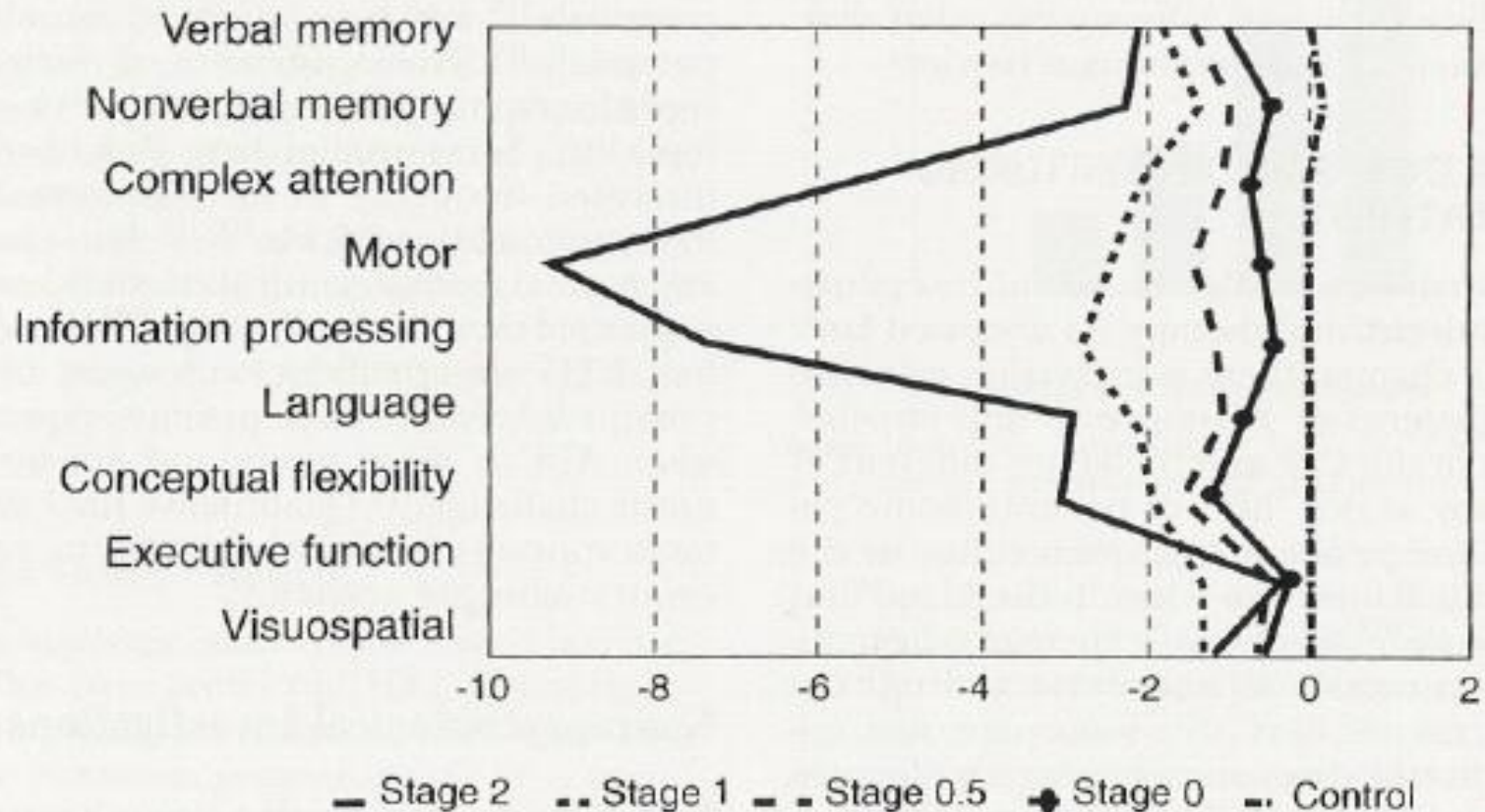
HIV Associated Neurocognitive Disorder (HAND) - HAD

- Subcortical dementia
 - Cognitive impairment
 - Psychomotor slowing
 - Behavioural changes (*Navia et al, Ann Neurol 1986*)
- Cause
 - HIV infection brain =>immune dysregulation and damage 2^o cytokines and viral toxins





Neuropsychological profiles



Updated research nosology for HIV-associated neurocognitive disorders

A. Antinori, MD

***Neurology*[®] 2007;69:1789-1799**



Definitions

■ HIV Associated Dementia (HAD)

- Acquired neurocognitive deficit => **functional** impact work and ADLs
- Evidence of motor and behavioural impairment
- No other plausible explanation for changes
 - » *(Report of a working group of the American Academy of Neurology AIDS Task Force. Neurology, 1991)*
- Validated Research Case Definition
 - » *(DANA Consortium. Clinical conformation of the American Academy of Neurology algorithm for HIV-1-associated cognitive/motor disorder, Neurology 1996)*



Definitions

■ Mild Neurocognitive Disorder - MND

- Acquired neurocognitive deficit => **Mild** impact work and ADLs
- Evidence of motor and behavioural impairment
- No other plausible explanation for changes
 - » *(Report of a working group of the American Academy of Neurology AIDS Task Force. Neurology, 1991)*



Definitions

- Asymptomatic Neurocognitive Impairment (ANI)
- (how much asymptomatic?, progressive, CROI, 2012)
- Patients have mild impairment that does not meet definition of HAD or MND
- Acquired neuropsychological abnormalities in N. assessment – 2 ability domains



Asymptomatic HIV-associated Neurocognitive Disorder Increases Risk for Future Symptomatic Decline: A CHARTER Longitudinal Study (Heaton R *et al*, CROI 2012. Abstract 77)

“It has been suggested that the ANI diagnosis is not valid, does not predict clinical outcomes, and may be a statistical artifact. Findings from this large longitudinal study demonstrate that ANI and MND are significant and comparable risk factors for incident cognitive worsening over 18 to 42 months, indicating that ANI and MND are both clinically important. The additional specific risk factors for such cognitive decline require further elucidation.”



Definition of HIV-Associated Neurocognitive Disorders (HAND)

	Acquired Impairment in 2 Cognitive Abilities	Interferes with Daily Functioning
Asymptomatic Neurocognitive Impairment (ANI)	YES	NO
Mild Neurocognitive Disorder (MND)	YES	MILD
HIV-Associated Dementia (HAD)	MARKED	MARKED

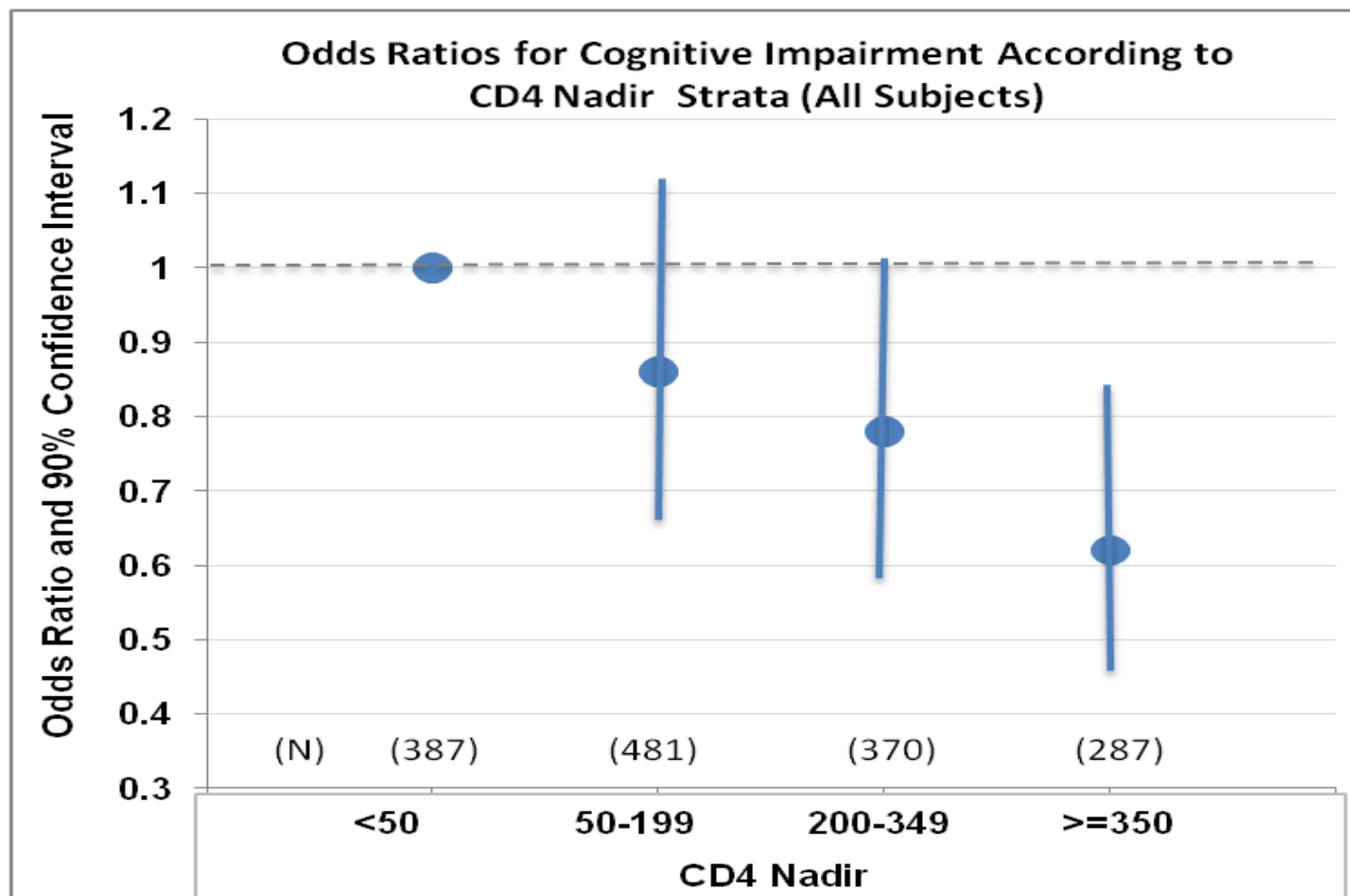
No Pre-Existing Cause, Delirium absent

Fatores de risco para HAND

Nadir de CD4, CD4 atual, *set point* viral, tempo de infecção, tempo de uso do HAART, idade, anemia, IMC, hepatite C, uso de drogas endovenosas, fatores genéticos do hospedeiro (p.e polimorfismos do promotor do TNF- α ou do MCP-1; isoforma E4 da apolipoproteína E).



HAND está associado com nadir de CD4

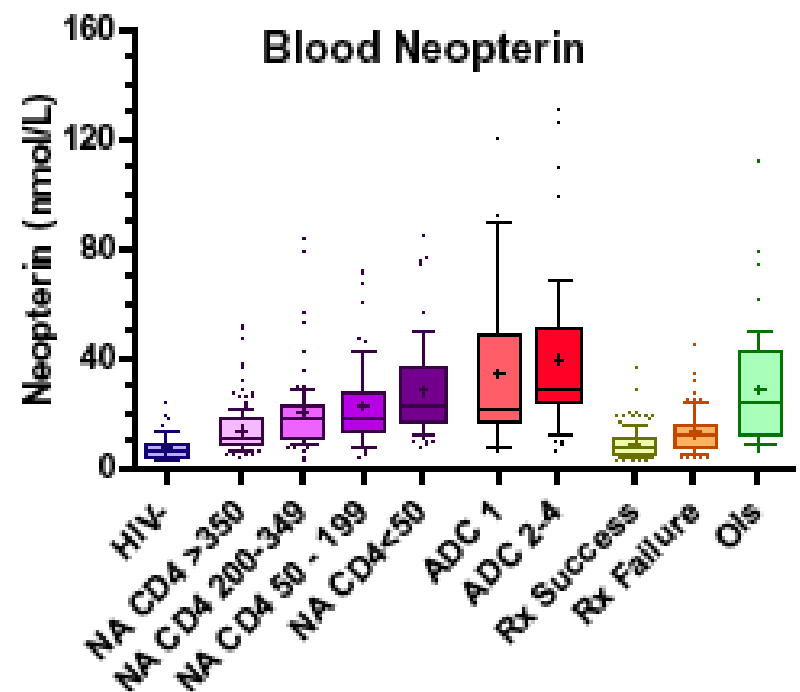
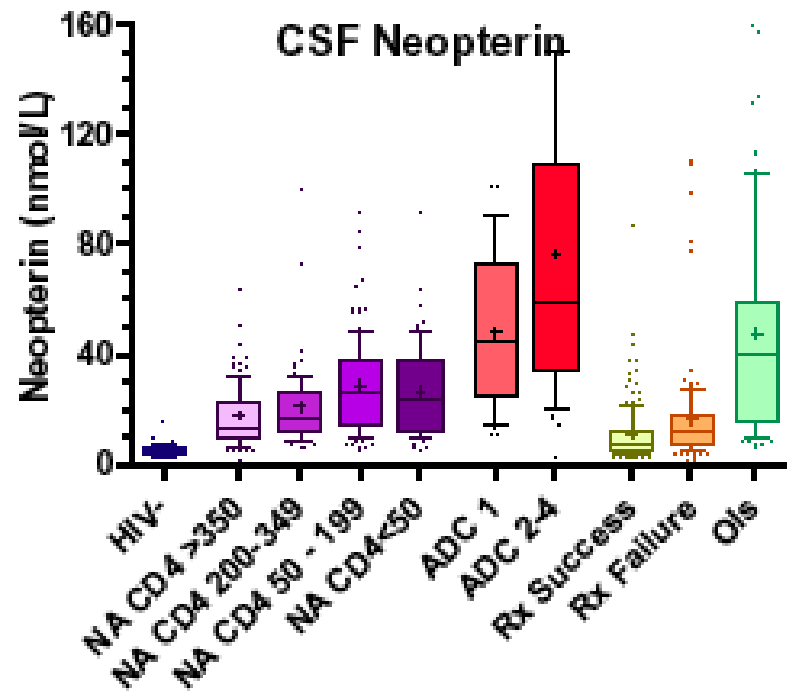


Blood Biomarkers

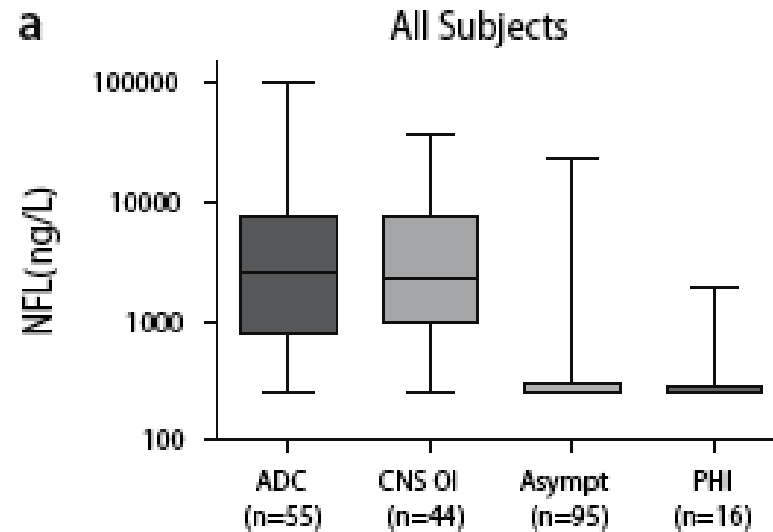
- CD4 Counts – especially nadir CD4
- Platelet Decline
- C-Reactive Protein
- Osteopontin
- Glucose, Lipids
- CVD & risk factors – (Smart - Neurology, 2010) – CROI 2016



CSF markers of immune activation



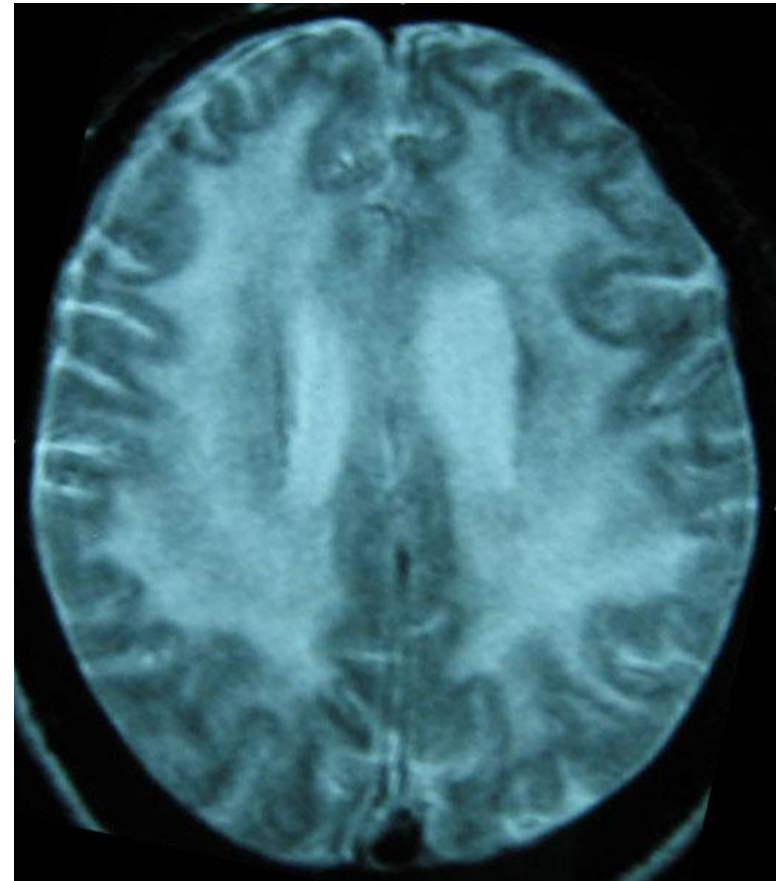
CSF Neurofilament (NFL) as marker of neuronal damage



The AIDS dementia complex (ADC)

AAN definition criteria (1991)

1. Acquired abnormality in at least two of the following cognitive abilities:
 - attention/concentration,
 - speed of processing of information,
 - abstraction/reasoning,
 - visuospatial skills,
 - memory/learning,
 - speech/language
2. At least one of the following:
 - a) Acquired abnormality in motor function or performance;
 - b) Decline in motivation or emotional control or change in social behavior
3. Absence of clouding of consciousness
4. Absence of evidence of other etiology



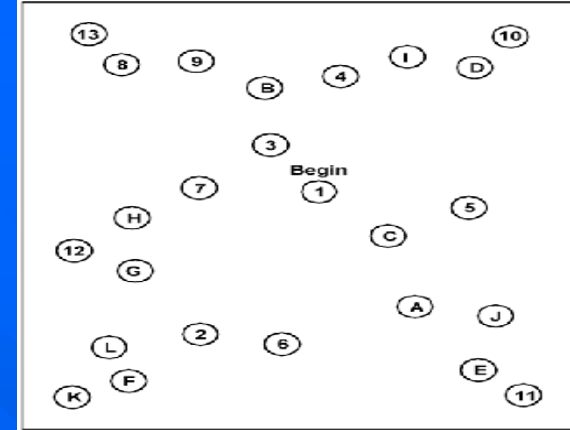
Screening for HAND

- MMSE – **not very useful** as concentrates on cortical features whereas HIV clinical features are more subcortical
- HIV Dementia Rating Scale – revised by Woods et al. with appropriate norms and improves sensitivity from 17% to 70%, respectively
- **Neuro-screening – IHDS - Sactor, 2005**



Diagnose - HAND

- Refer for neuropsychological testing, **OR** carry out
 - Grooved pegboard
 - Trails A and B
 - Digit-symbol
 - Action words/verbs/doing words rather than verbal fluency

[illegible]

HIV-1 Associated Neurocognitive Disorders (HAND) - classification

1. **Asymptomatic Neurocognitive Impairment (ANI)**
 - **15-60% patients**
 - Asymptomatic: only detectable with formal neuropsychological testing
2. **Mild Neurocognitive Disorder (MND)**
 - **Up to 40% patients pre- & post-HAART**
 - Causes mild-moderate impact on function at work and home
3. **HIV-Associated Dementia (HAD)**
 - **Incidence 7% per year CD4+ cells < 200/uL pre-HAART and 3% per year post-HAART'**
 - Causes significant impact upon function at home and work

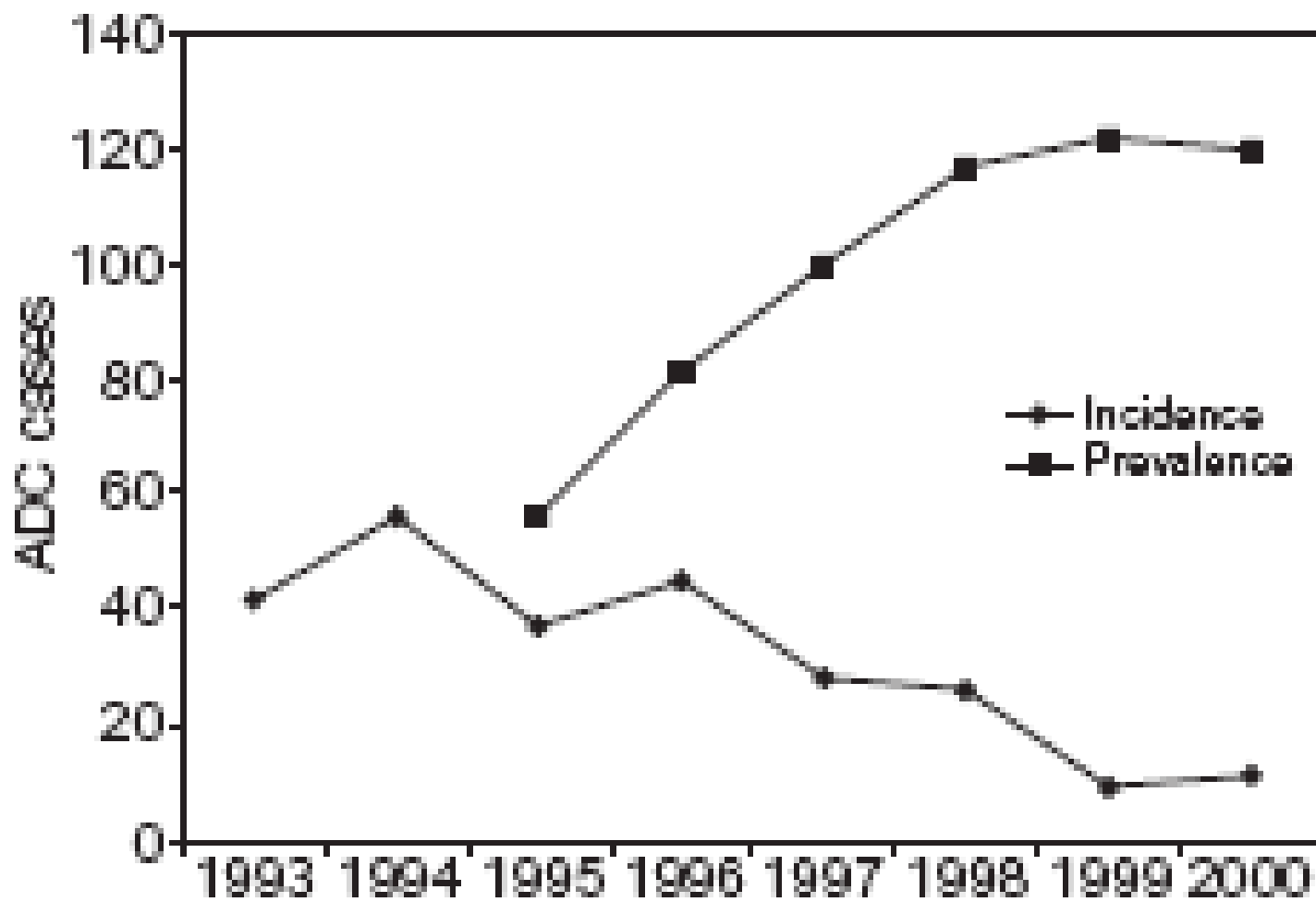


HAART - HAD

Johns Hopkins University - J. McArthur, 2003

- Incidence - decrease 50% after 1996
- Prevalence - 6,6% - 1994
- Prevalence - 10,1% - 2000





Dore *et al.* AIDS 2003;17:1539-45



HAART era - HAD

Sacktor N, *et al.* Neurology 56:257, 2001

- Pre - 20-30%
- Post - 10,5%
- Increased as AIDS defining illness
- Increased cases with CD4+>200
- Increased - MND



Change in the Natural History of HAD in HAART era: CD4 cell count “disconnect”

Study	1990-1995 Mean CD4 cell count/mm ³ at diagnosis ADC	1996-1998 Mean CD4 cell count/mm ³ at diagnosis ADC	1999-2001 Mean CD4 cell count/mm ³ at diagnosis ADC
MACS	150	286 (Sacktor, 2001)	518 (Sacktor, 2003)



Demência e contagem de células CD4

(média de CD4 ao momento do diagnóstico da demência)

Estudo	1990-1995	1996-1998	1999-2001	2001-2003
MACS	150	286 <i>(Sacktor et al 2001)</i>	518 <i>(Sacktor et al, 2003)</i>	
AUS	70	160 <i>(Dore et al 1999)</i>		418 <i>(Cysique et al 2004)</i>



HIV-related Neurocognitive Impairment - MND

- 40% HIV positive outpatients (*Cysique et al, 2002*)
 - » Mean CD4 cell count at testing 339 cells/uL
 - » 52% undetectable plasma HIV viral load
- Dana & NEAD cohorts
 - No change in neurocognitive impairment pre & post HAART (*Sacktor et al, 2002*)



HIV-Related Neurocognitive Disorder

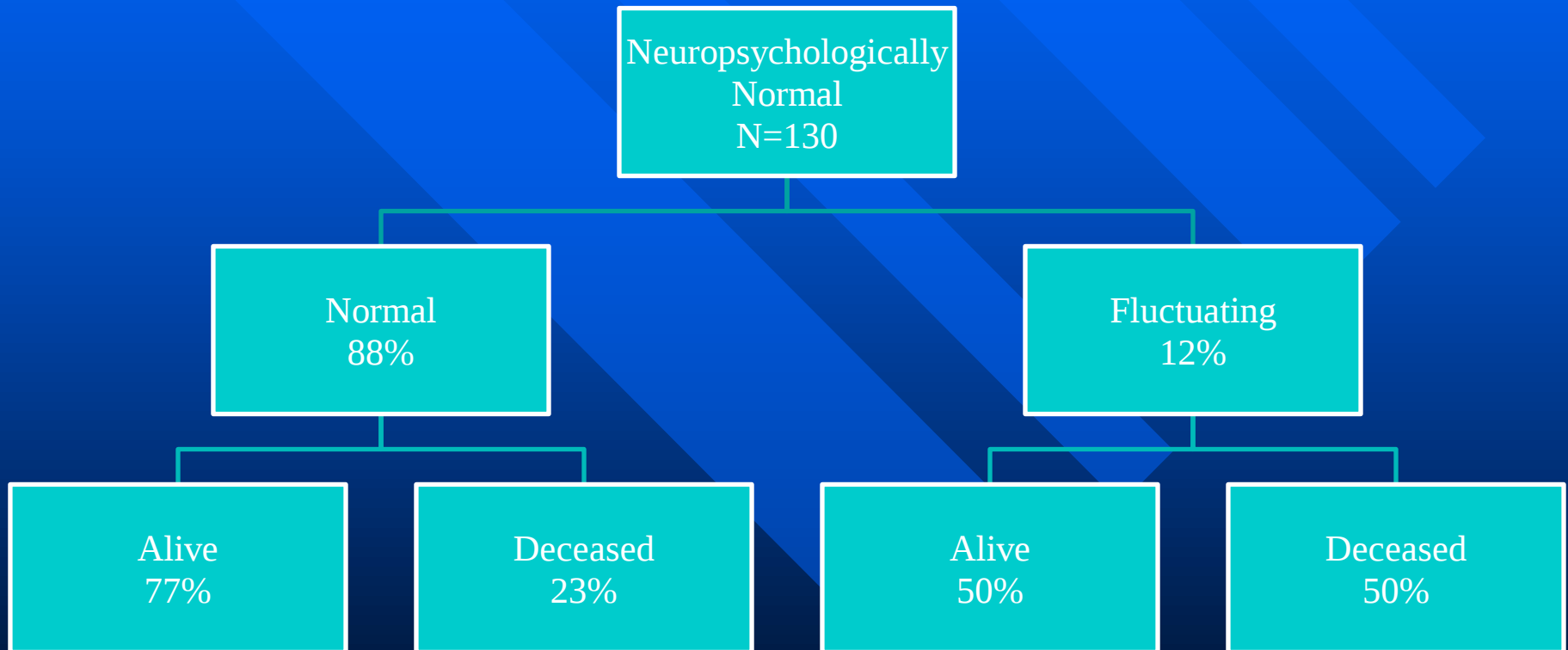
HIV-related Neurocognitive Impairment – MND

- Predicts underlying HIV-related Disease of Brain
(*Cherner et al ,2002*)
- Associated with Increased Risk for:
 - » Mortality (*Wilkie et al 1998;Sacktor et al 1996; Mayeux et al 1993; Price et al 1999*)
 - » ADC (*Stern et al ,2001*)
 - » Job loss (*Albert et al,1995*)
 - » Driving ability decline (*Marcotte et al, 1999*)
 - » Poor medication adherence in more severe neurocognitive impairment (*Hinkin et al, 2002*)

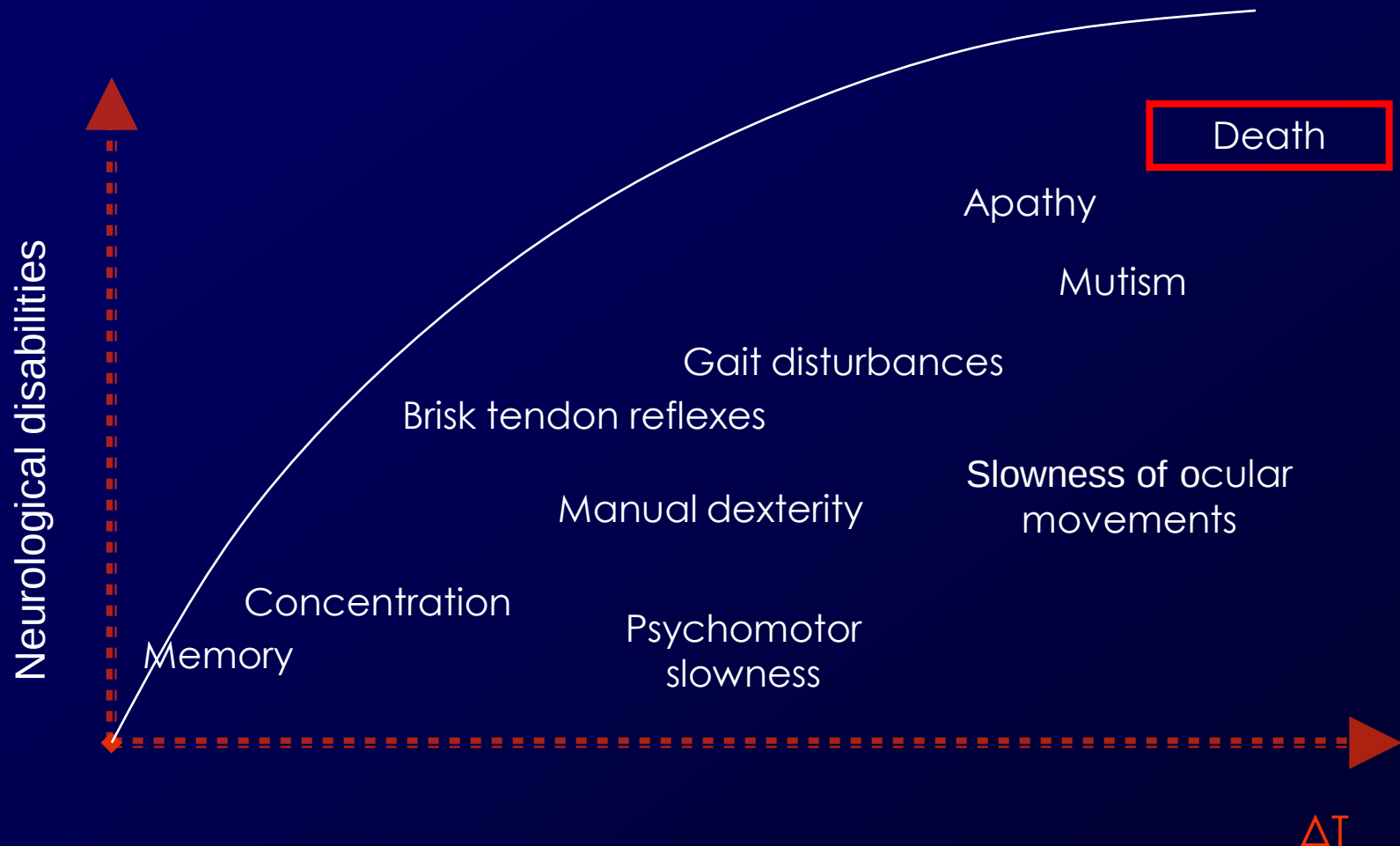


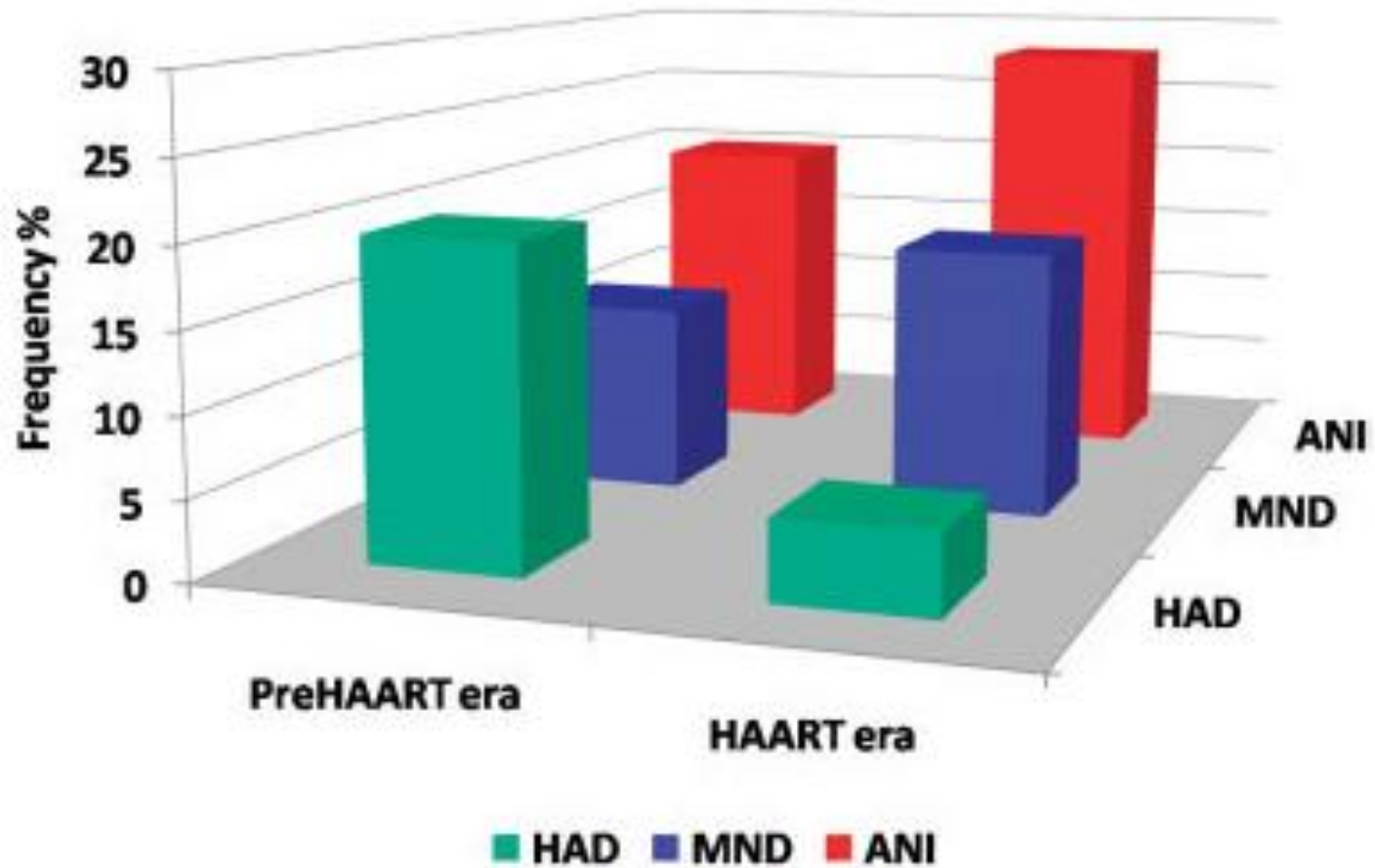
Clinical Progress

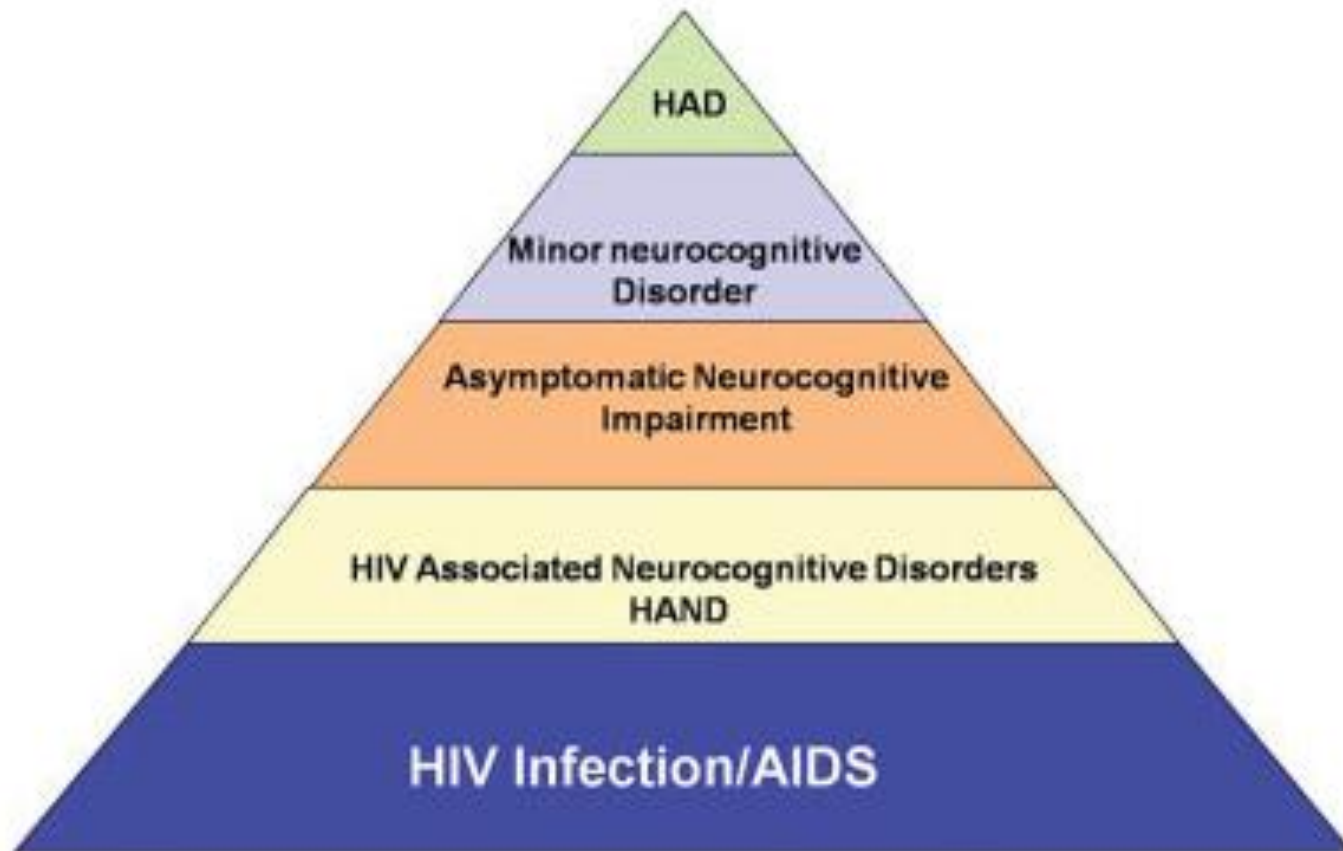
Consequences of neuropsychological impairments (over a minimum of 2 and up to 8 yrs) HNRC Study



HIV Dementia – without HAART

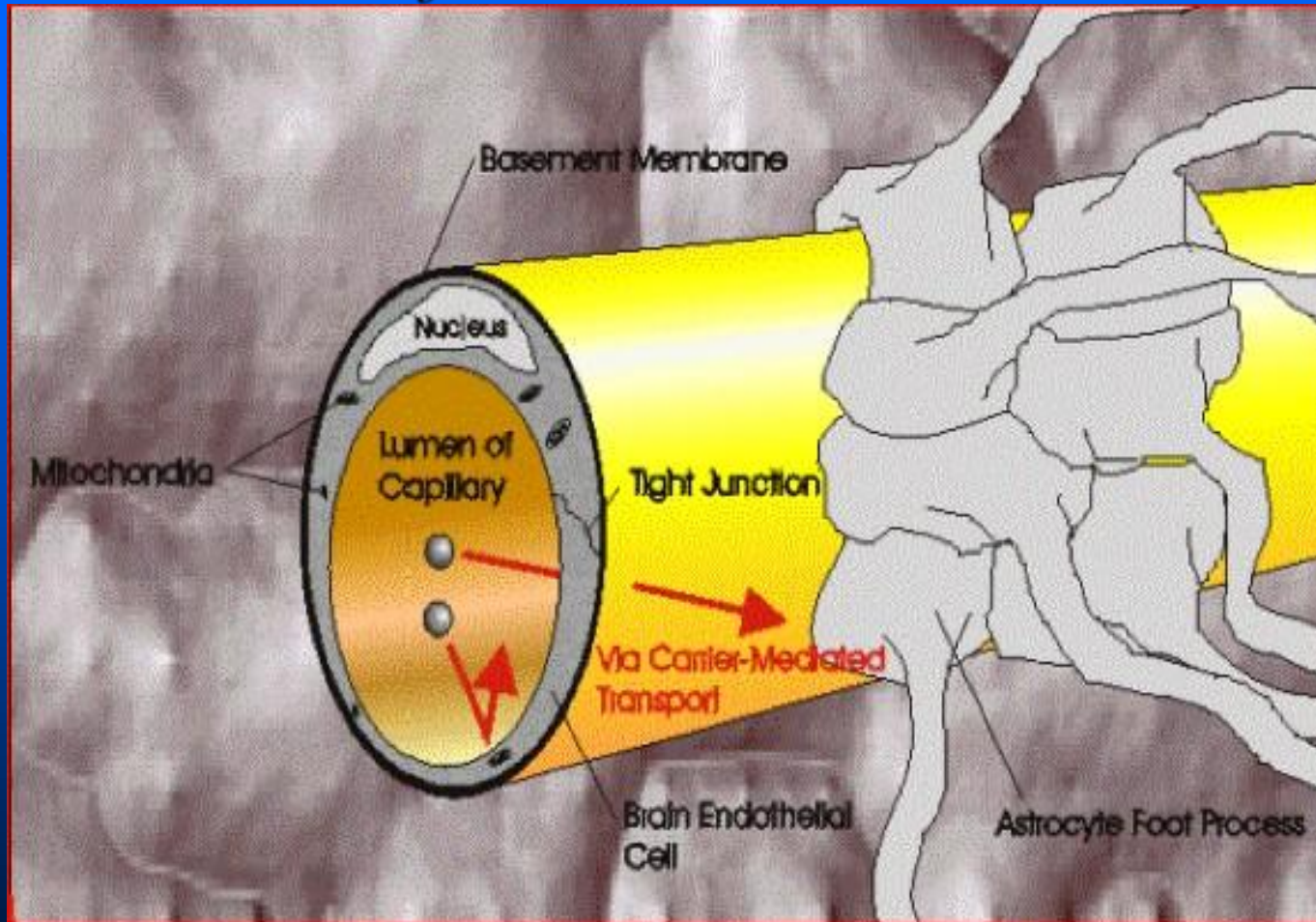






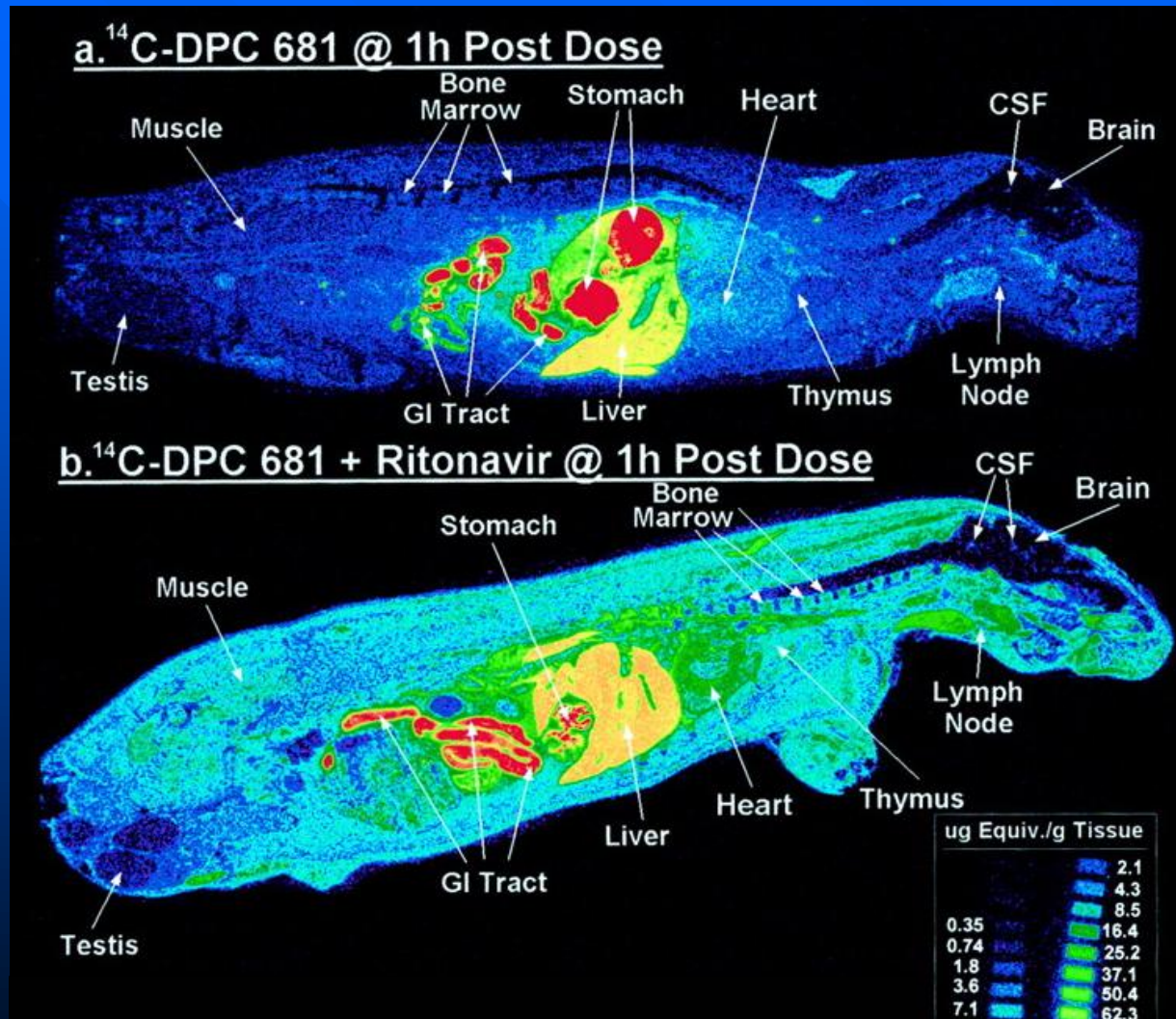
Antiretroviral Distribution

Structure of the Blood-Brain Barrier



Antiretroviral Distribution

Distribution to the Brain Can Be Limited



HAART – Neurocognitive Impairment

- Antiretroviral - variable penetrance in CSF
- HAART improve ADC
(Sacktor, et al, 2001)



HAART - NI

- **Equivalent impact of CSF-penetrating HAART or not in psychomotor slowing treatment**

(Sacktor, et al, Neurology, 2001)



Human Immunodeficiency Virus Encephalopathy

Cognitive and Radiologic Improvement After Antiretroviral Therapy

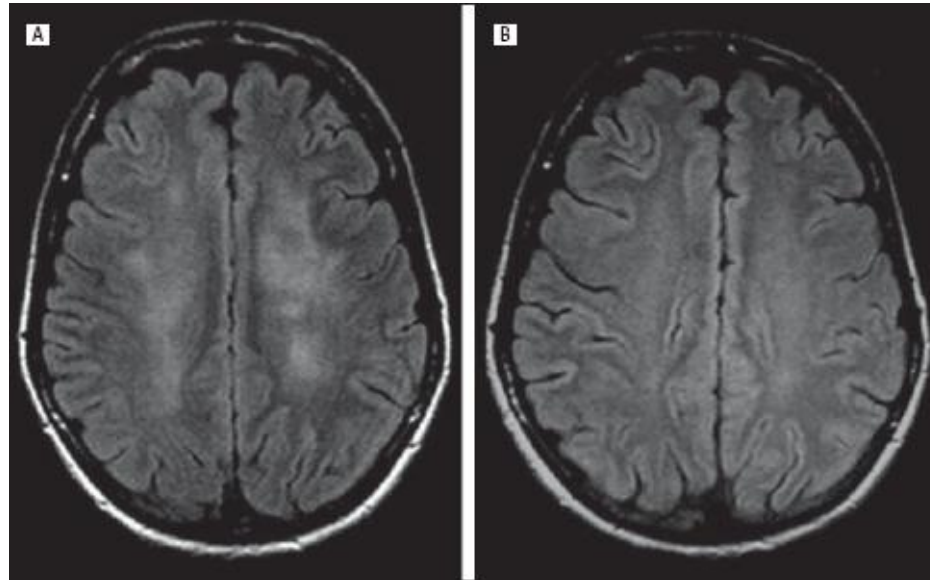


Table. Neuropsychological Assessment Before and After HAART

Assessment	Before HAART	After HAART
Grooved pegboard, min:s		
Dominant hand	1:48	1:01
Nondominant hand	1:57	1:12
Timed gait, s ^a	19.6	13.3
Verbal fluency test ^b	10	16
Finger tapping ^c		
Dominant hand	23.8	42.8
Nondominant hand	20.6	43
HDS ^d	3/12	12/12

Silva, Wagner et Grinsztejn. Arch Neurol 2009.



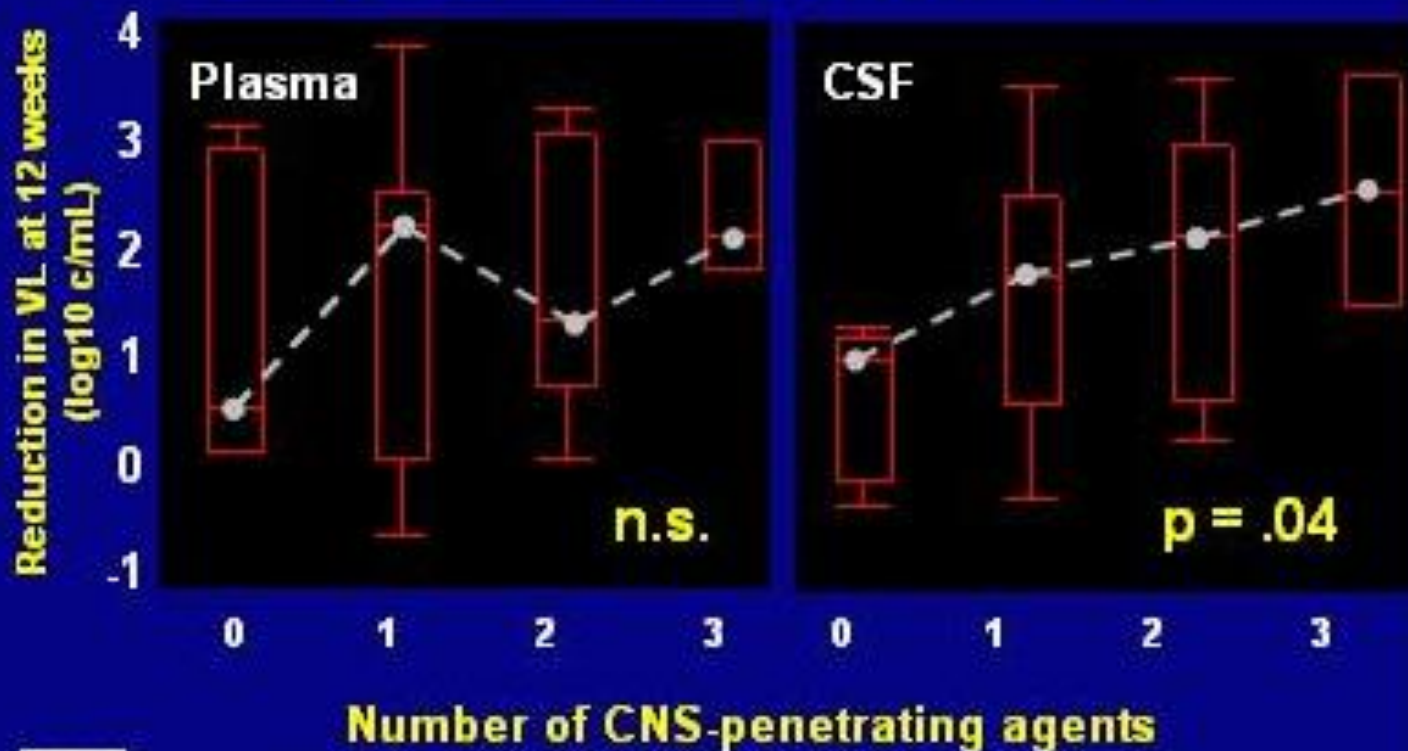
HAART - NI

- **CSF HIV-1-RNA reduction according to use of three CSF-penetrating ARV drugs**

(Antinori A, et al. AIDS, 2002)



Reduction in viral load vs. # of CNS-penetrating ARVs



UCID HNRG, AVRC, CFAR



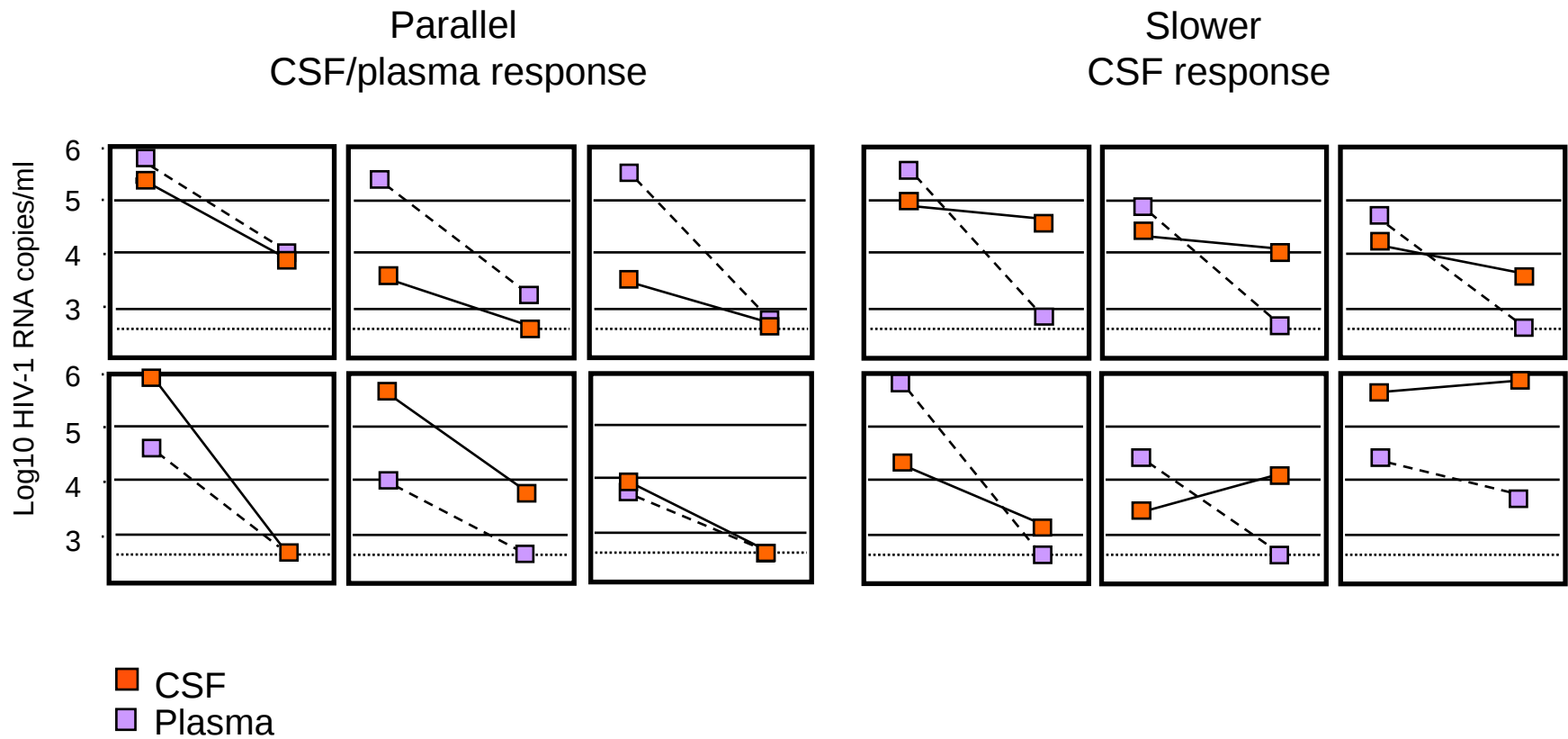
HAART - NI

- **ADC associated with delayed virus elimination in the CSF during HAART**

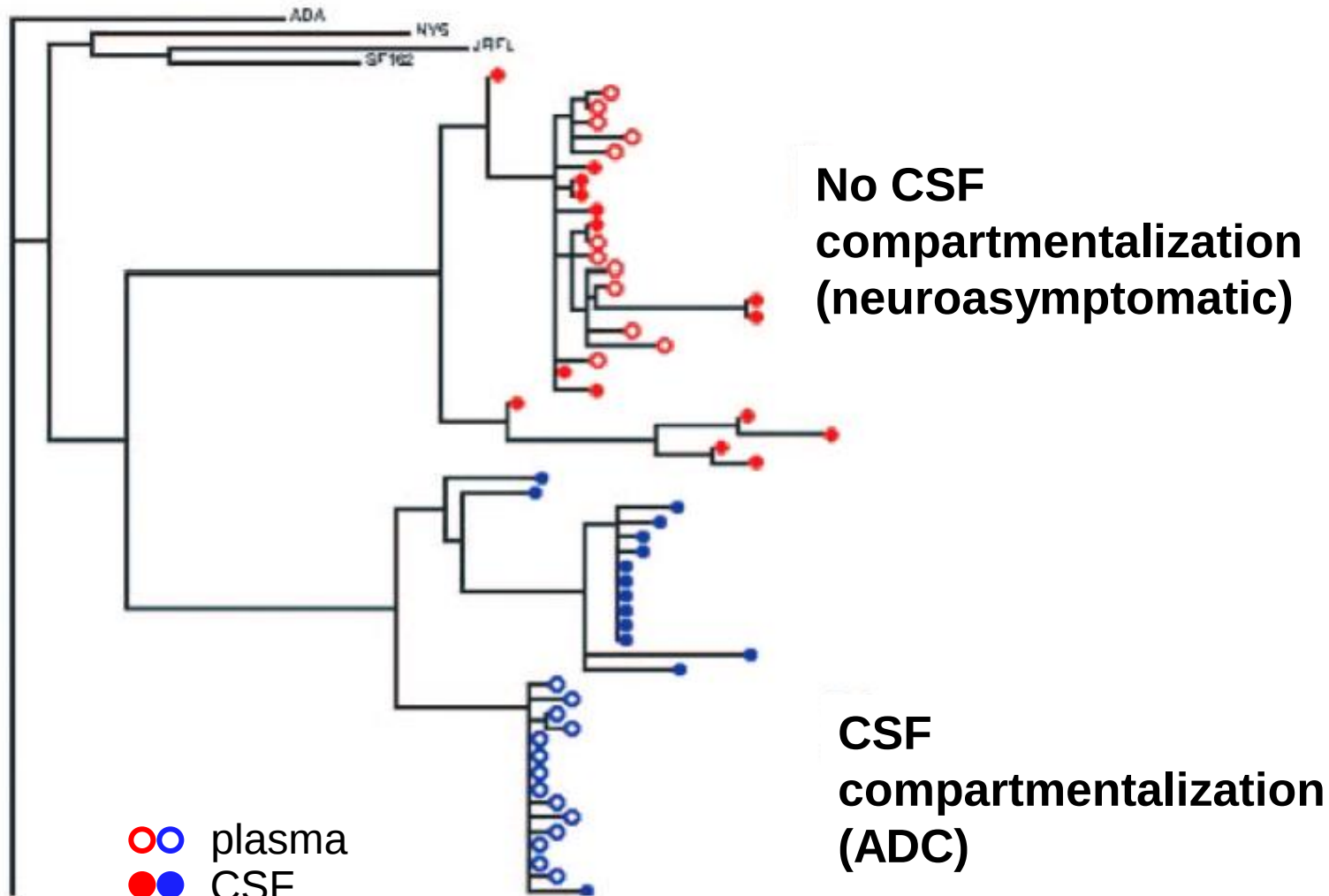
(Egges C, et al. AIDS, 2003)



Short-term kinetics of virological response in CSF and plasma of ART-treated patients



HIV strains are usually non compartmentalized in CSF of neuroasymptomatic patients



HIV CNS Compartmentalization

Seroconversion study¹

Seroconversion - 17 patients

■ 3/17 patients - HIV cns compartmentalization



HAART - NI

- **ARV resistance different patterns - Plasma/CSF**

(Cunningham PH, *et al.* AIDS 14: 1949, 2000)

- **CNS escape**

(J McArthur et al, J Neurovirol, 2003)



HAART - NI

- SIV gp120 sequences – laser capture micro-dissection

(Monocytes & BM macrophages ➤ CNS)

- SPIONS - Macrophages CD163+

(CNS ➤ Cervical LN + CNs + BP + SC)

(K Willians et al, Matera, 2015)



Transendothelial Migration

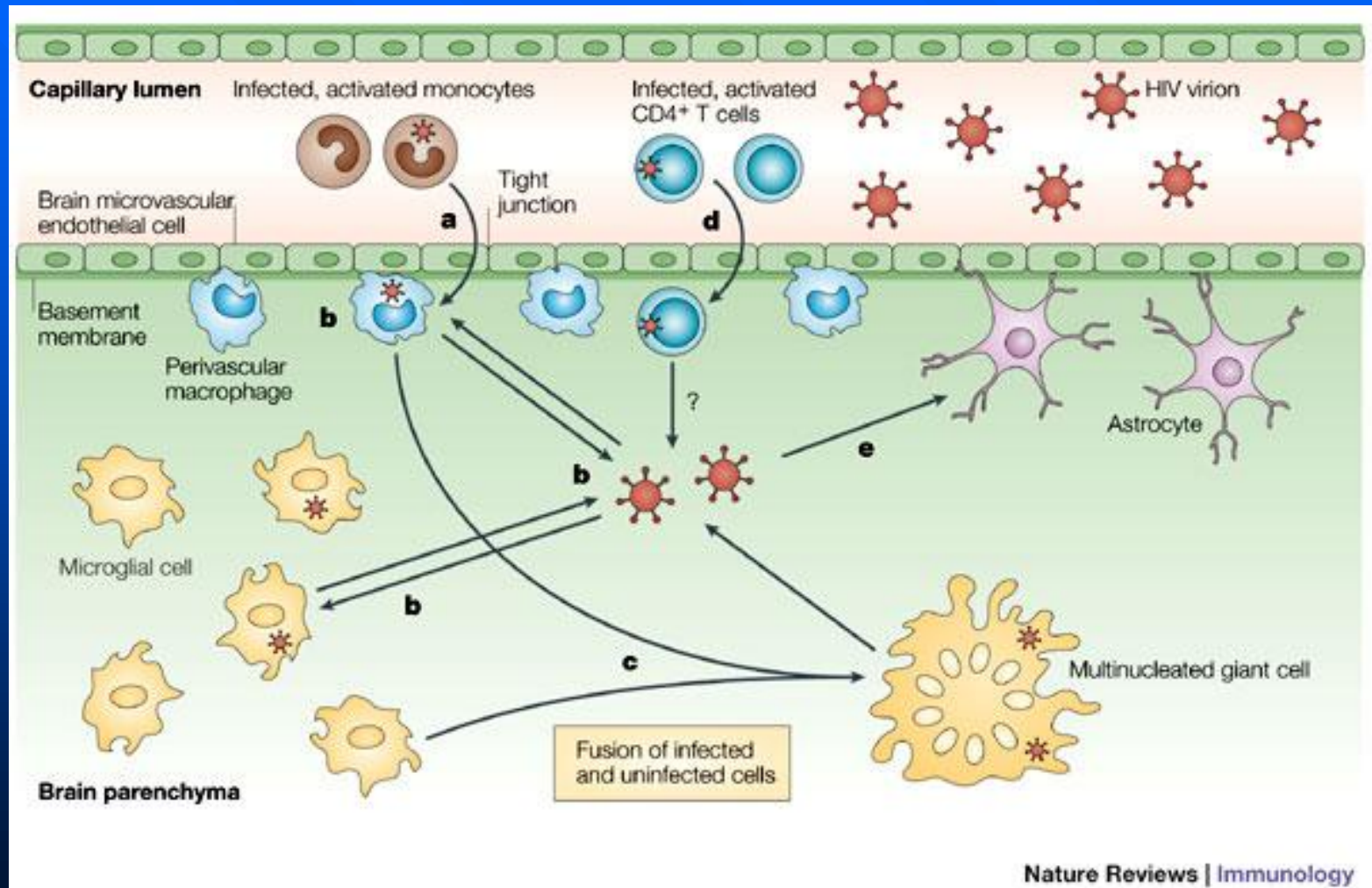
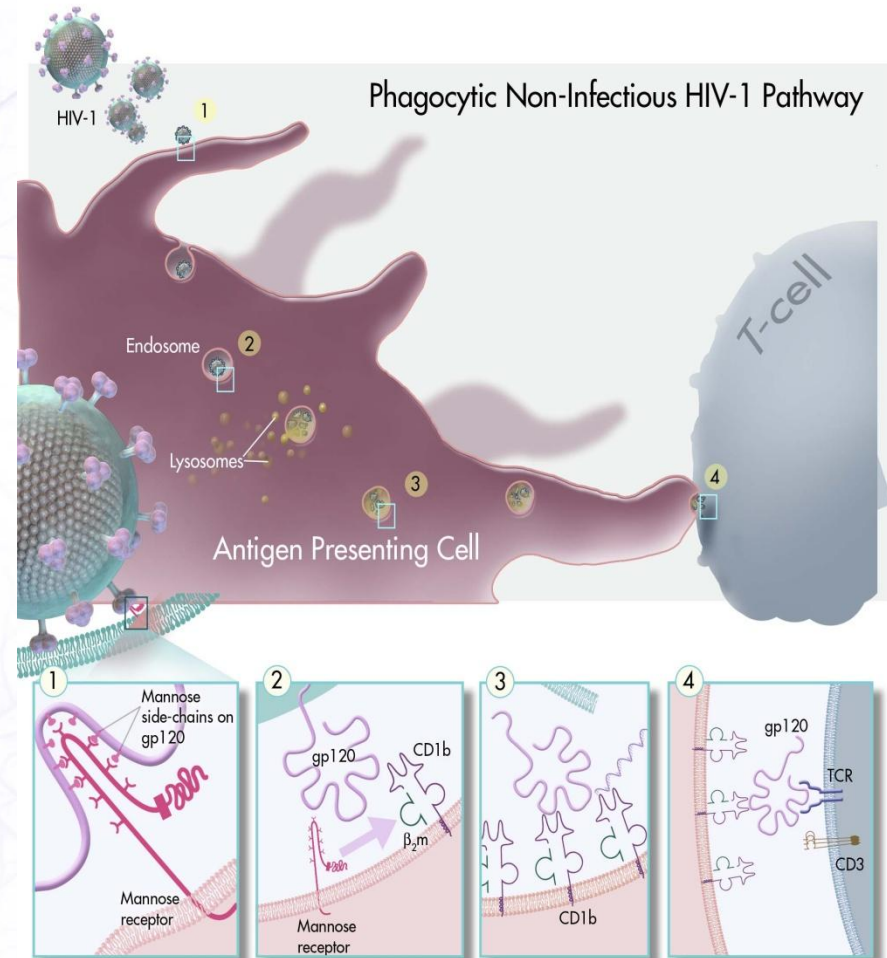
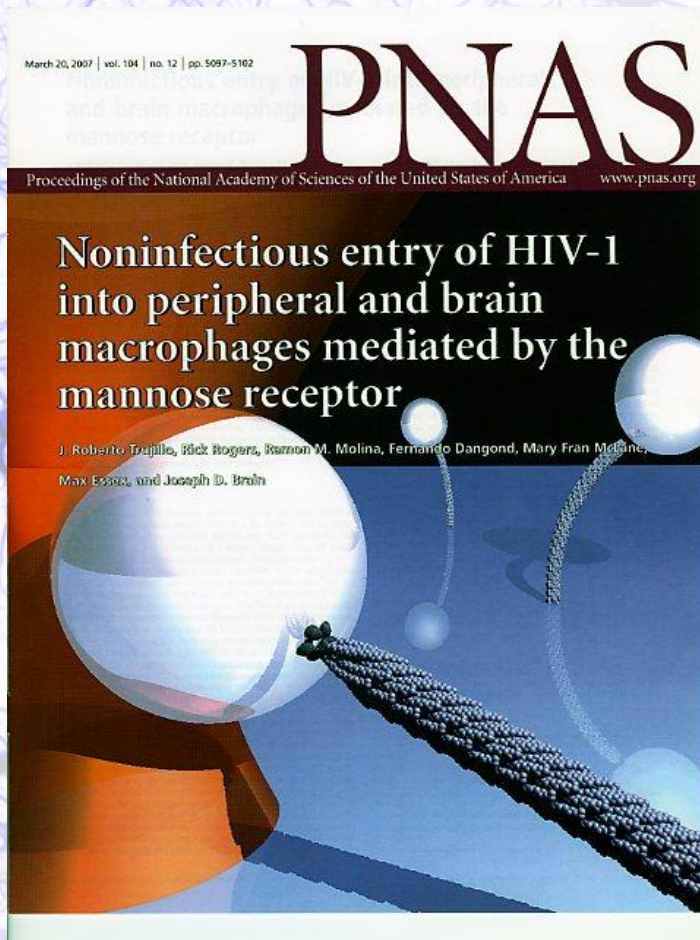
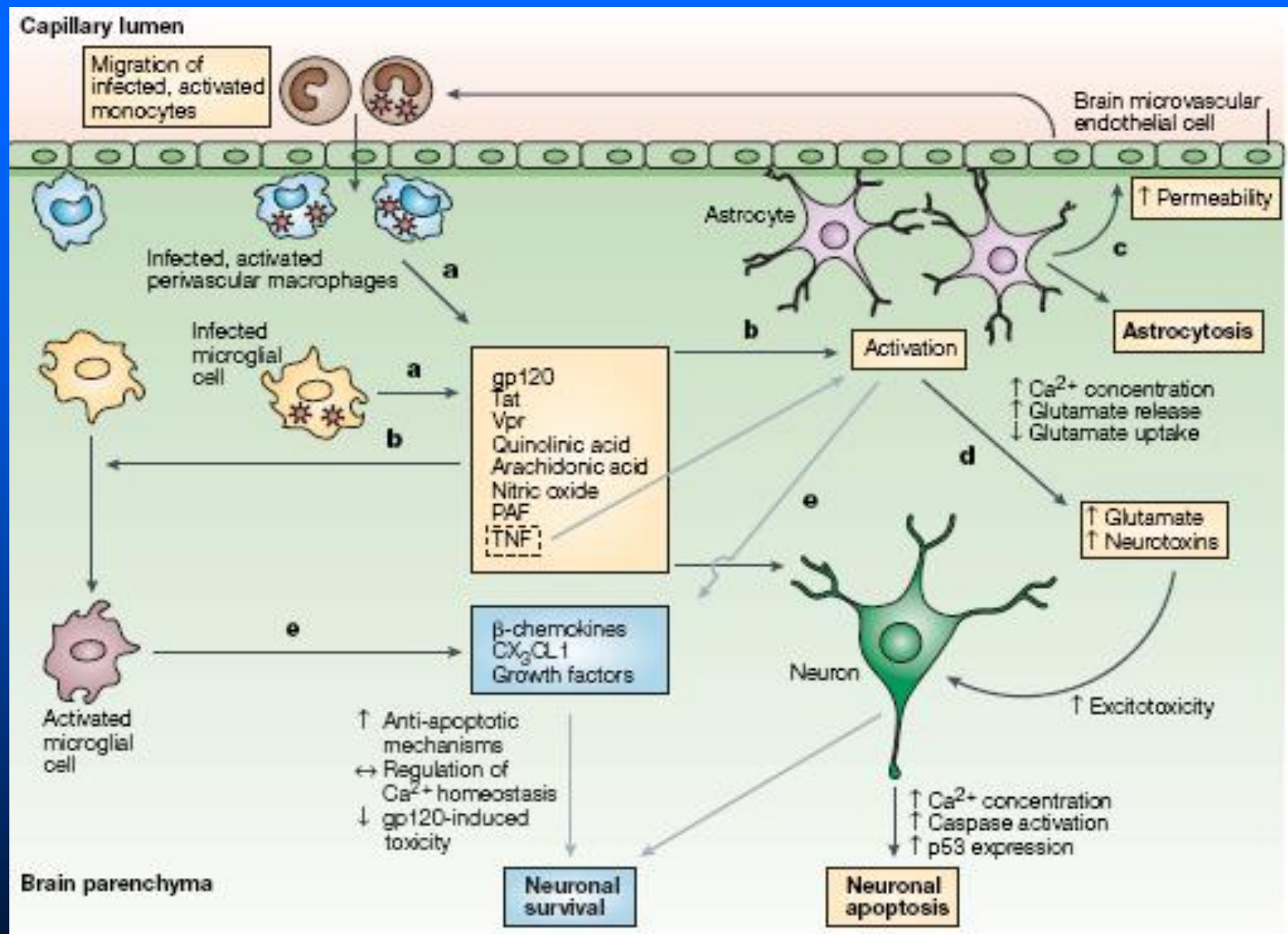


Table 1 Susceptibility of cells of the central nervous system to infection with HIV				
Cell type	CD4 antigen	Chemokine receptors	HIV susceptibility	Productive infection
Perivascular macrophages	Yes	Yes	Yes	Yes
Microglia	Yes	Yes	Yes	Yes
Astrocytes	No	Yes	Yes	No
Oligodendrocytes	No	Yes	<i>In vitro</i>	No
Neurons	No	Yes	No	No
Brain microvascular endothelial cells	No	Yes	<i>In vitro</i>	No



NeuroAIDS Pathogenesis: Mannose Receptor



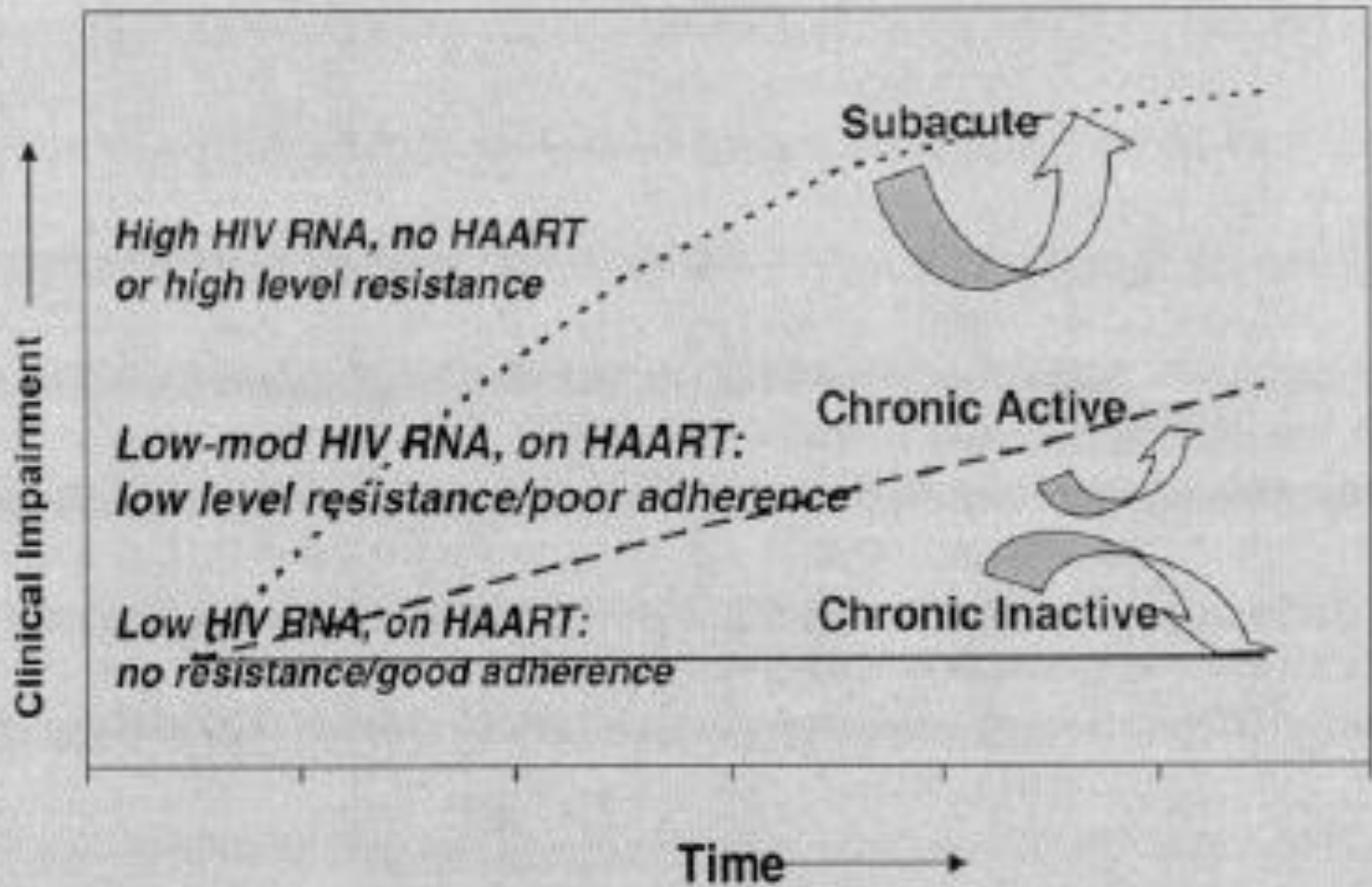


Terapia combinada - NI

- Duração do impacto sistêmico X
- Ação no SNC X
- Tempo de evolução

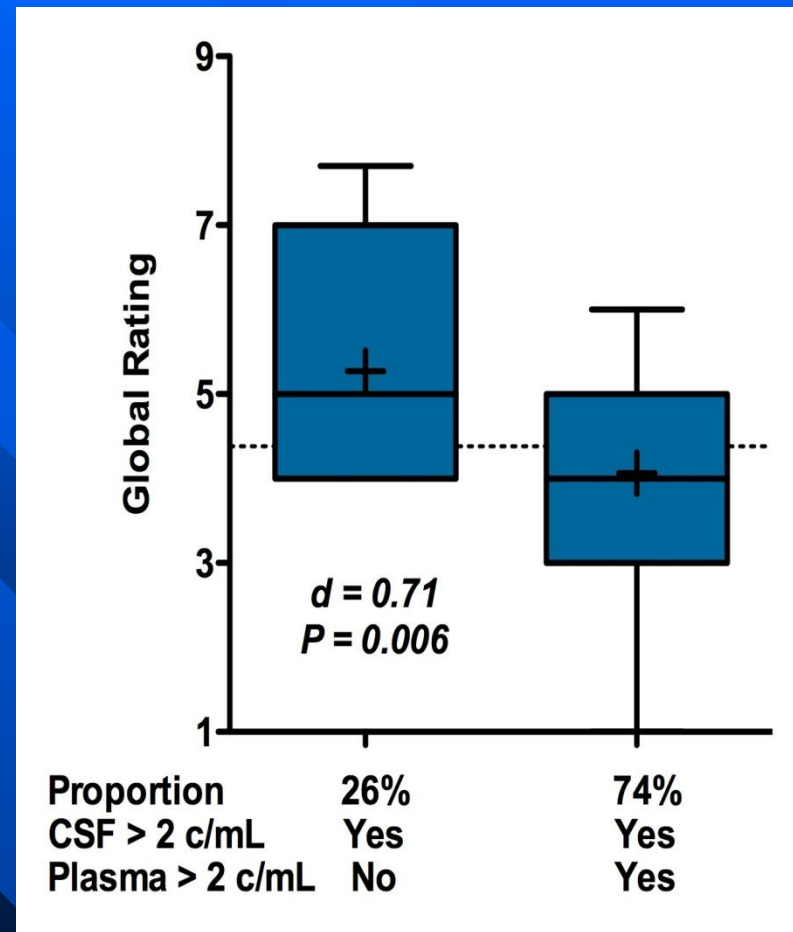
(Gartner S. Science 287:602, 2000)



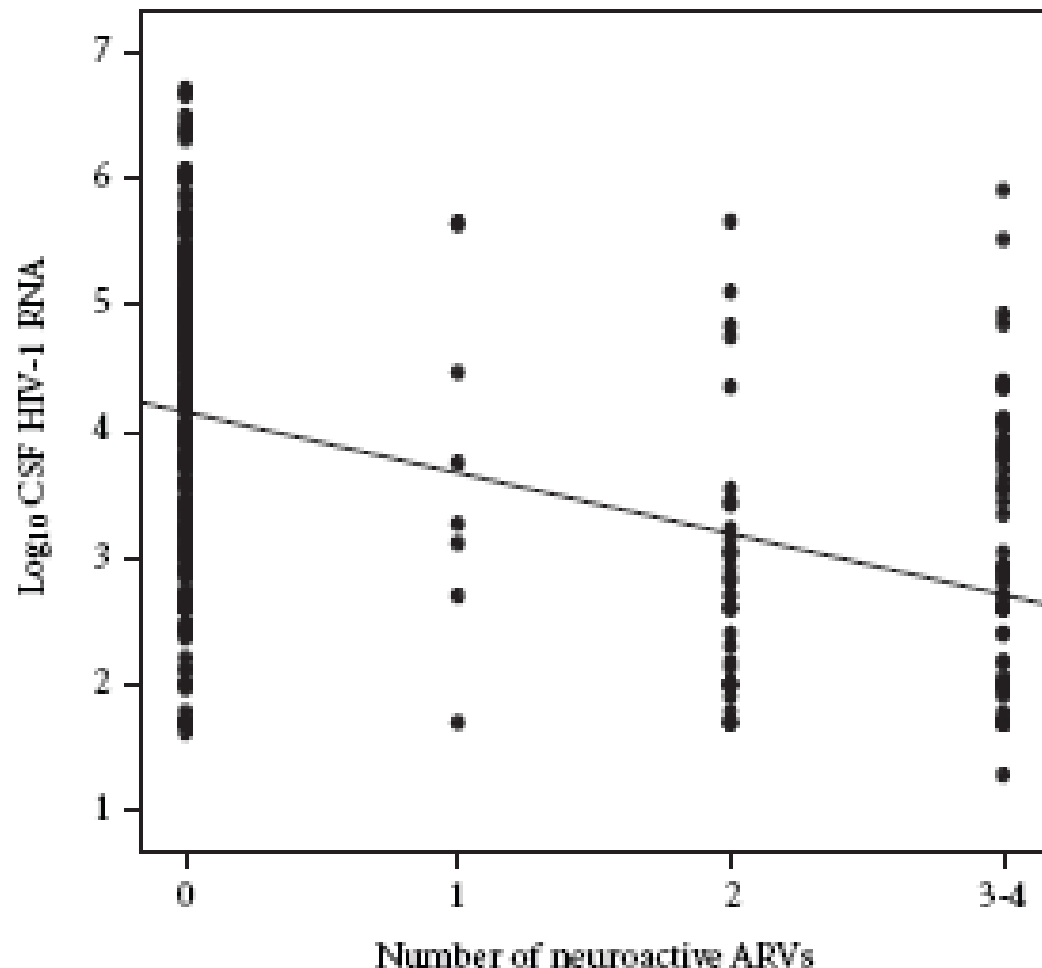


HIV persists in CSF in 41% during ART

- 122 of 300 (41%) CSF specimens that had HIV RNA < 50 c/mL were still detectable with a more sensitive assay
- Detectable HIV was associated with worse CPE scores ($d = 0.25$, $p = 0.03$)
 - Was associated with worse NP performance



Virological Response in Cerebrospinal Fluid to Antiretroviral Therapy in a Large Italian Cohort of HIV-Infected Patients with Neurological Disorders

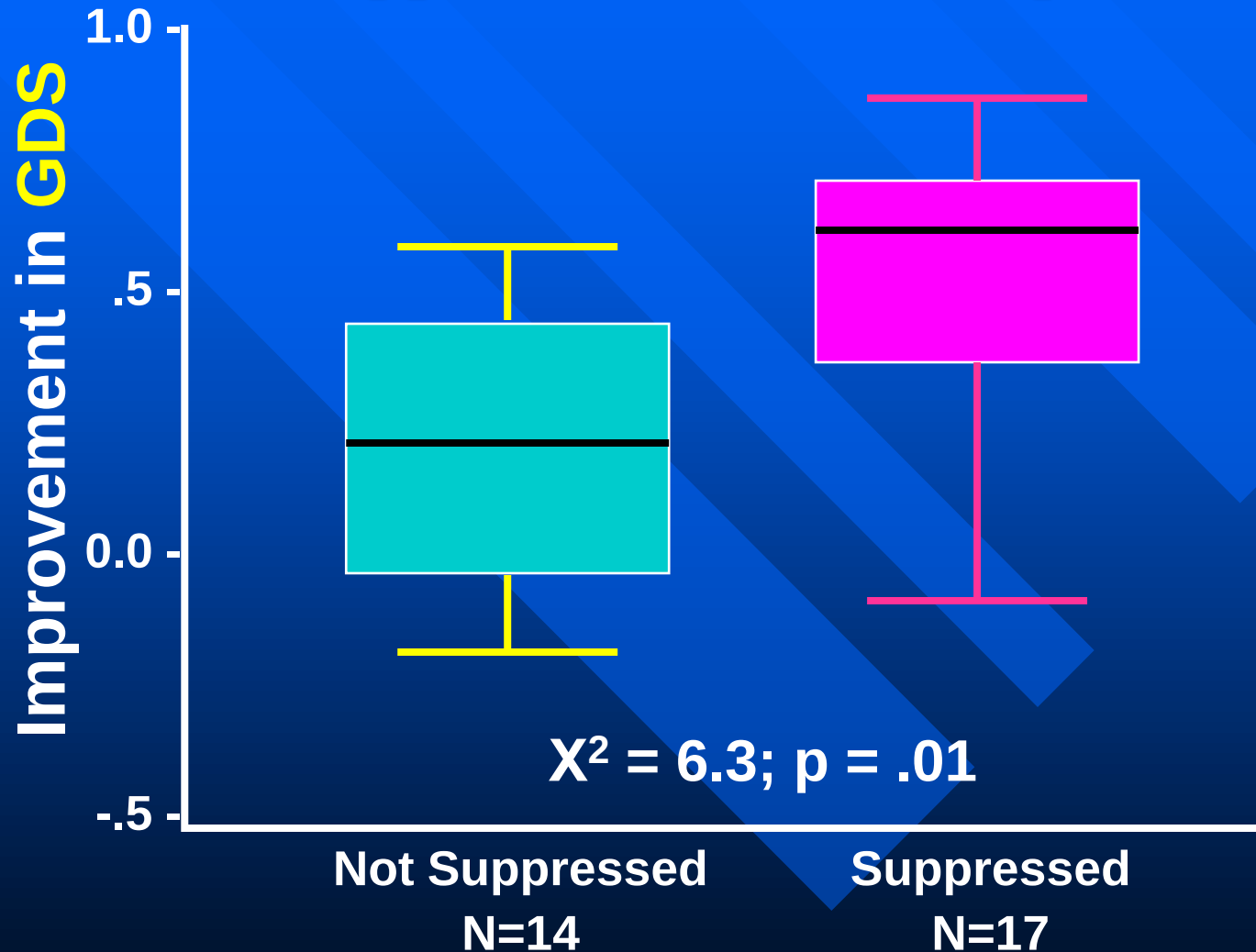


CSF HIV-RNA. Compared to regimens containing no CNS-penetrating ARVs, the use of two (OR = 4.11; 95% CI = 1.22–13.79) or at least three (OR = 5.48; 95% CI = 1.94–15.48) penetrating CNS ARVs markedly improved the probability of having a CSF HIV RNA level below the detection limit of 50 copies/mL.



Antiretroviral Effectiveness

HIV RNA Suppression and NP Improvement



Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load

Michael J. Peluso^a, Francesca Ferretti^b, Julia Peterson^c, Evelyn Lee^c, Dietmar Fuchs^d, Antonio Boschini^e, Magnus Gisslén^f, Nancy Angoff^a, Richard W. Price^c, Paola Cinque^b and Serena Spudich^a

AIDS 2012, 26:1765–1774



HAART - NI

■ Two or 3 CSF penetrating HAART drugs

(Portegies, et al, 2004; Lettendre et al, 2005; Price et al, 2008)



Revised categorization of ARV CNS penetration

	4 (Best)	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion / Entry Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		



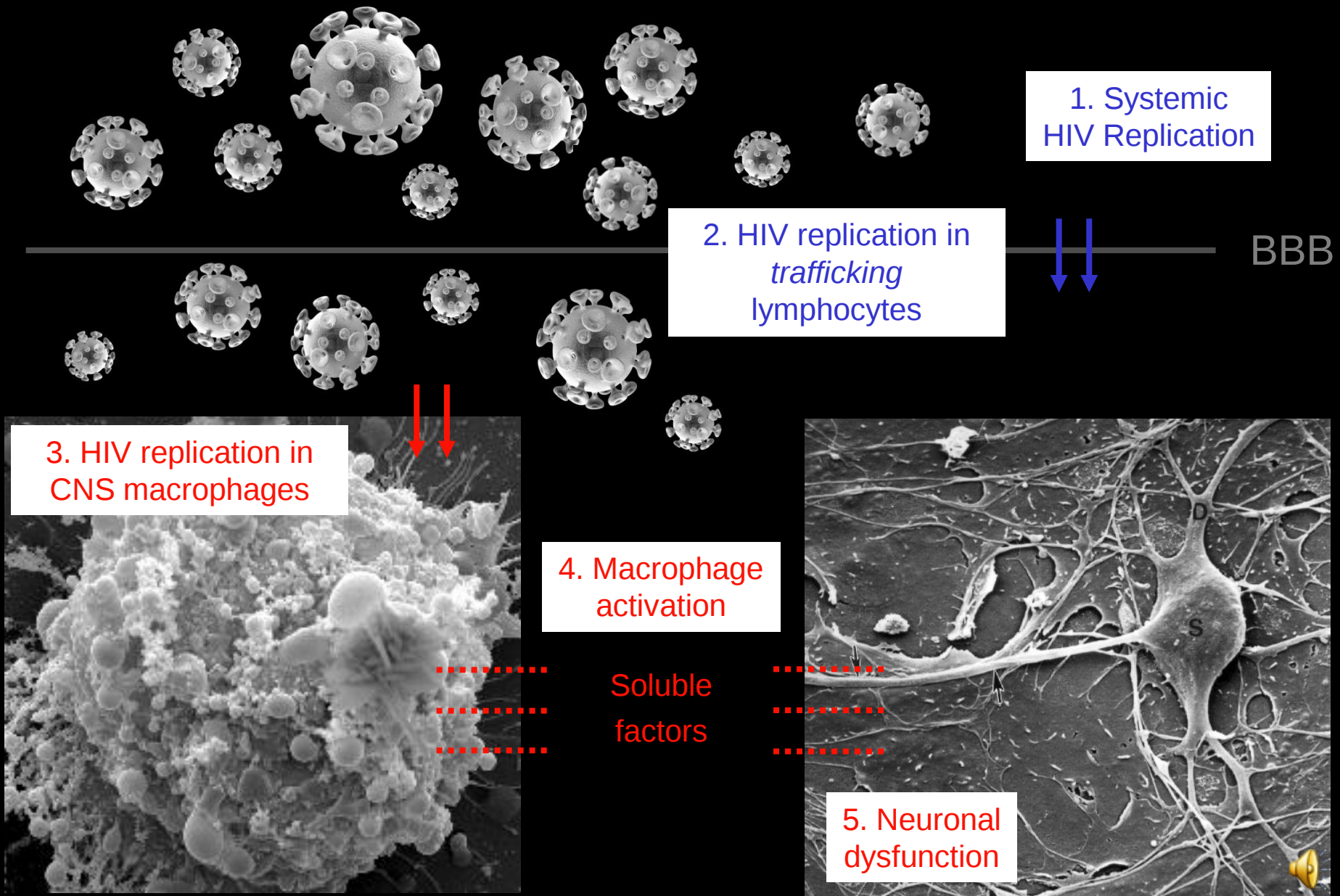
Definition of 'potentially CNS-active' drugs

ARV drugs with either demonstrated clear CSF penetration when studied in healthy HIV-infected populations (concentration above the IC90 in > 90 % examined patients) or with proven short-term (3-6 months) efficacy on cognitive function or CSF viral load decay when evaluated as single agents or in controlled studies in peer-reviewed papers:

- Agents with demonstrated clear CSF penetration:
 - NRTIs: ZDV, ABC
 - NNRTIs: EFV, NVP
 - Boosted PIs: IND/r, LPV/r, DRV/r
 - Other classes: MAR
- Drugs with proven "efficacy":
 - NRTIs: ZDV, d4T, ABC
 - Boosted PIs: LPV/r



HIV brain infection and neurocognitive dysfunction



1. Systemic HIV Replication



BBB

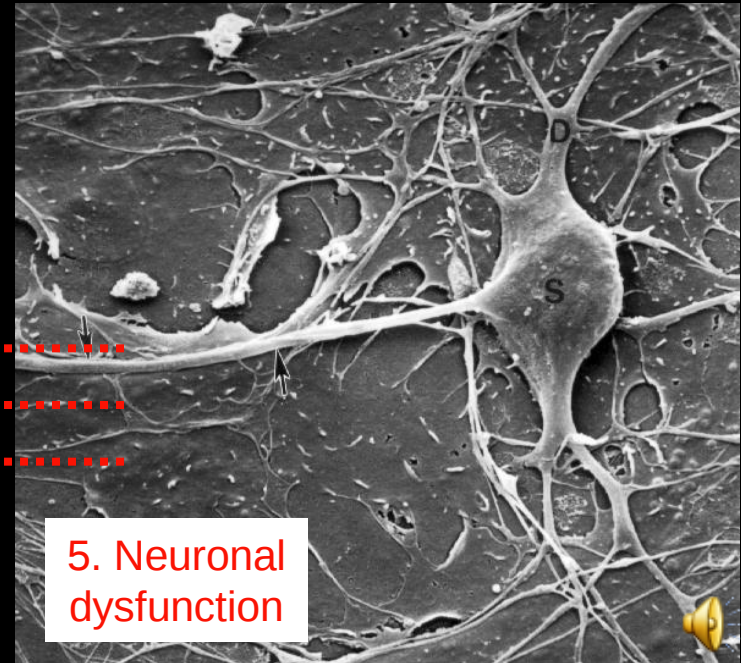
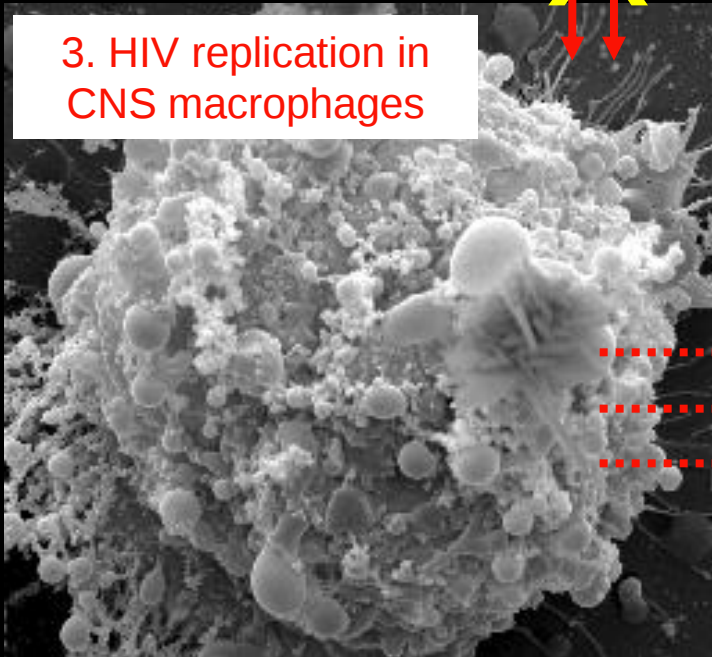
ART

3. HIV replication in CNS macrophages

4. Macrophage activation

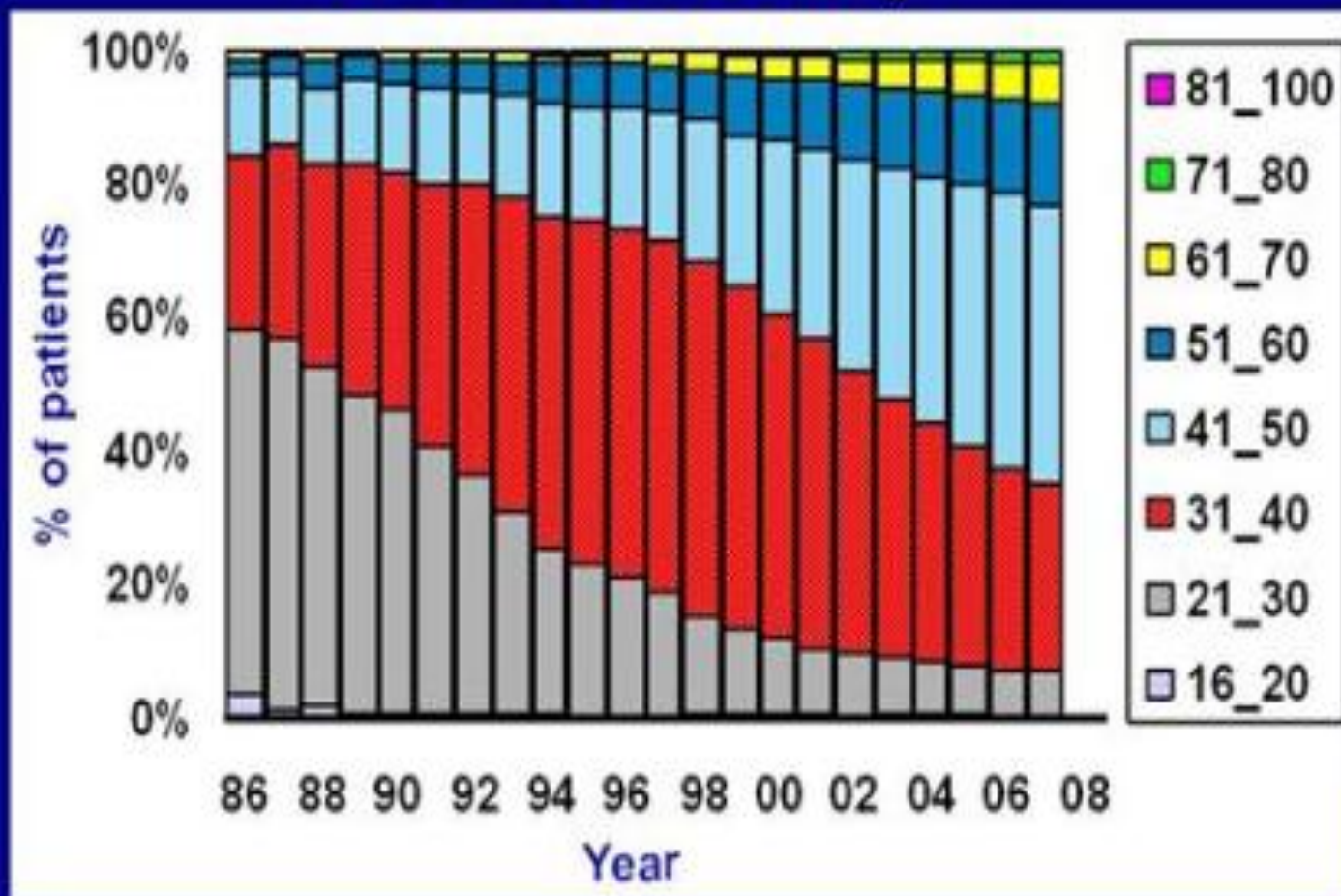
Soluble factors

5. Neuronal dysfunction



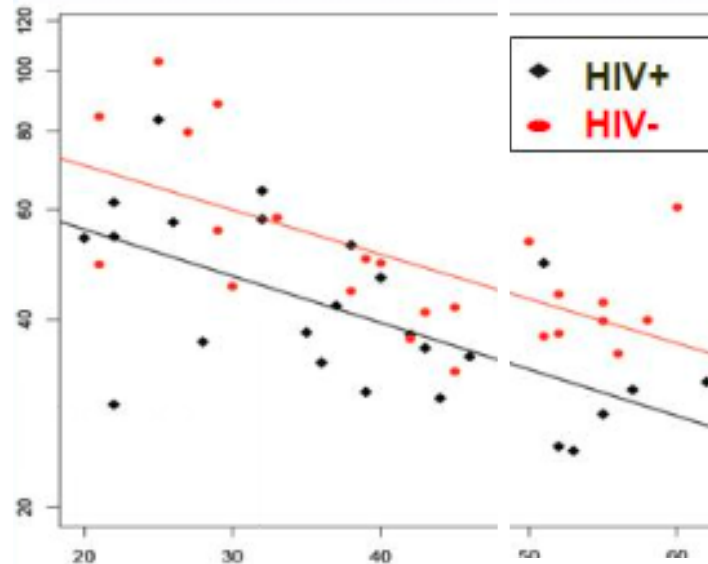
Increase in older adults (> 50 yrs) living with HIV/AIDS

Swiss Cohort Study



Additive effect of aging and HIV serostatus on cerebral blood flow (CBF)

Baseline CBF



$P < 0.0001$ (age)

$P = 0.0001$ (HIV)



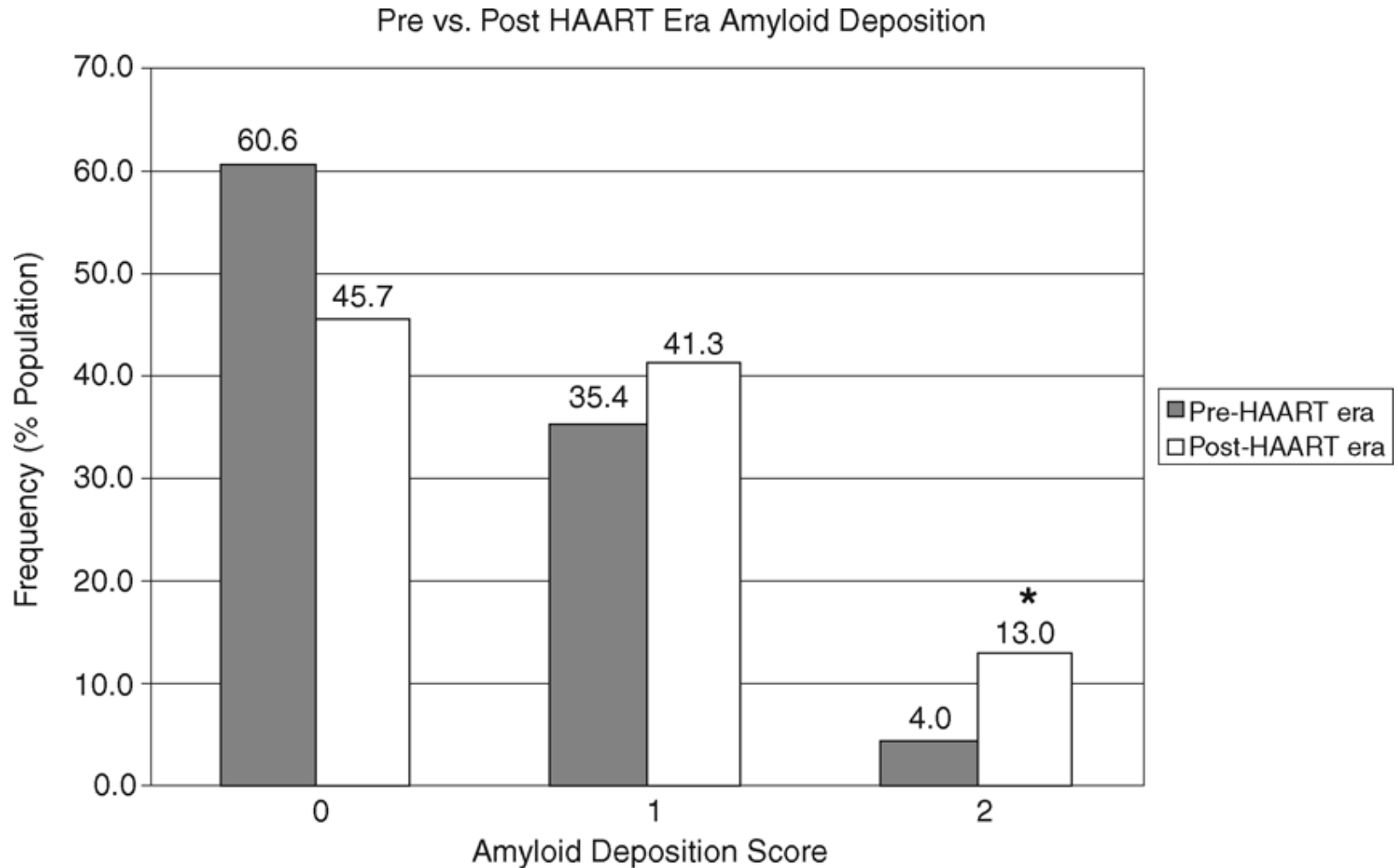
PONTOS CRÍTICOS

- Envelhecimento
 - Dislipidemia
 - Vascular
 - Injúria axonal
 - tat - neprilisyn
- Inibição degradação - beta amilóide
 - HCV

(Brew, AIDS, 2003)



β -amyloid deposition is increased in HAART-treated patients



Doença de Alzheimer

Aspectos metabólicos: SPECT

Estádio I



Estádio II



Estádio III



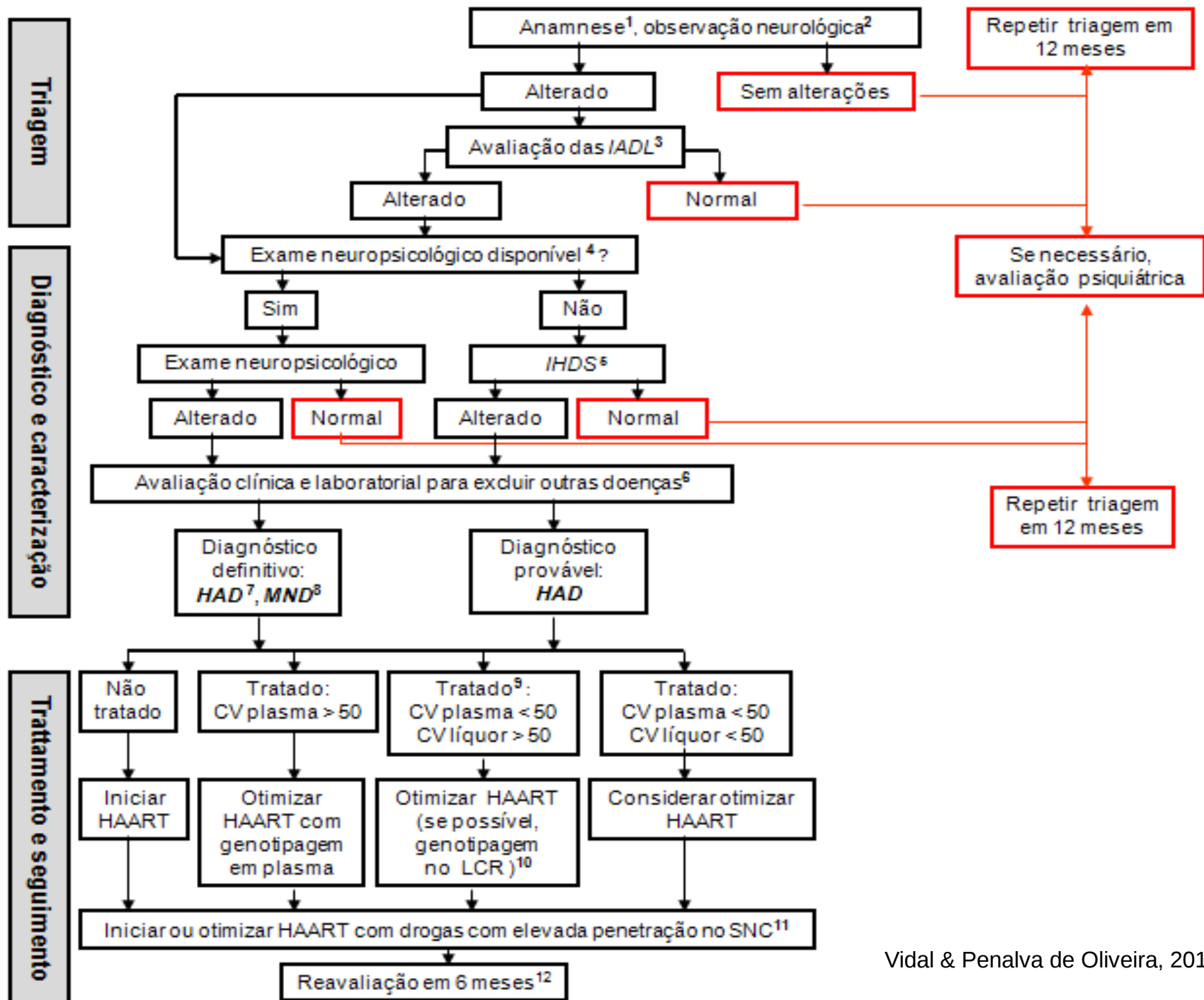
Prevalência e fatores associados as alterações neurocognitivas em pacientes com HIV-1

Marcadores líquidos – Ana Carolina (CR)
Senescência – Marília (JC)

Coordenador: Maria Rita Polo Gascón

Instituição: Instituto de Infectologia Emílio Ribas

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Terapia antiretroviral em pacientes com MND e HAD

Cenários	
Paciente sem tratamento ARV prévio	Terapia ARV com 2 e idealmente 3 drogas potencialmente neuroativas .
Paciente em tratamento ARV com falha terapêutica	Modificação da terapia ARV guiada por testes de resistência atuais e prévios, considerando 2 e idealmente 3 drogas potencialmente neuroativas
Paciente em tratamento ARV com carga viral sérica indetectável	Modificação da terapia ARV guiada por testes de resistência prévios, considerando 2 e idealmente 3 drogas potencialmente neuroativas. Alternativamente, intensificar o esquema com uma ou mais drogas potencialmente neuroativas.

Strategic Timing of Antiretroviral Treatment

START Neurology Substudy



HIV and Cognitive Health

- Quality of life and longevity are of paramount importance to individuals living with HIV in the post-HAART era
- Preservation of neurocognitive health is integral to good quality of life and sustained well being in HIV positive individuals



