4th International Symposium on

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Pathogenesis of Neurocognitive Impairment in HIV-infected persons

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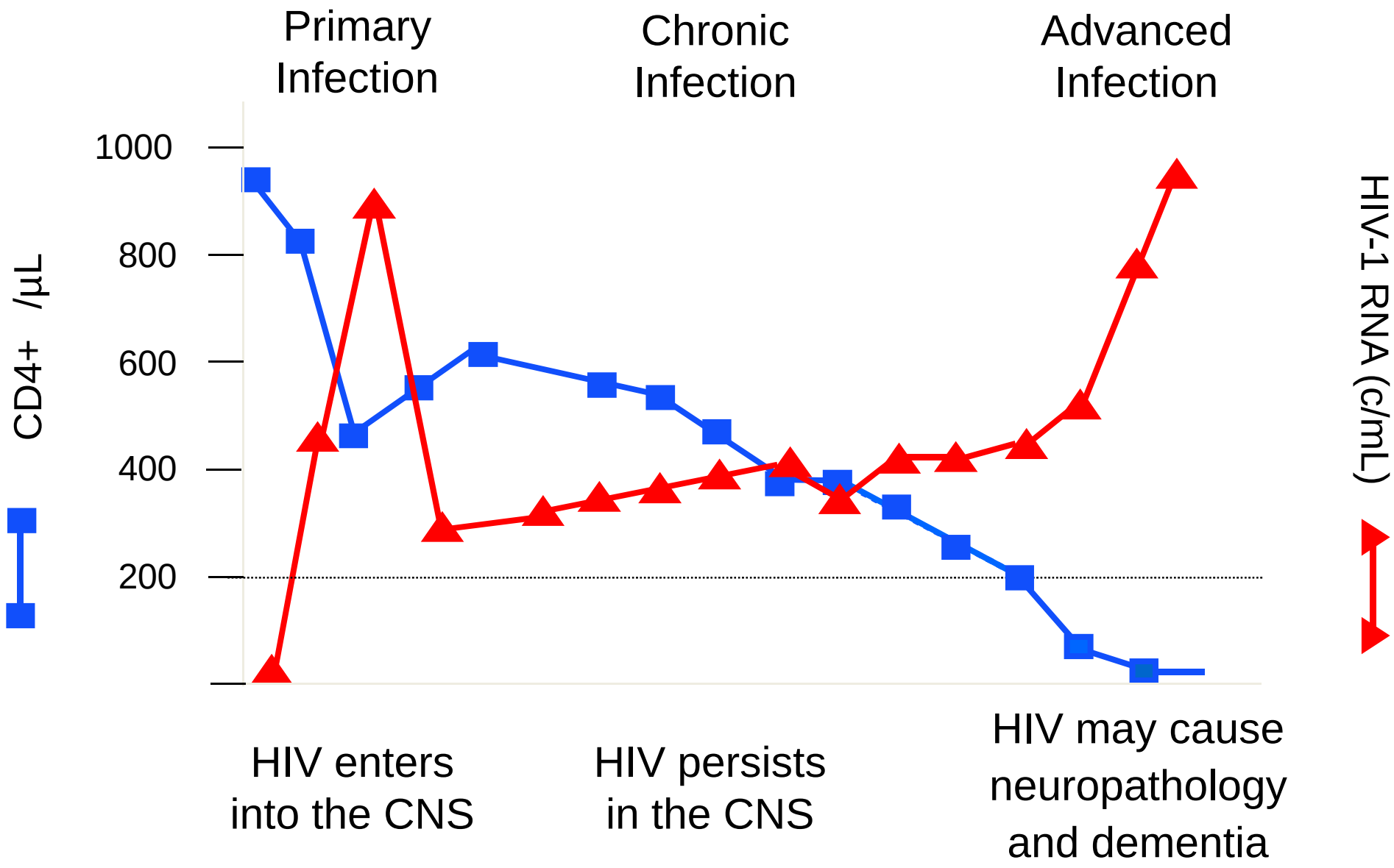
NCI Pathogenesis

- In untreated HIV infection
- In treated HIV infection

HIV and the CNS - Natural History

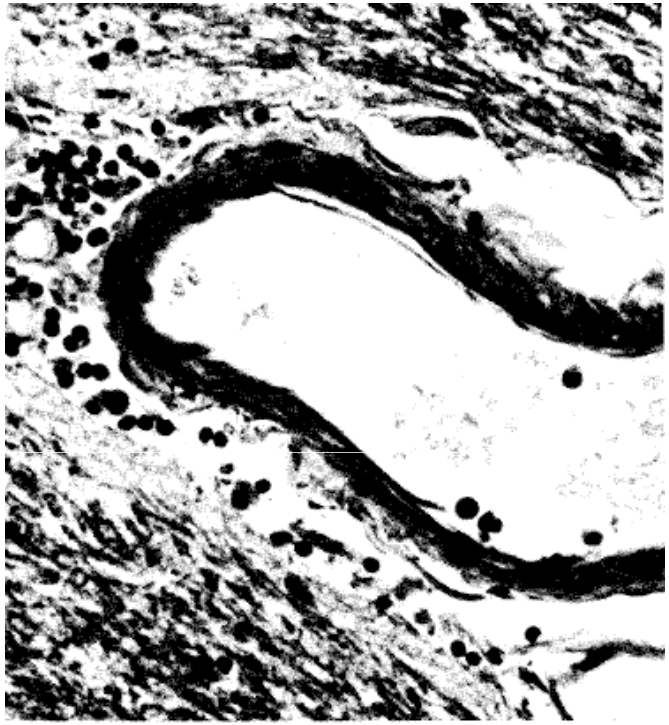


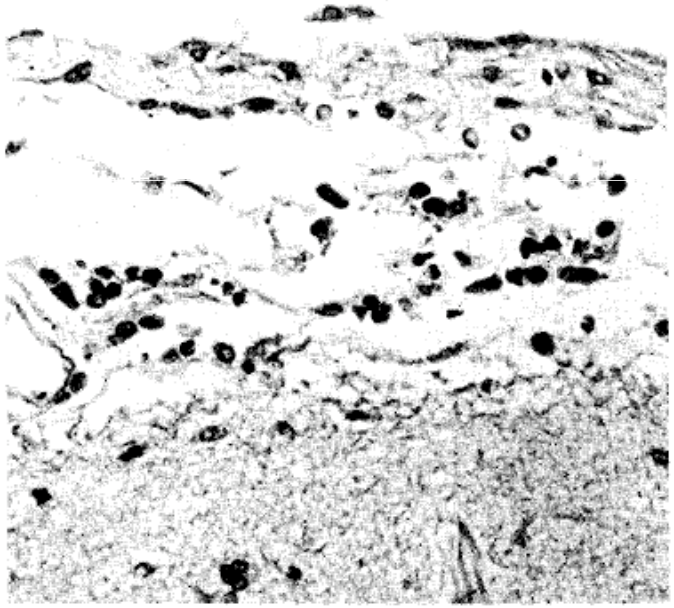
Early viral invasion of the brain in iatrogenic HIV infection

Table. HIV isolation and PCR studies of HIV-1–infected WBC infusion recipient

HIV-1 detection method	Days after HIV-1–infected WBC infusion				
	0	1	8	14	15 autopsy
Blood					
Virus isolation	Neg	Neg	Neg	Pos	ND
Proviral DNA by PCR	Neg	Neg	Pos	Pos	ND
Brain					
Virus isolation					Pos
Proviral DNA by PCR					Pos

ND Not done.

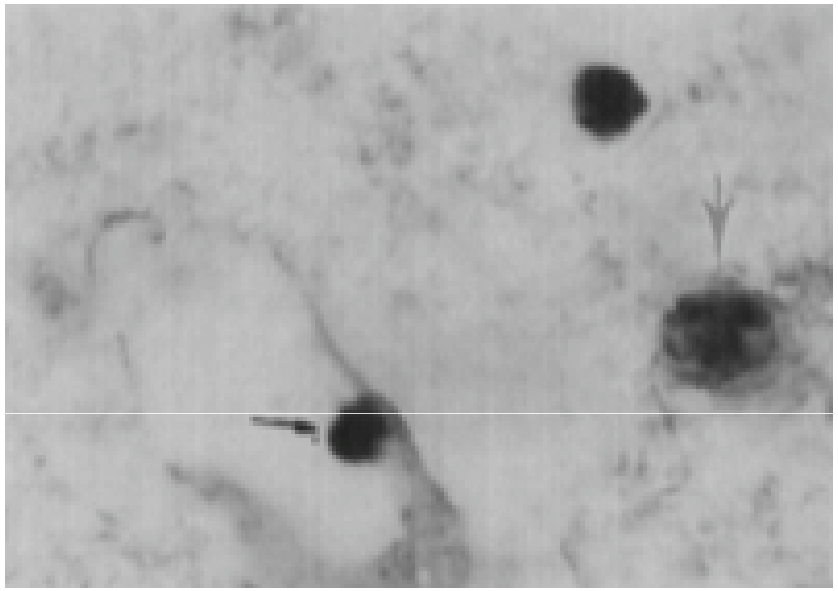




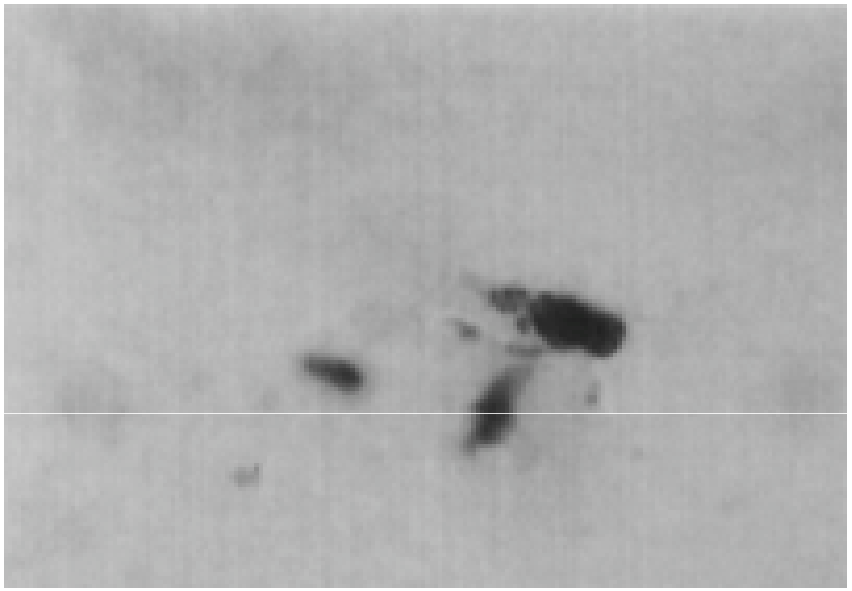
Davis LE. et al., Neurology 1992

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

HIV DNA in microglial cells

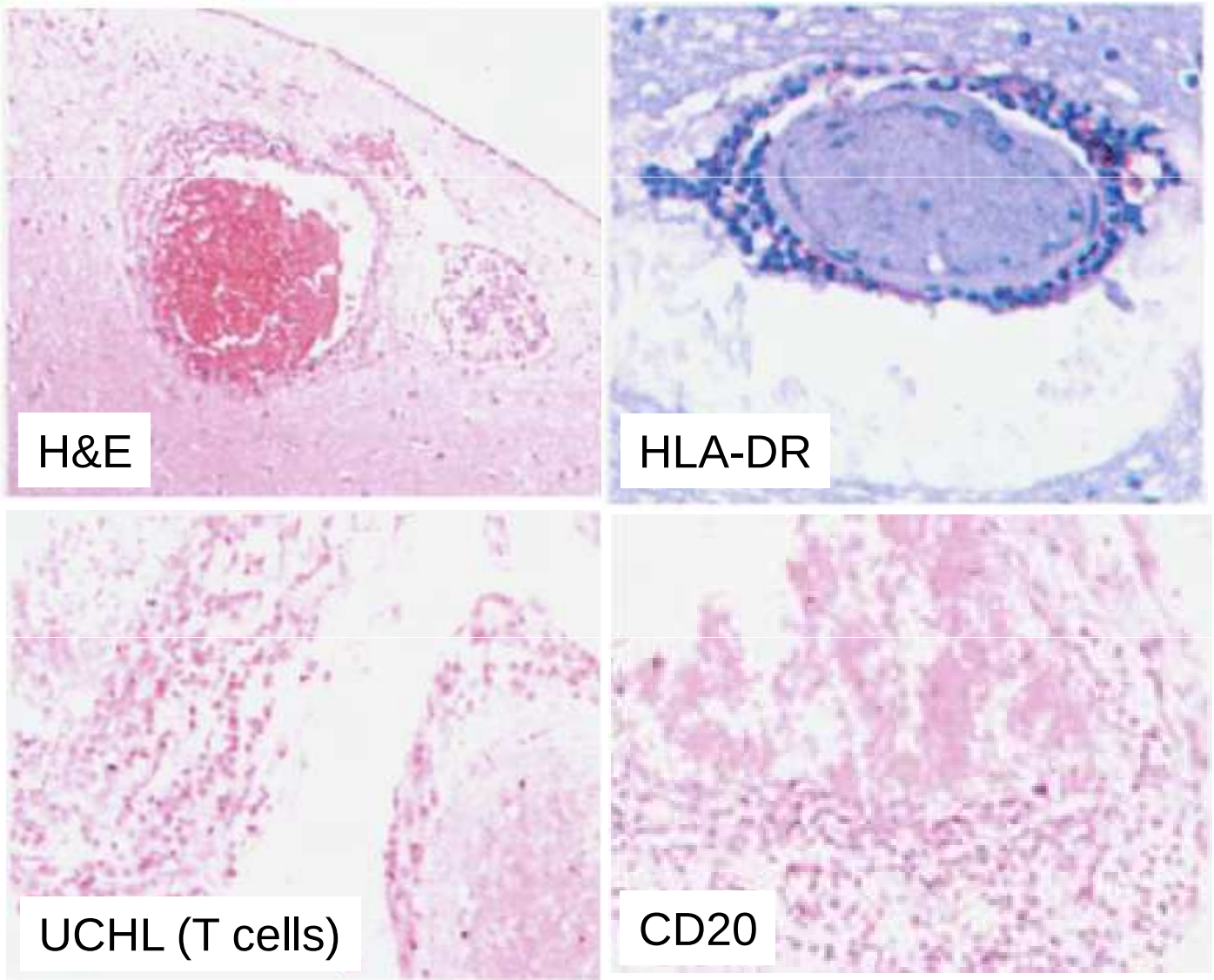


HIV DNA in astrocytes and endothelial cells



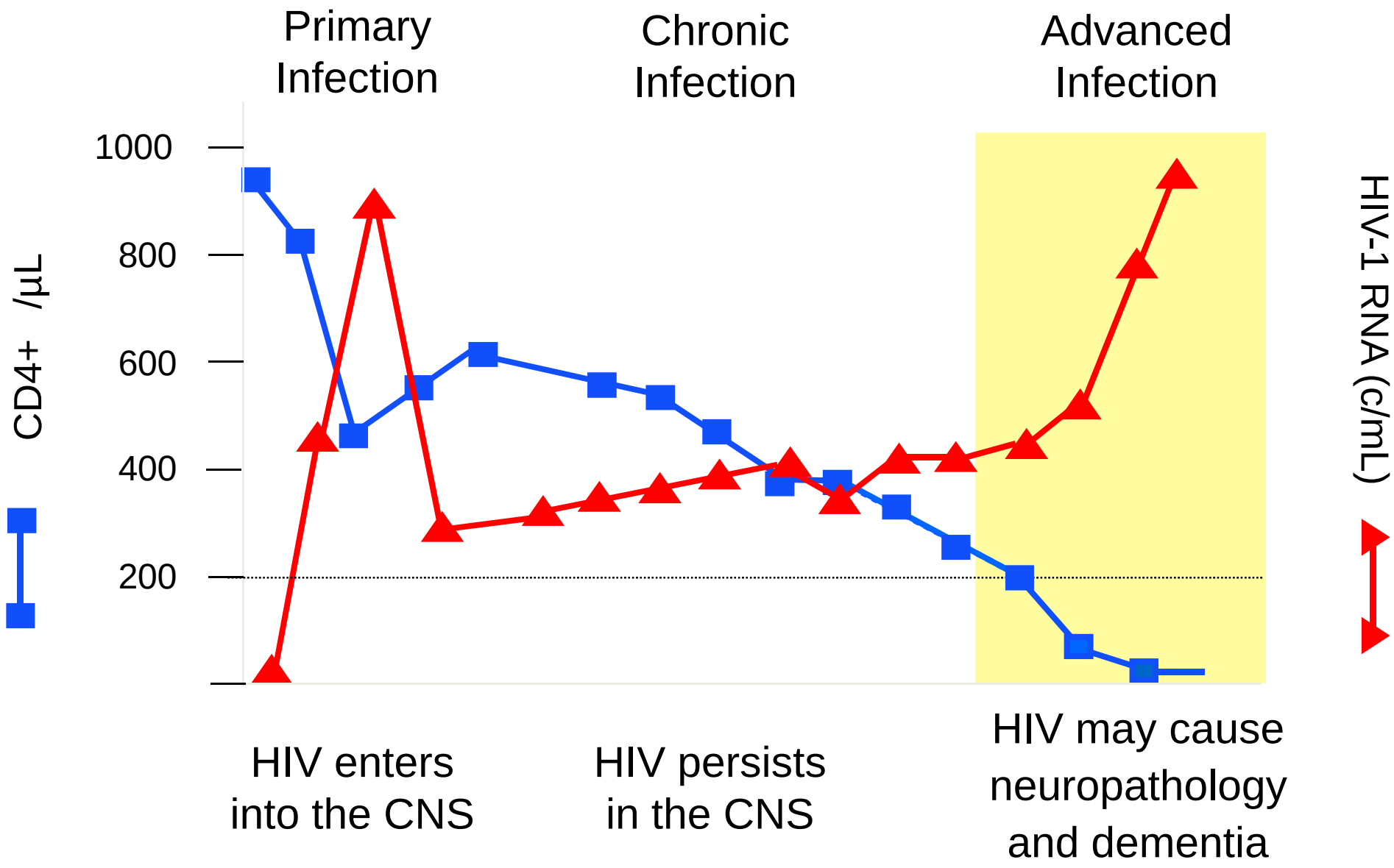
An SF et al. J Neuropath Exp Neurol 1999

Inflammatory changes in the brain of untreated asymptomatic HIV-1 infection

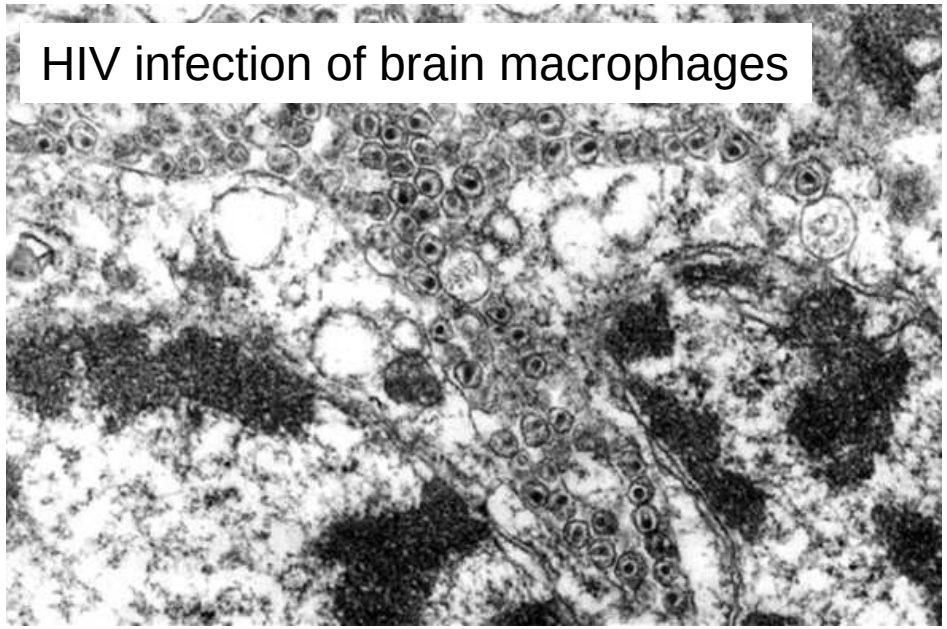


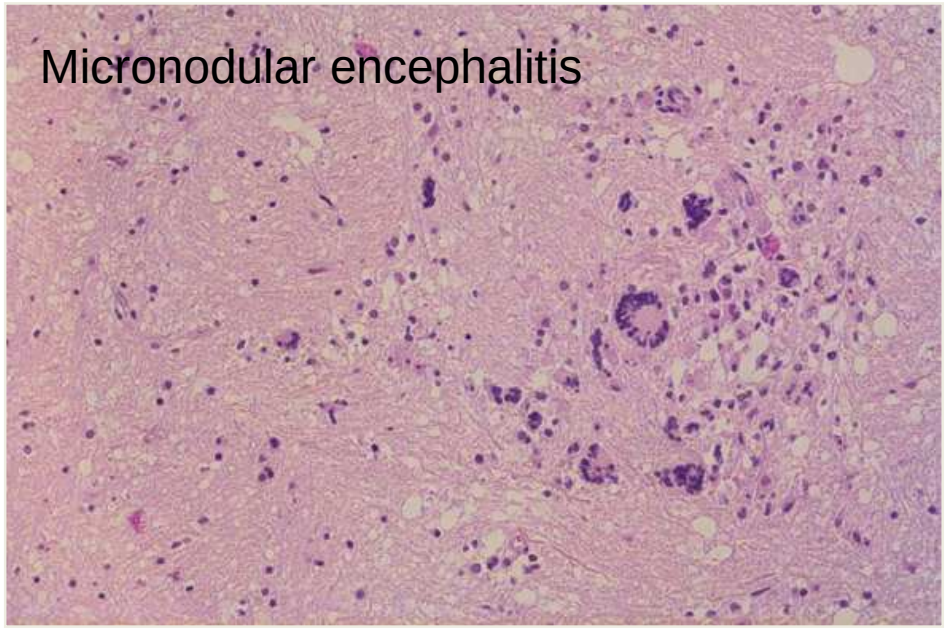
Grey F. e al., Brain Pathol 1996

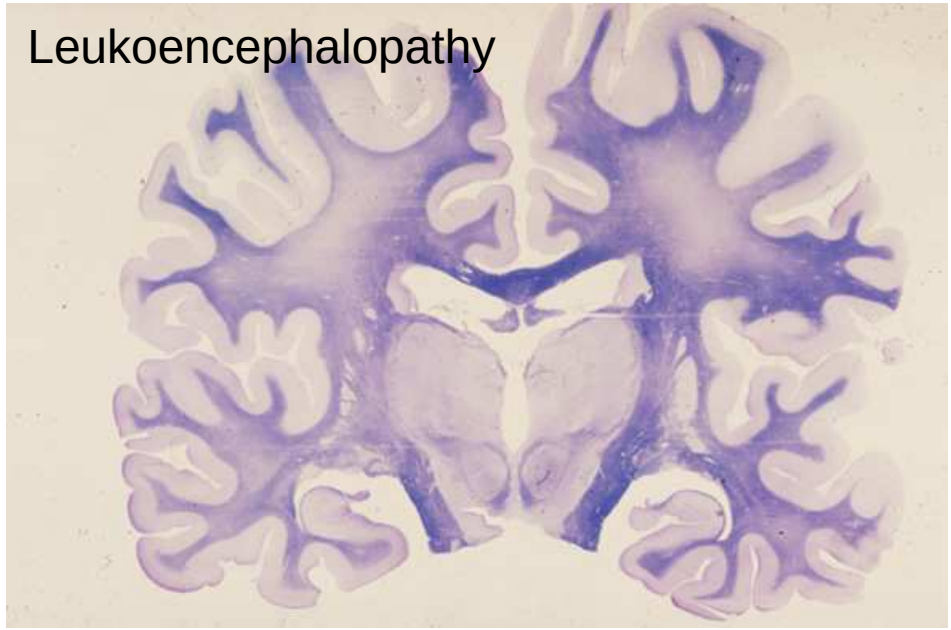
HIV and the CNS - Natural History

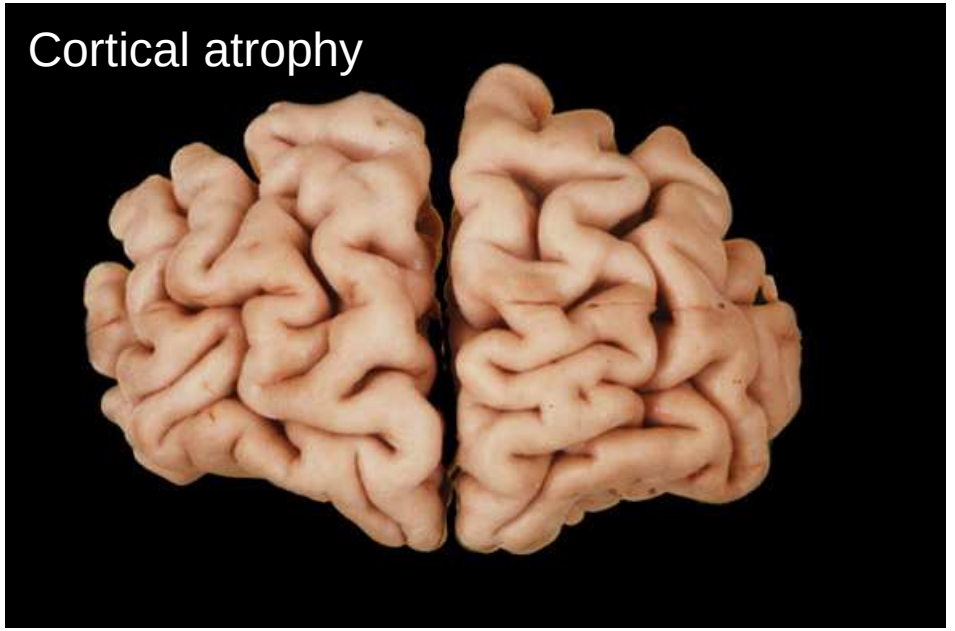


HIV neuropathology









Courtesy of L. Vago and M. Nebuloni, Pathology Dept, L.Sacco Hosp. Milan

The AIDS dementia complex (ADC)

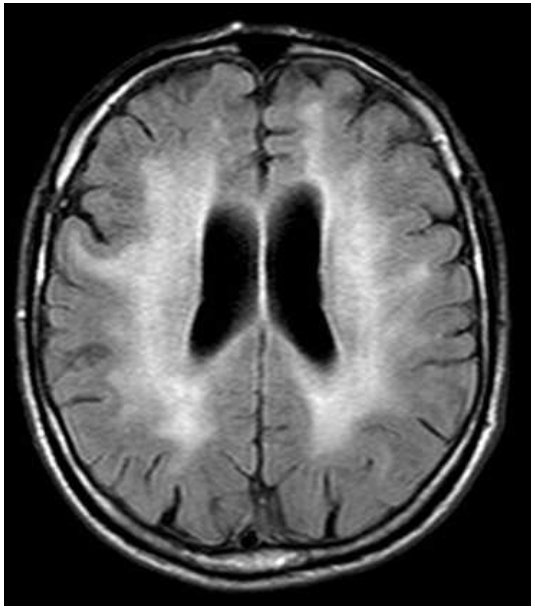
AAN definition criteria (1991)

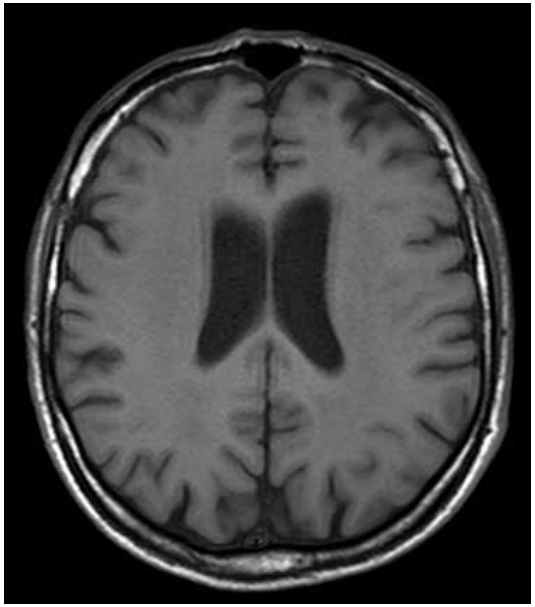
1. Acquired abnormality in at least two of the following cognitive abilities:
   - Attention/concentration
   - Speed of processing of information
   - Abstraction/reasoning
   - Visuospatial skills
   - Memory/learning
   - Speech/language

2. At least one of the following:
   - Acquired abnormality in motor function or performance
   - Decline in motivation or emotional control or change in social behavior

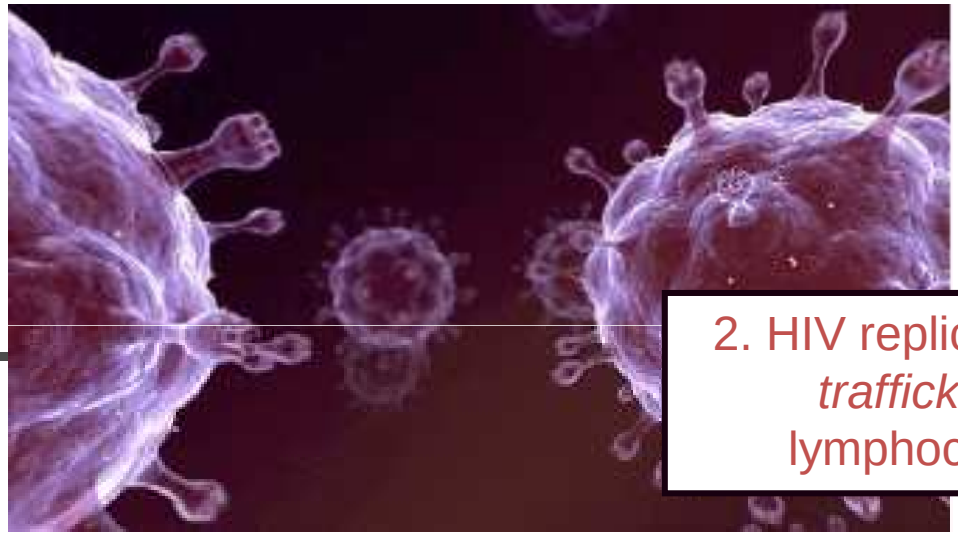
3. Absence of clouding of counsciousness

4. Absence of evidence of other etiology





Model for HIV-induced NCI in untreated infection

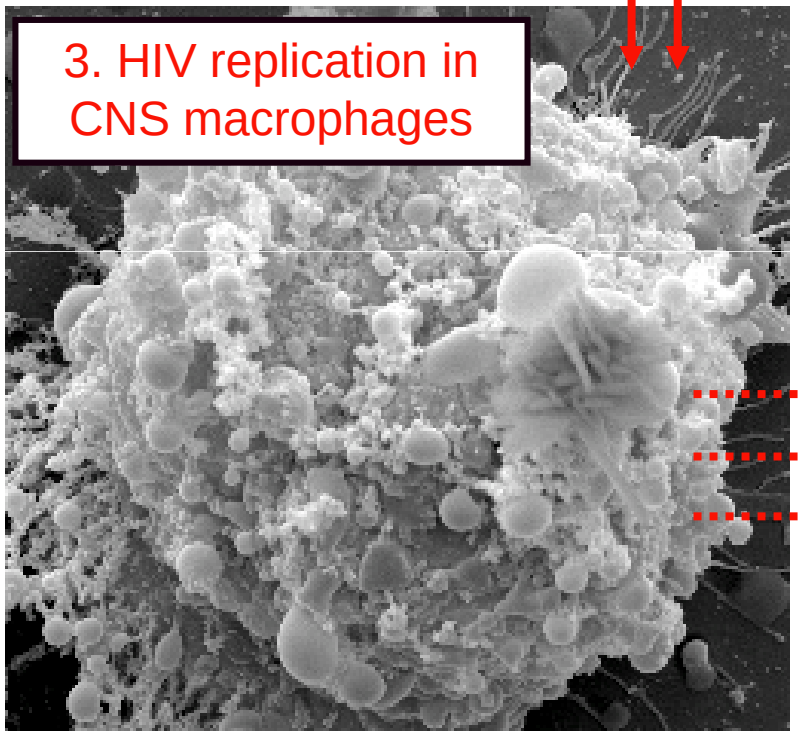


1. Systemic HIV Replication

2. HIV replication in *trafficking* lymphocytes

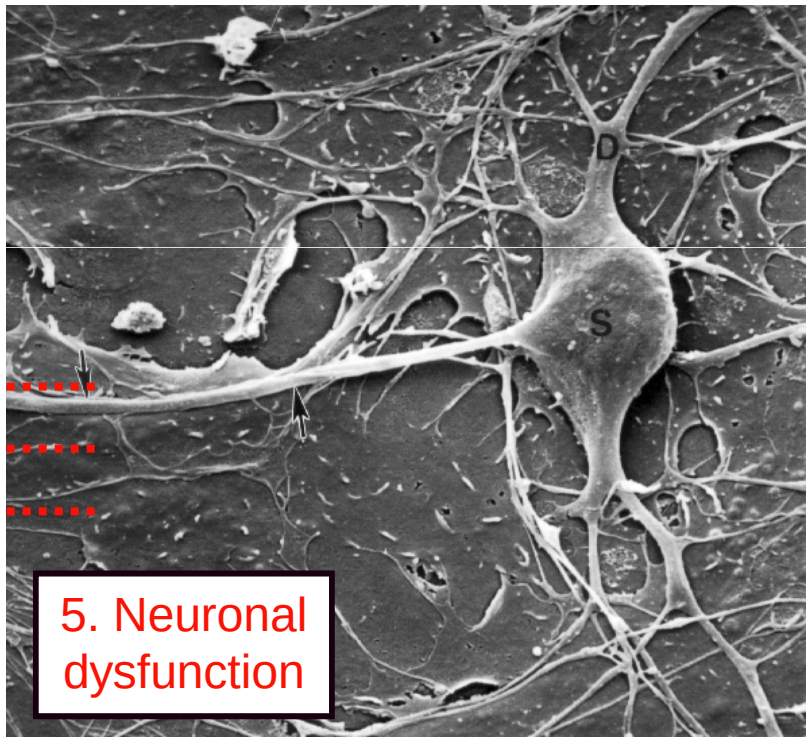
BBB

3. HIV replication in CNS macrophages



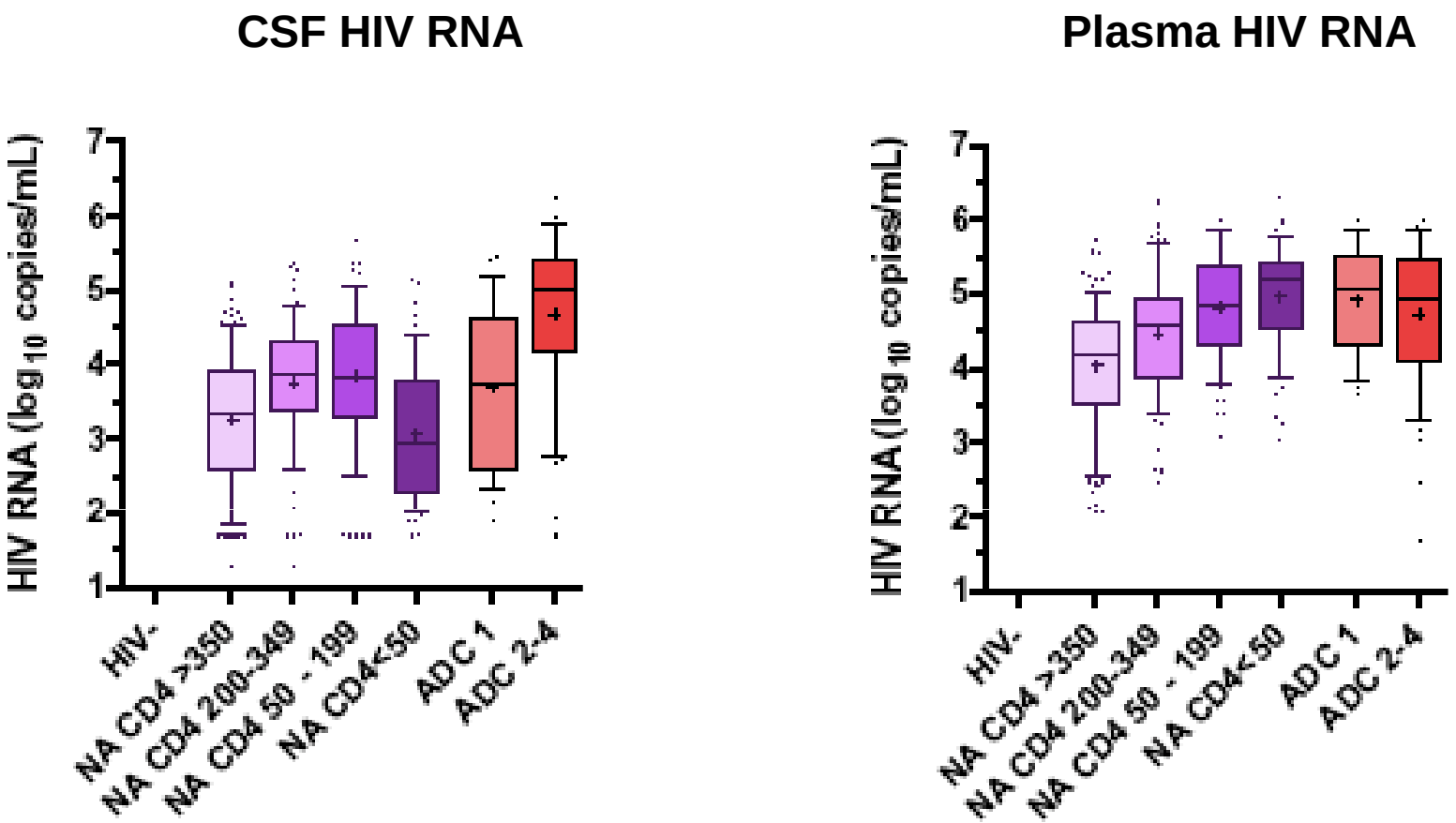
4. Macrophage activation

Soluble factors



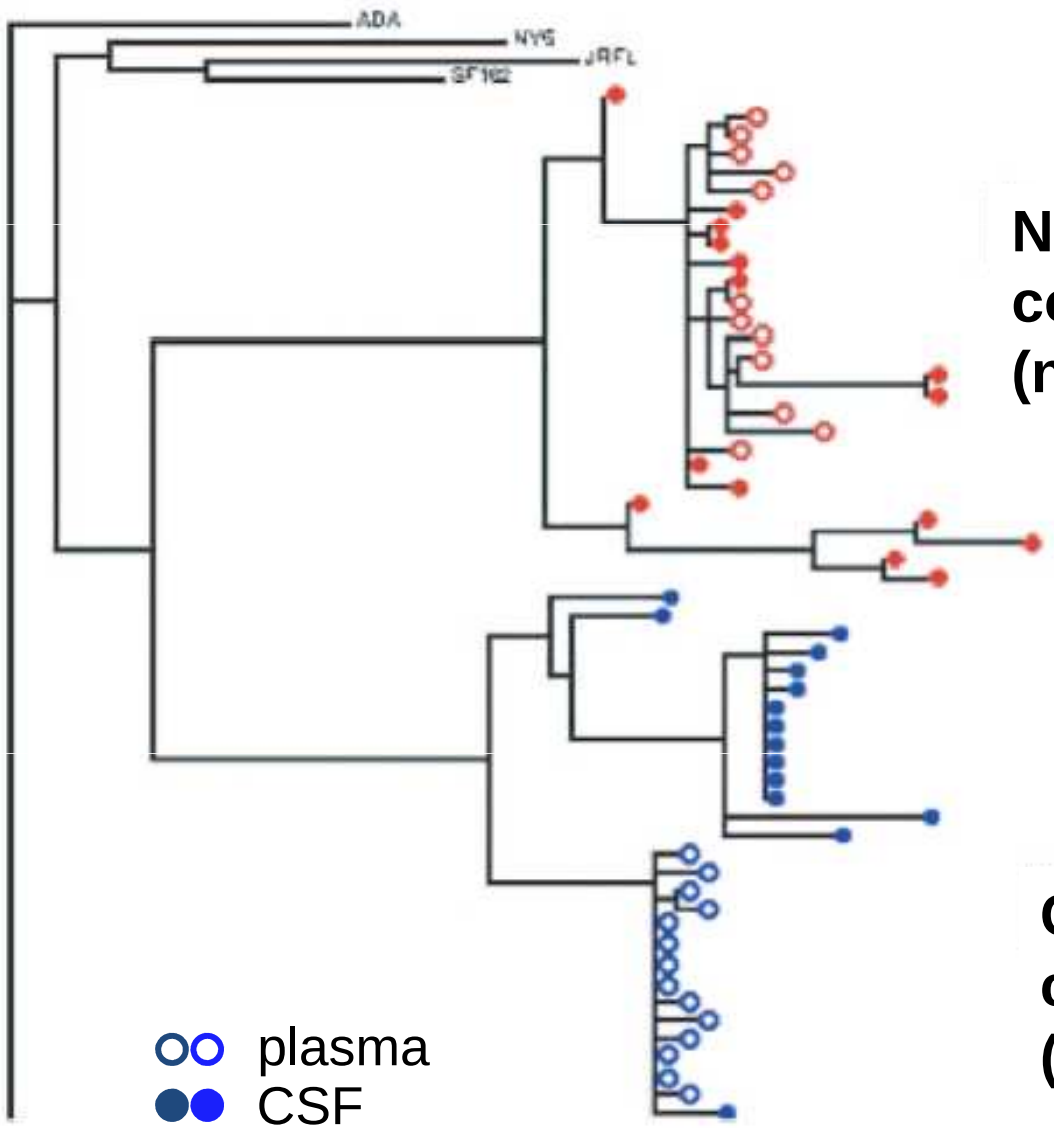
5. Neuronal dysfunction

CSF markers of HIV replication in untreated patients



Hagberg L. et al., 2010

HIV strains are usually non compartmentalized in CSF of neuroasymptomatic patients

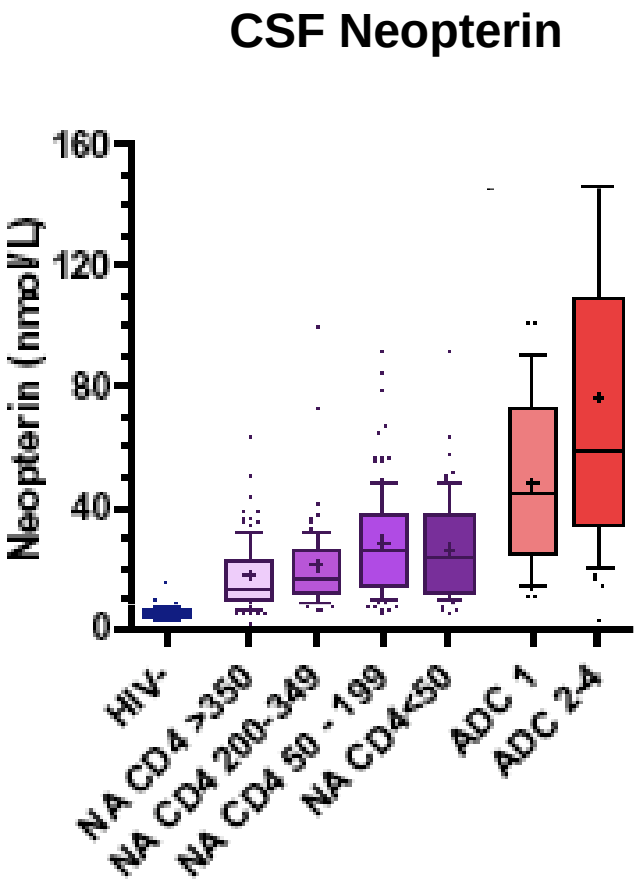


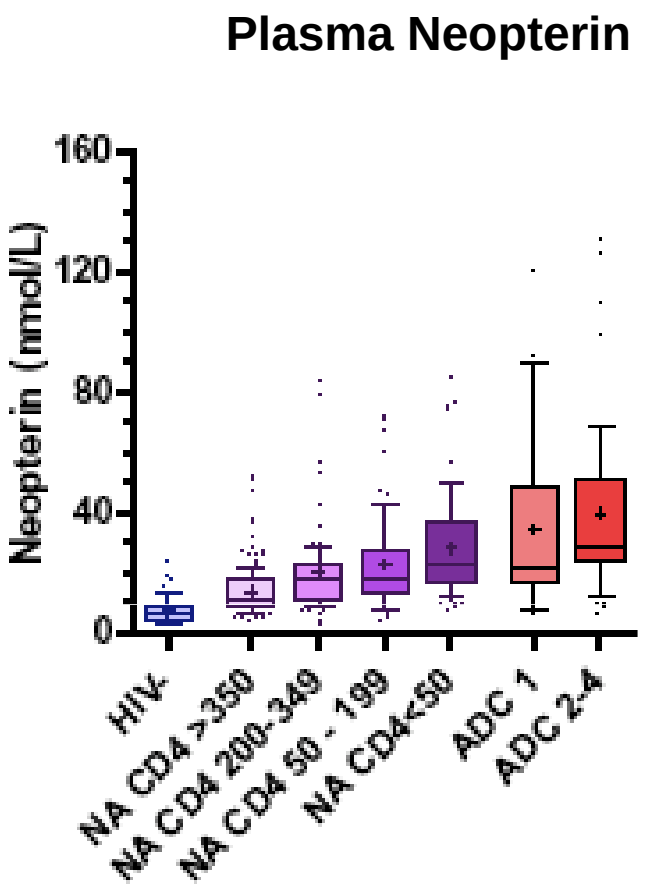
No CSF compartmentalization (neuroasymptomatic)

CSF compartmentalization (ADC)

Pillai SK et al., Brain 2006

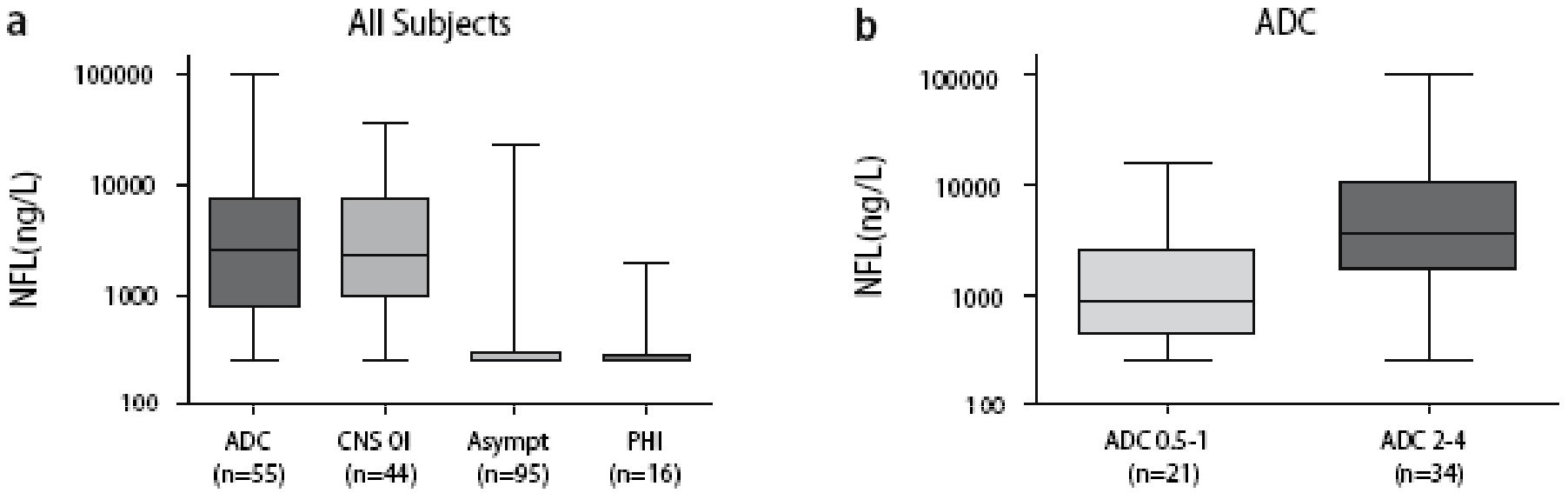
CSF markers of immune activation in untreated patients





Hagberg L. et al., 2010

CSF NFL as marker of neuronal damage in untreated patients

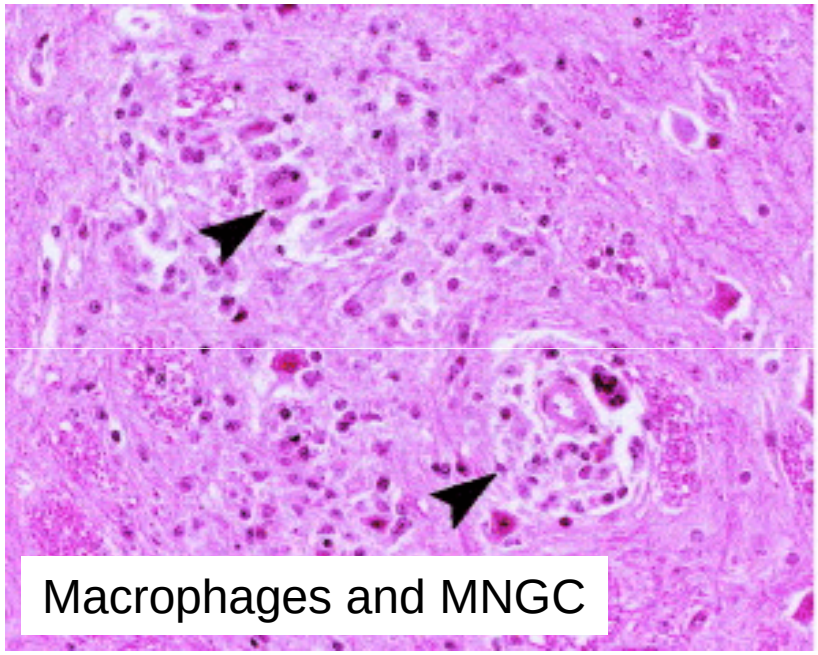


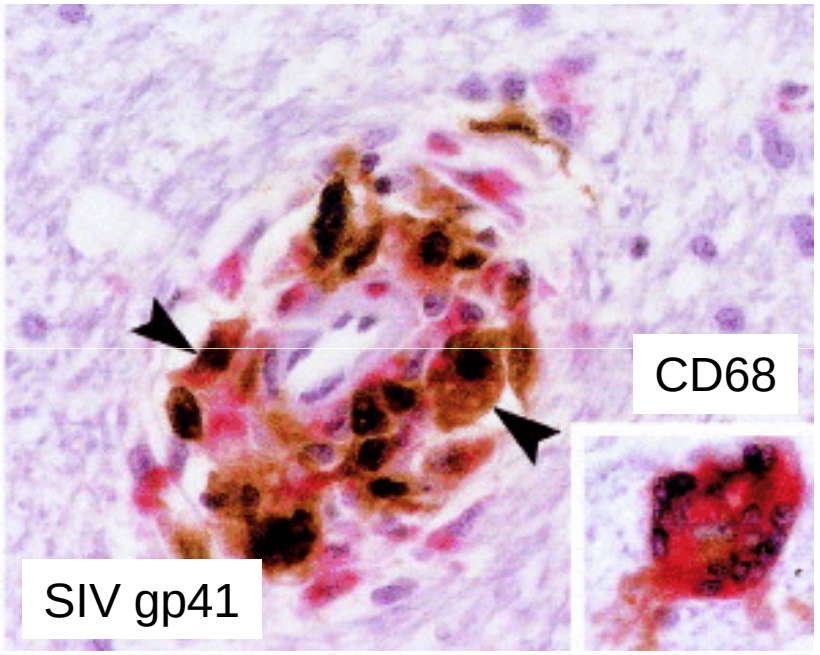
Abdulle S. et al., J Neurol 2007

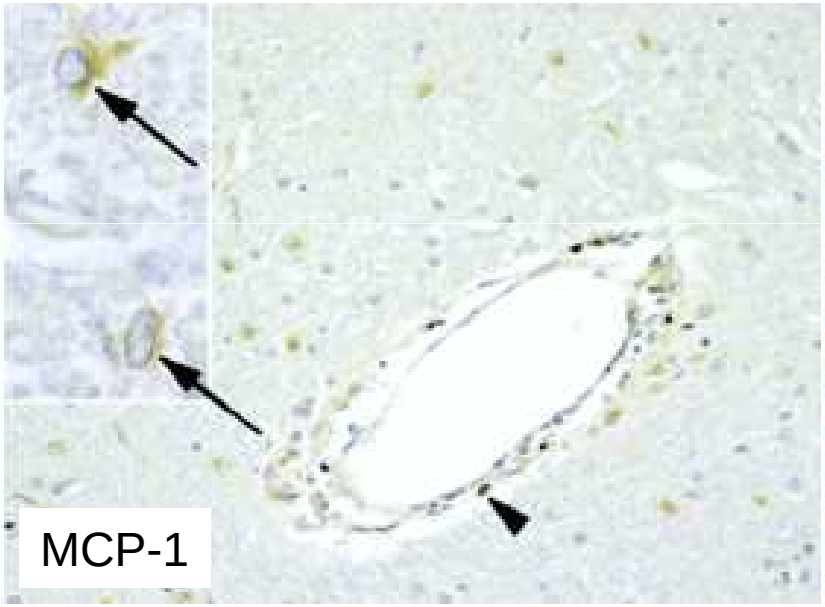
The SIV-encephalitis macaque model

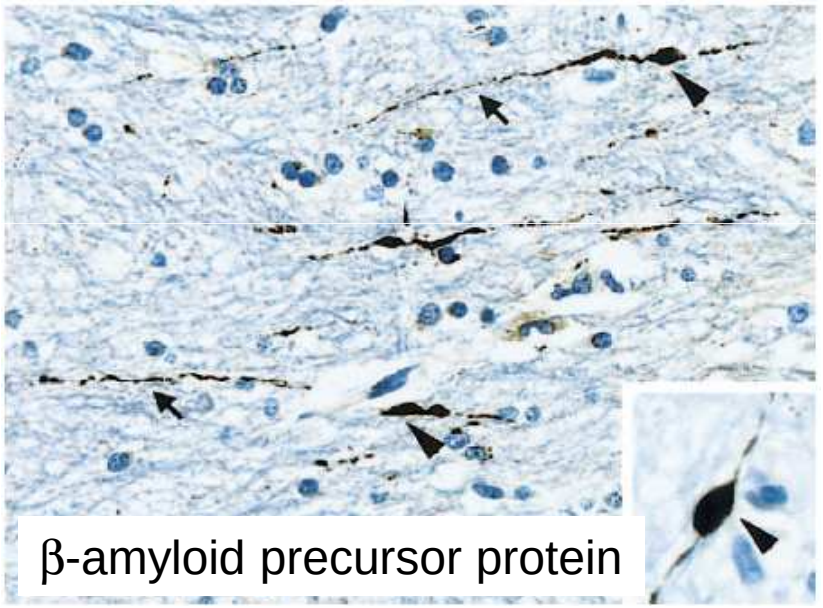
QuickTime™ e un
decompressore
sono necessari per visualizzare quest'immagine.

SIV-encephalitis in macaques







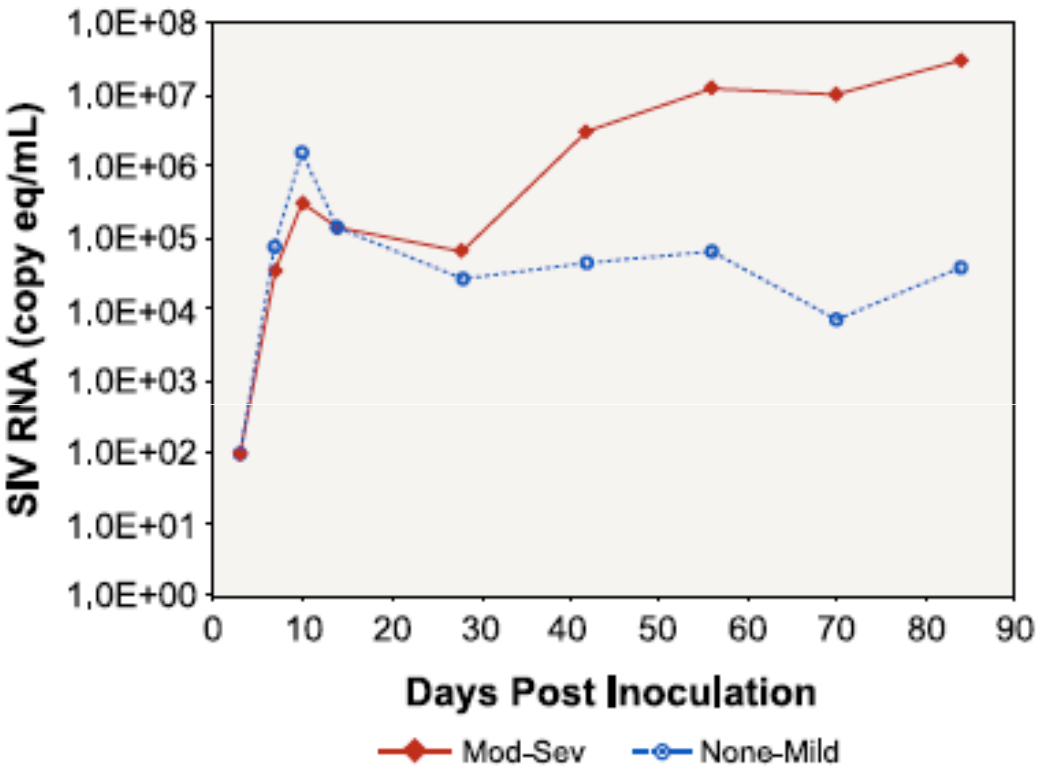


Mankowski JL & Zink MC., JNI & JID 2002-4

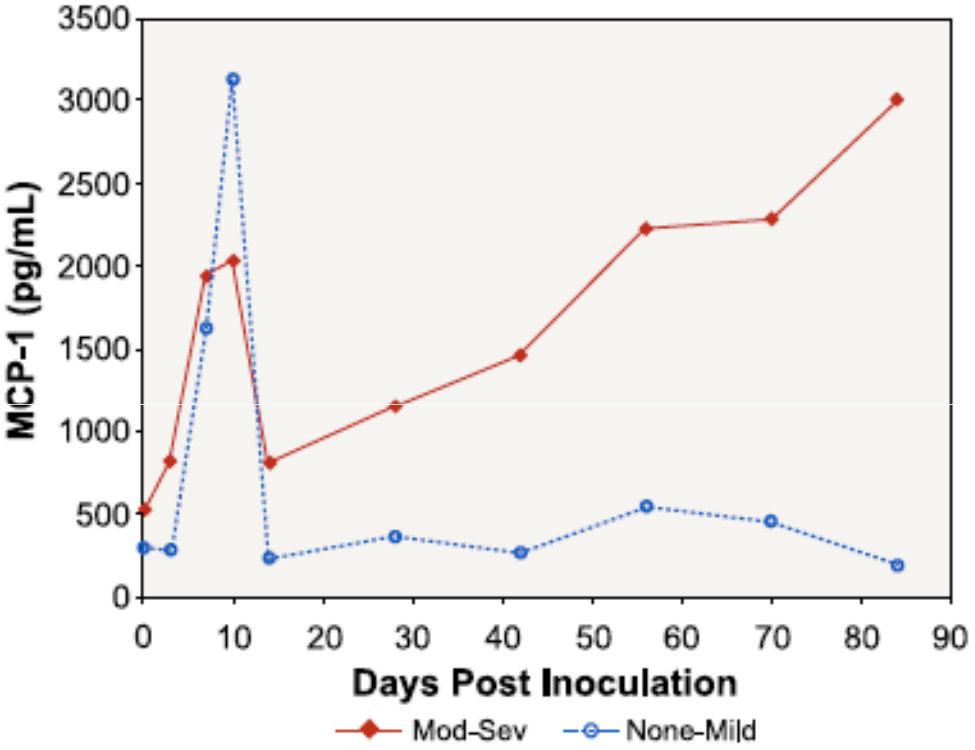
CSF markers of encephalitis in SIV-infected macaques

Accelerated model of SIV encephalitis: inoculation with both neurovirulent and highly pathogenic virus causes moderate/severe SIV-E in 84 days in 14/18 animals

CSF SIV-RNA

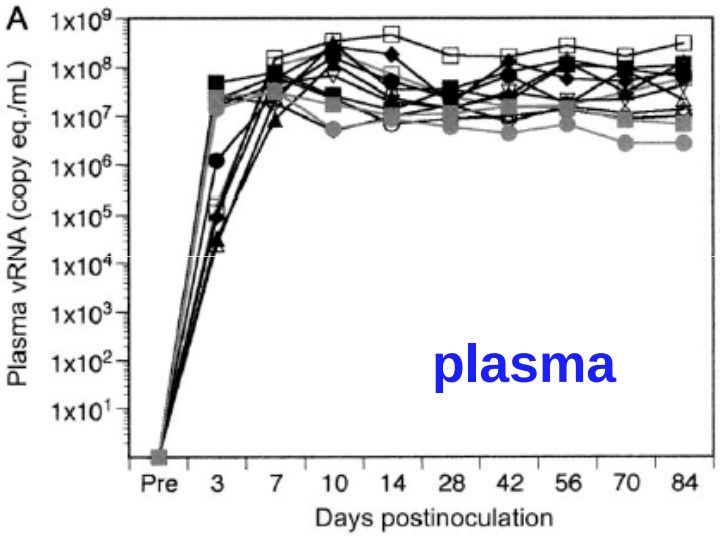


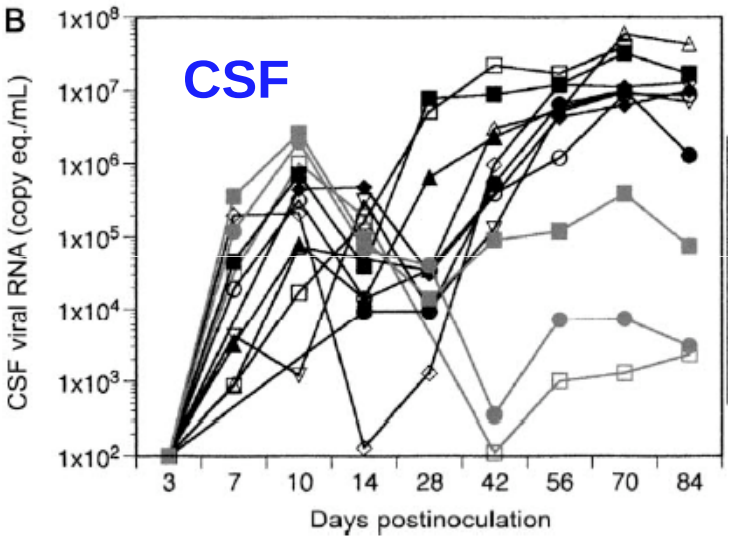
CSF MCP-1



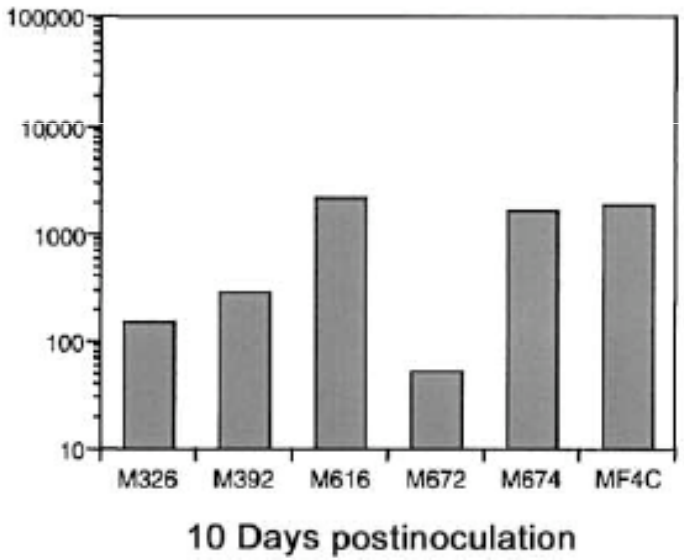
Mankowski JL et al., JNI 2004

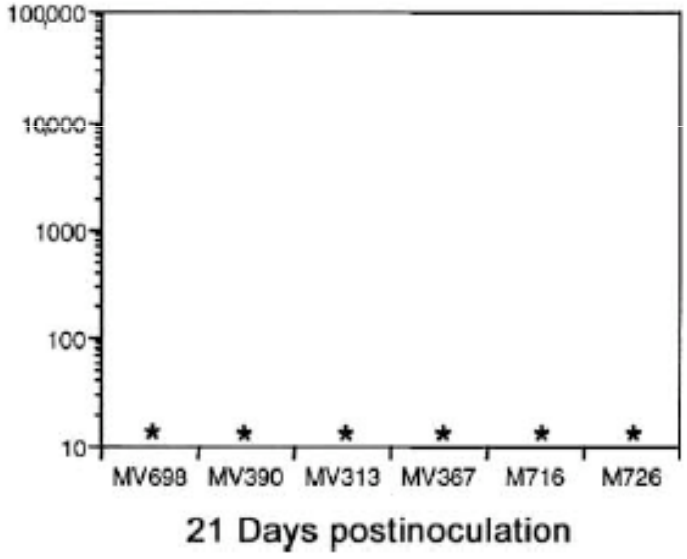
Early phases of SIV replication (SIV-RNA) in CSF and brain in a macaque model of accelerated HIV brain infection

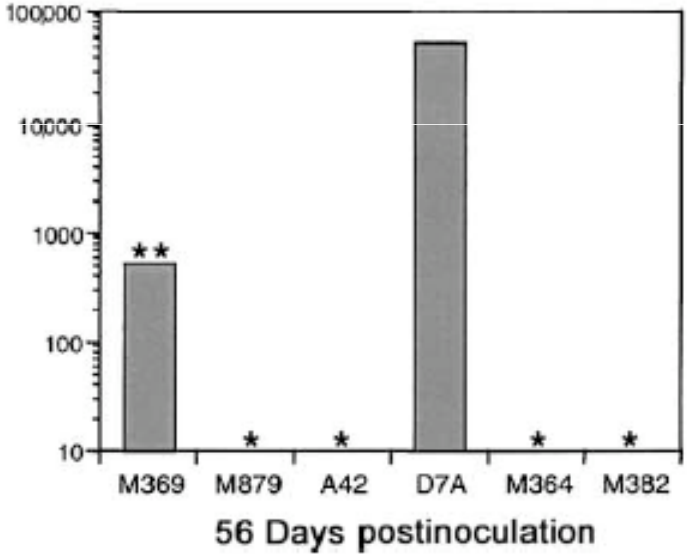




Brain tissue (copies/2 µg total RNA)





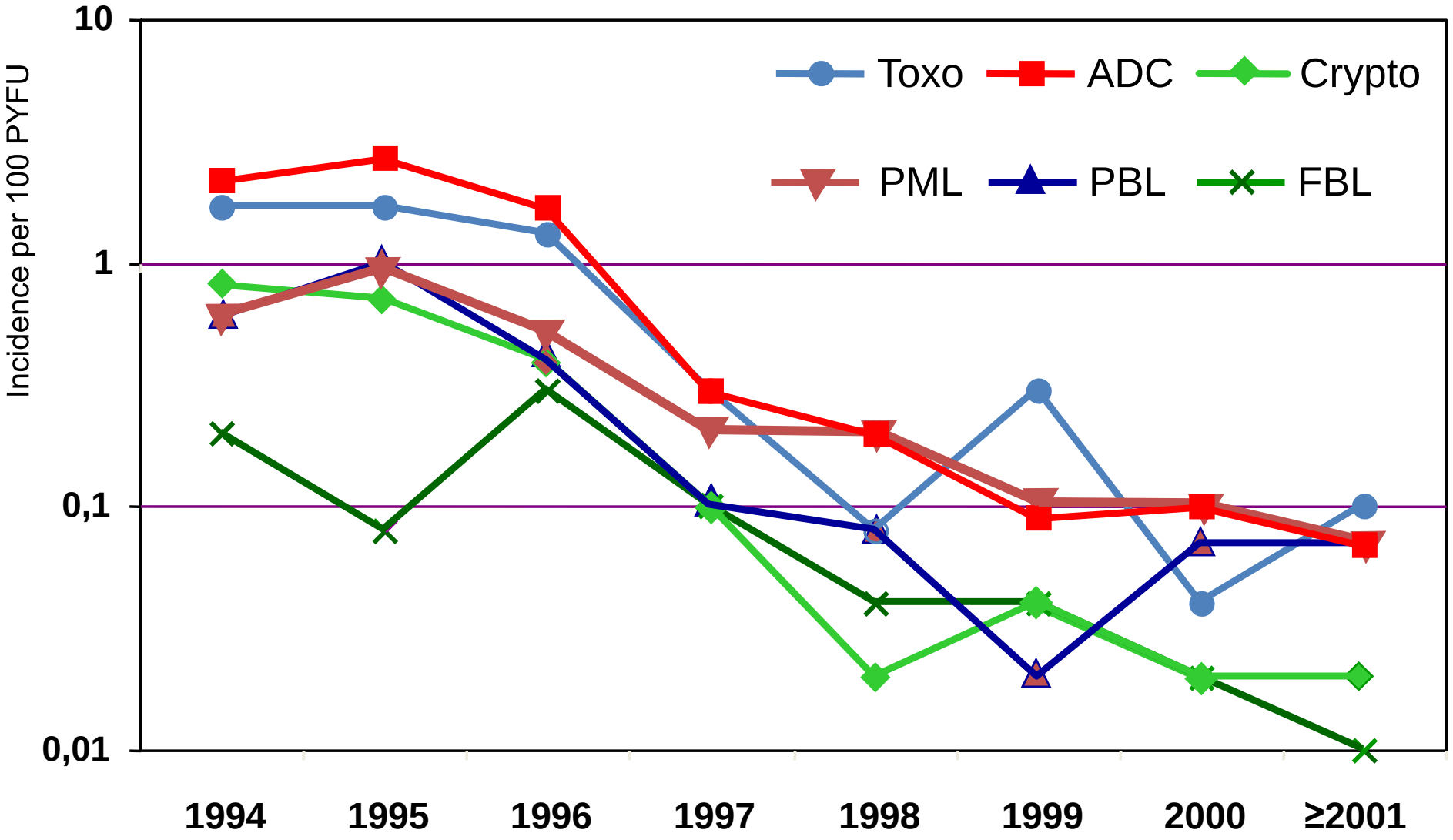


Mankowski JL et al., JID 2004

NCI Pathogenesis

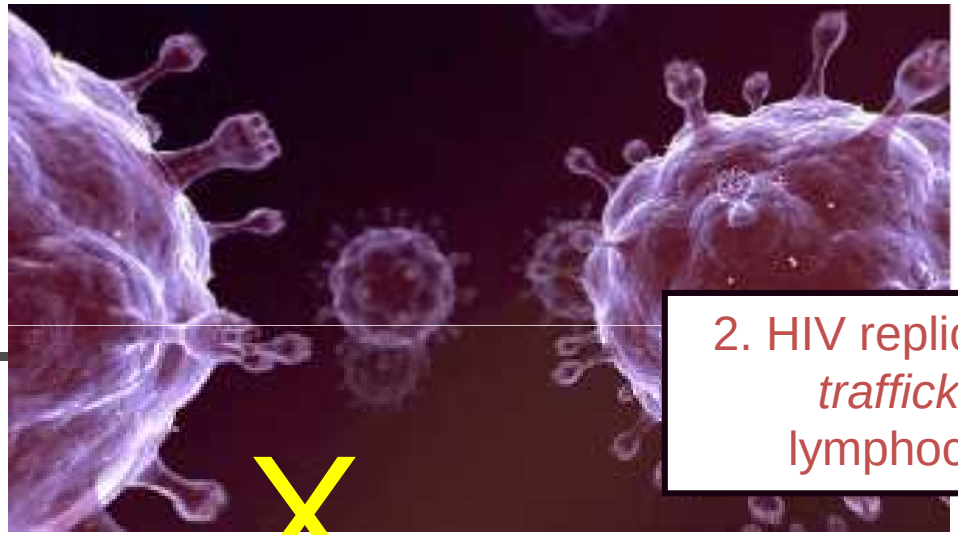
- In untreated HIV infection
- In treated HIV infection

Reduced incidence of CNS-D in the EuroSIDA cohort



D'Arminio Monforte et al, Ann Neurol 2004

The effect of cART on HIV infection of the CNS



ART

1. Systemic HIV Replication

2. HIV replication in *trafficking* lymphocytes

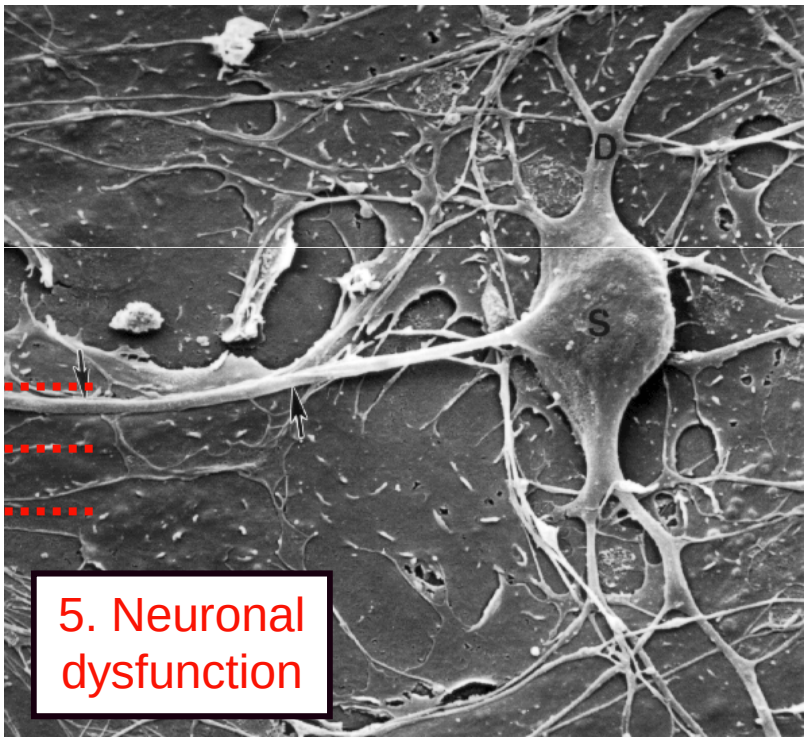
BBB

ART

3. HIV replication in CNS macrophages

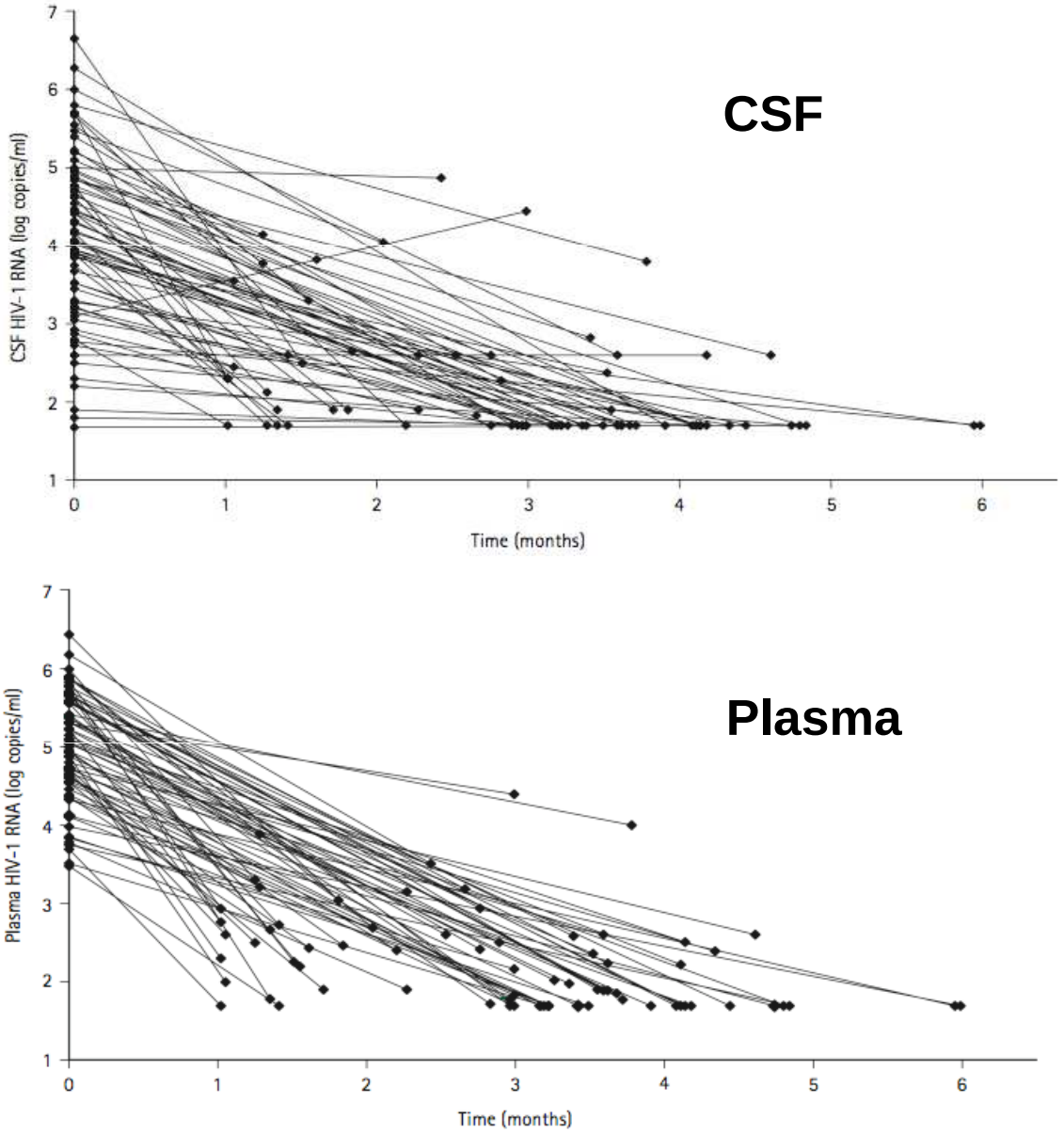
4. Macrophage activation

Soluble factors



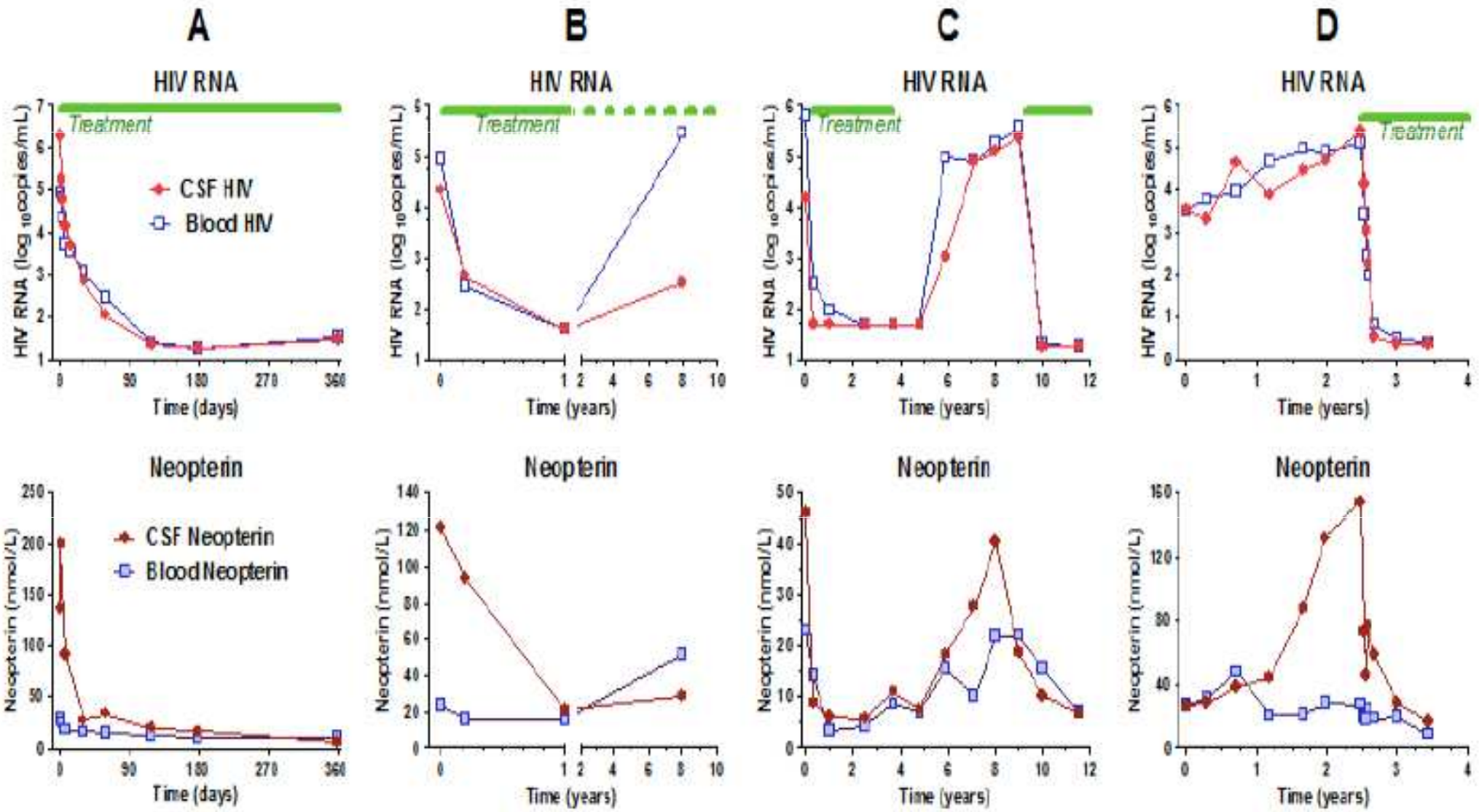
5. Neuronal dysfunction

cART is followed by reduction of CSF HIV RNA level



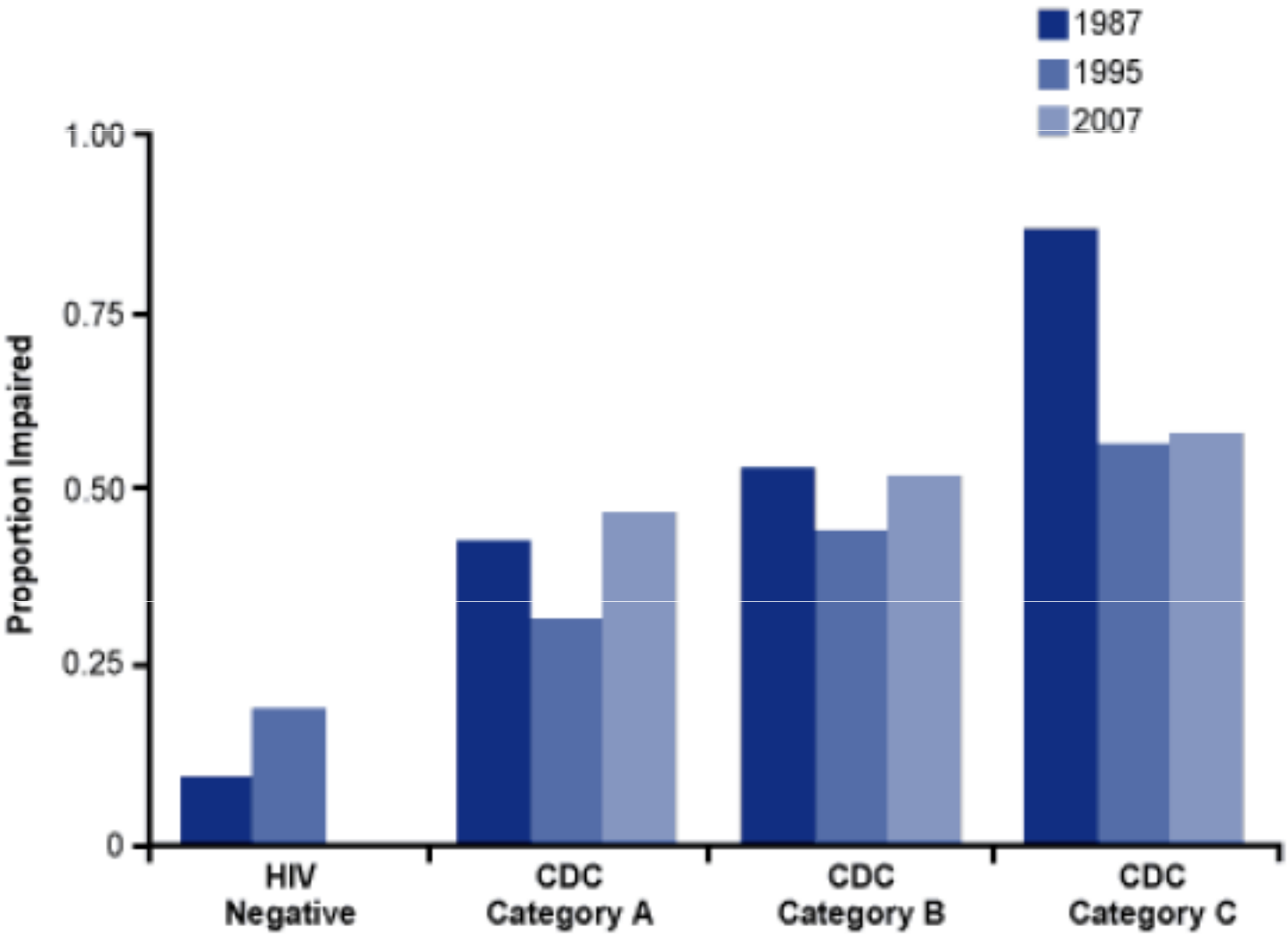
Mellgren A et al., Antiviral Ther 2006

cART induces changes of CSF markers of HIV replication and immuneactivation



Hagberg L. et al., 2010

Prevalence of HIV-associated Neurocognitive Impairment (HAND) is not substantially reduced after the introduction of cART



Grant I, Int Rev Psy 2008

Possible causes of neurocognitive impairment in HIV-infected patients

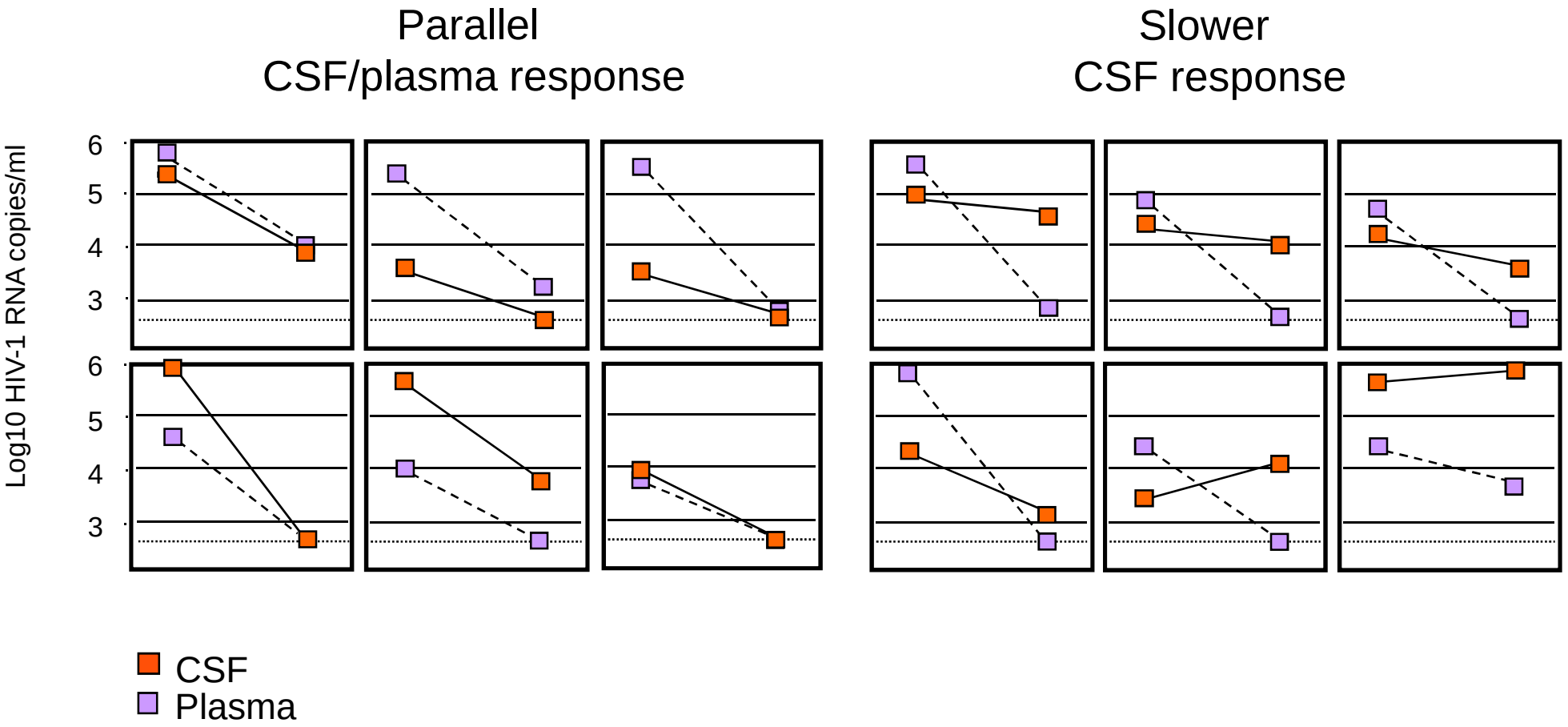
- HIV
- Other causes?
  - Psychiatric disorders
  - Drugs, alcool
  - “Physiological” aging
  - Forms of age-related dementia (Alzheimer’s and other neurodegenerative diseases, cerebrovascular disorders)
  - Cerebro-vascular disease
  - HCV infection
  - Drug toxicity

HIV in the CNS
as main cause of NCI in treated patients

- Active low-level replication
  - "CSF (or CNS) escape"
  - Below detection limit

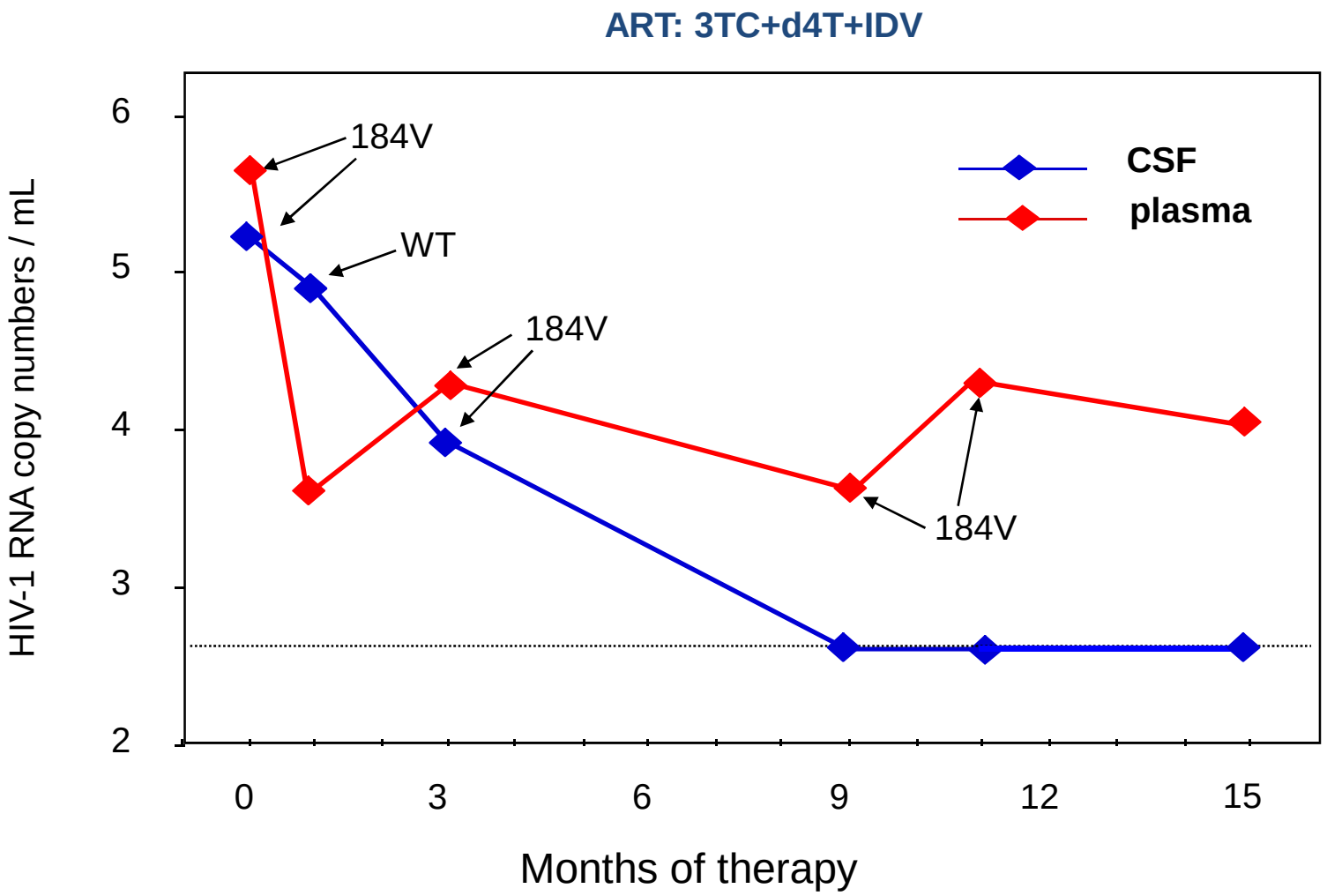
- Established irreversible tissue damage, e.g., of neurons, astrocytes

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

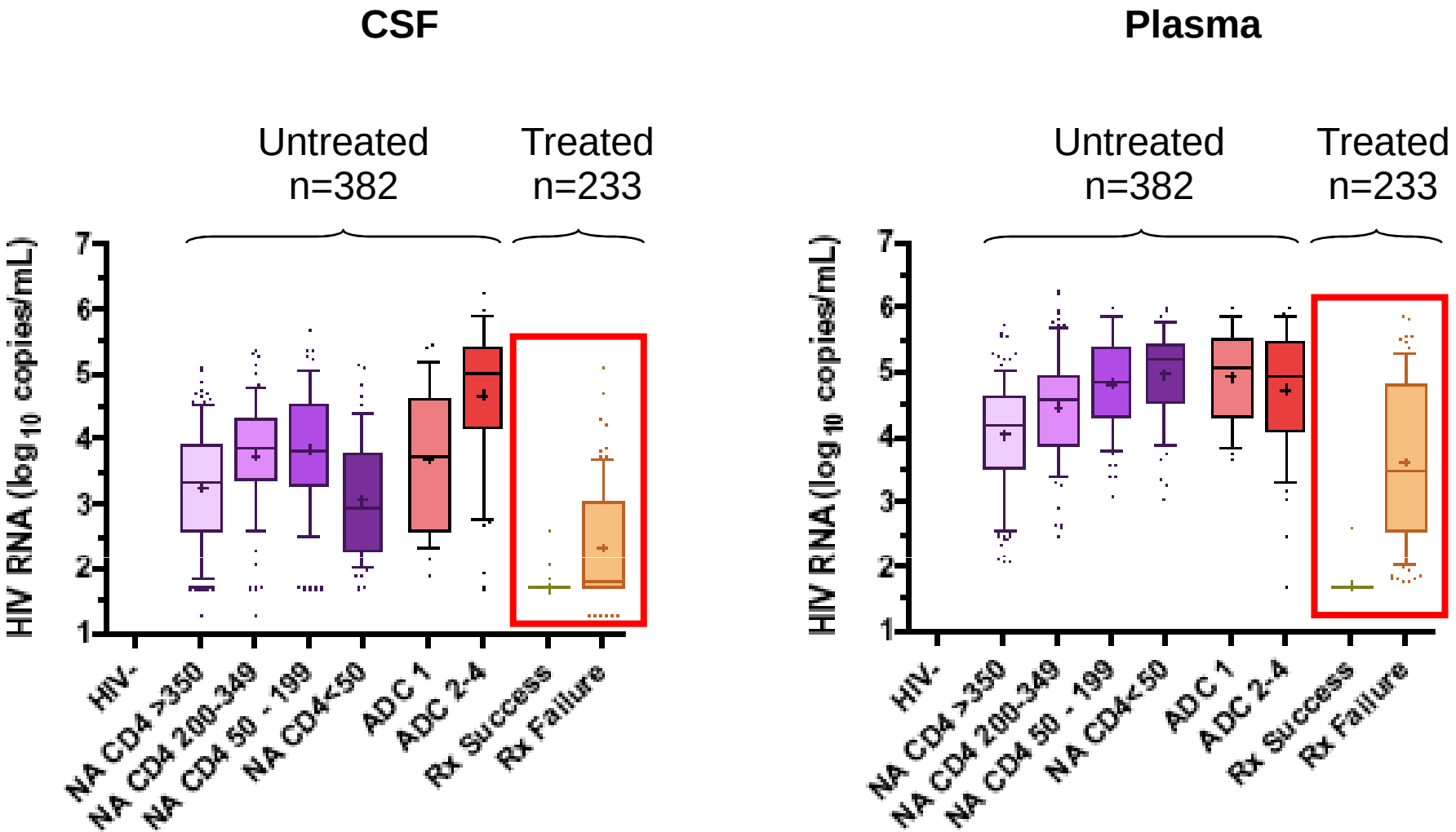


Cinque et al., ARHR 2001

Long-term virological response in CSF despite plasma failure in a patient with ADC



Relatively low rate of HIV replication in CSF of treated failing patients



Hagberg L. et al., AIDS Res Ther 2010

CSF escape with CNS symptoms in cART-treated, systemically suppressed patients

Patient	Age, years	Nadir CD4+ T cell count, cells/mm³	CD4+ T cell count, cells/mm³	Time with plasma HIV RNA level <50 copies/mL, months	Neurological symptoms	Treatment	CSF HIV RNA level, copies/mL	CSF ART concentration trough, ng/mL	Plasma HIV RNA level, copies/mL	Plasma ART concentration trough, ng/mL	Resistance mutations detected in CSF	Change in treatment
1	50	250	592	3?	Persistent headache	TDF FTC ATVr	12,095	12 NA <30	147	52 19 539	NRTI: M41L/E44D/D67N/L74V/M184V/L210W/T215Y; NNRTI: none; PI: 30I	AZT, 3TC, IDVr
2	49	4	190	11	Memory disorders, cerebellar ataxia	AZT 3TC IDVr T20	845	28 201 154 <50	<50	<10 244 555 1427	NRTI: M41L/E44D/D67N/M184V/L210W/T215Y; NNRTI: V179I; PI: L63P/V82T/I85V	AZT, 3TC, IDV, LPVr, NVP
3	43	52	400	18	Cerebellar syndrome, cerebellar ataxia	3TC ABC ATV IDVr	1190	NA 75 <30 57	<50	587 60 990 520	NRTI: M41L/D67N/T69D/L74V/M184V/L210W/T215Y; NNRTI: L100I/K103N; PI: L10I/I13V/E35D/M36I/R41K/I54V/L63P/H69K/V82S	3TC, ABC, ATV, IDV, LPVr
4	50	221	422	69	Tactile allodynia	TDF FTC FAPVr	870	NA NA 47	78	NA NA 1495	NRTI: M41L/D67N/K70R/M184V/T215F/K219Q; NNRTI: none; PI: L10I/K20V/L63P	3TC, ABC, IDV, fAPVr
5	36	55	107	75	Glasgow Coma Score of 3	3TC ABC TDF DRVr	5035	<10 332 191 207	<50	<10 270 618 6892	NRTI: none; NNRTI: none; PI: none	Foscarnet, AZT, 3TC, ABC, TDF, LPVr, MRV
6	41	64	62	64	Persistent headache	DRVr	590	<5	<50	2522	NRTI: M184V/L74I; NNRTI: none; PI: none	3TC, ABC, DRVr
7	44	211	544	14	Memory disorders, cerebellar ataxia, pyramidal syndrome	FTC ABC ATVr	559	NA NA 18	<50	NA NA 194	NA	FTC, ABC, EFV, fAPVr
8	53	25	360	12	Lower limb dysesthesia and hypoesthesia	3TC AZT ABC EFV	1073	NA NA NA	<50	NA NA NA	NA	None
9	68	110	147	12	Memory disorders, left lower limb dysesthesia	3TC ddI TDF NVP	536?	NA NA NA	<50	268 NA 29 4864	NA	3TC, NVP, ATVr
10	63	25	534	18	Temporospatial disorientation, cerebellar ataxia	3TC AZT ATV	990	NA NA NA	<50	NA NA NA	NRTI: M41L/E44D/D67N/K70R/M184V/L210W/T215Y/K219Q; NNRTI: none; PI: I13V/L63P	3TC, AZT, fAPV, LPVr
11	55	2	593	10	Memory disorders, cerebellar dysarthria	LPVr	6209	NA	483	NA	NRTI: none; NNRTI: none; PI: M46I/I54V/L63P/V82A	3TC, ABC, EFV, LPVr

NOTE. ABC, abacavir; ATV, atazanavir; ATVr, atazanavir boosted with ritonavir; AZT, zidovudine; CSF, cerebrospinal fluid; DRVr, darunavir boosted with ritonavir; EFV, efavirenz; fAPV, fosamprenavir; fAPVr, fAPV boosted with ritonavir; FTC, emtricitabine; IDV, indinavir; IDVr, indinavir boosted with ritonavir; LPV, lopinavir; LPVr, lopinavir boosted with ritonavir; MRV, maraviroc; NA, not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir; 3TC, lamivudine; T20, enfuvirtide.

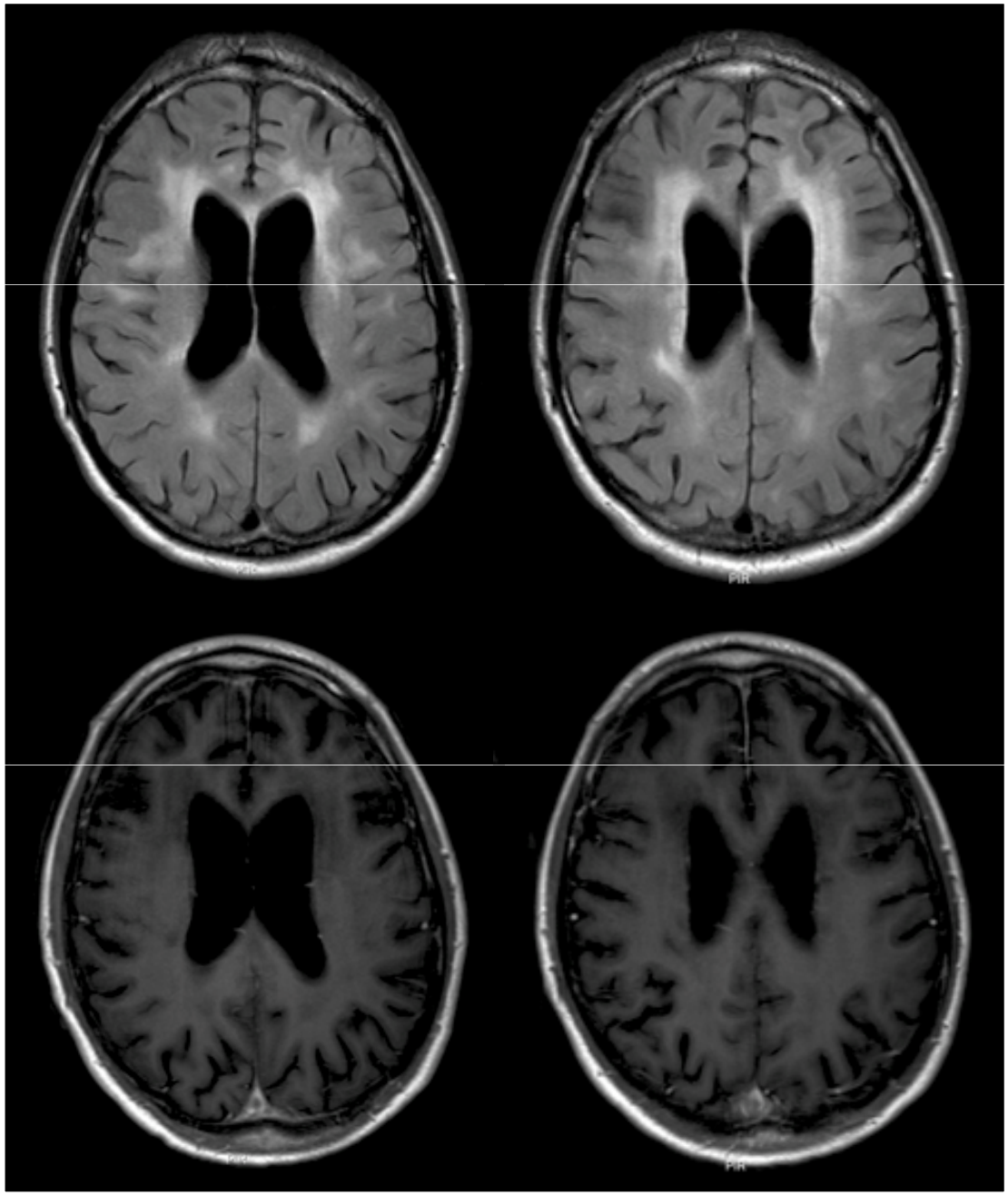
Canestri et al., CID 2010

“CSF escape” and chronic HIV encephalopathy

1991: Start ART
Since 2005: FTC,TDF,LPV/r

Since 2000:
- Initially mild but progressing cognitive deficit
- HIV-RNA between 50-1000 c/mL

January 2008
-Severe NCI
-Leukoencephalopathy at MRI
-CD4: 632
-Plasma VL: 200 c/mL
-CSF VL: 750 c/mL

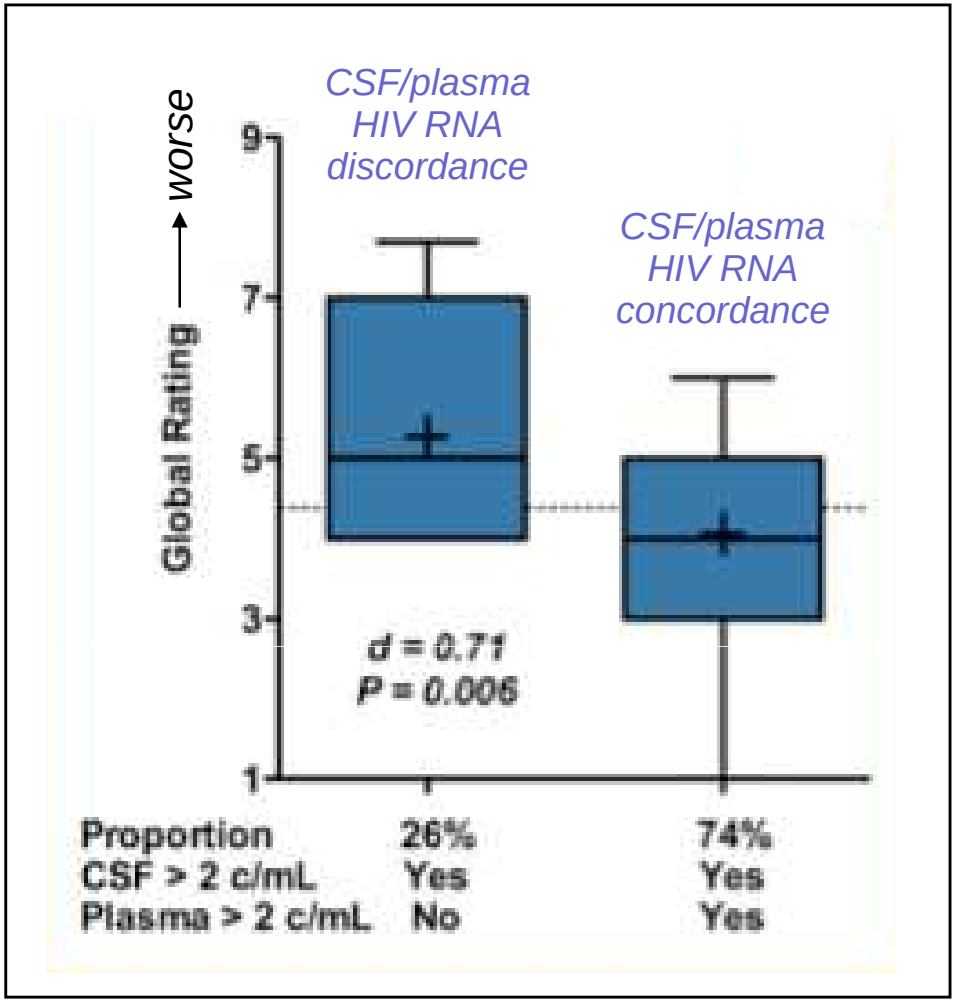


HIV may persist in CSF below 50 c/mL during cART

CHARTER cohort (UCSD)

- 300 patients with CSF HIV RNA < 50 c/mL

- CSF HIV RNA >2 c/mL in 122/300 (41%)



Letendre S et al., CROI 2009

HIV in the CNS
as main cause of NCI in treated patients

- Active low-level replication
  - "CSF (or CNS) escape"
  - Below detection limit

- Established irreversible tissue damage, e.g., of neurons, astrocytes

Risk factors for NC impairment in HIV-infected persons

- Nadir CD4 < 200/µL

- Older age
- Metabolic problems
- Host genetic factors ?
- Viral genetic factors ?
- Others…?

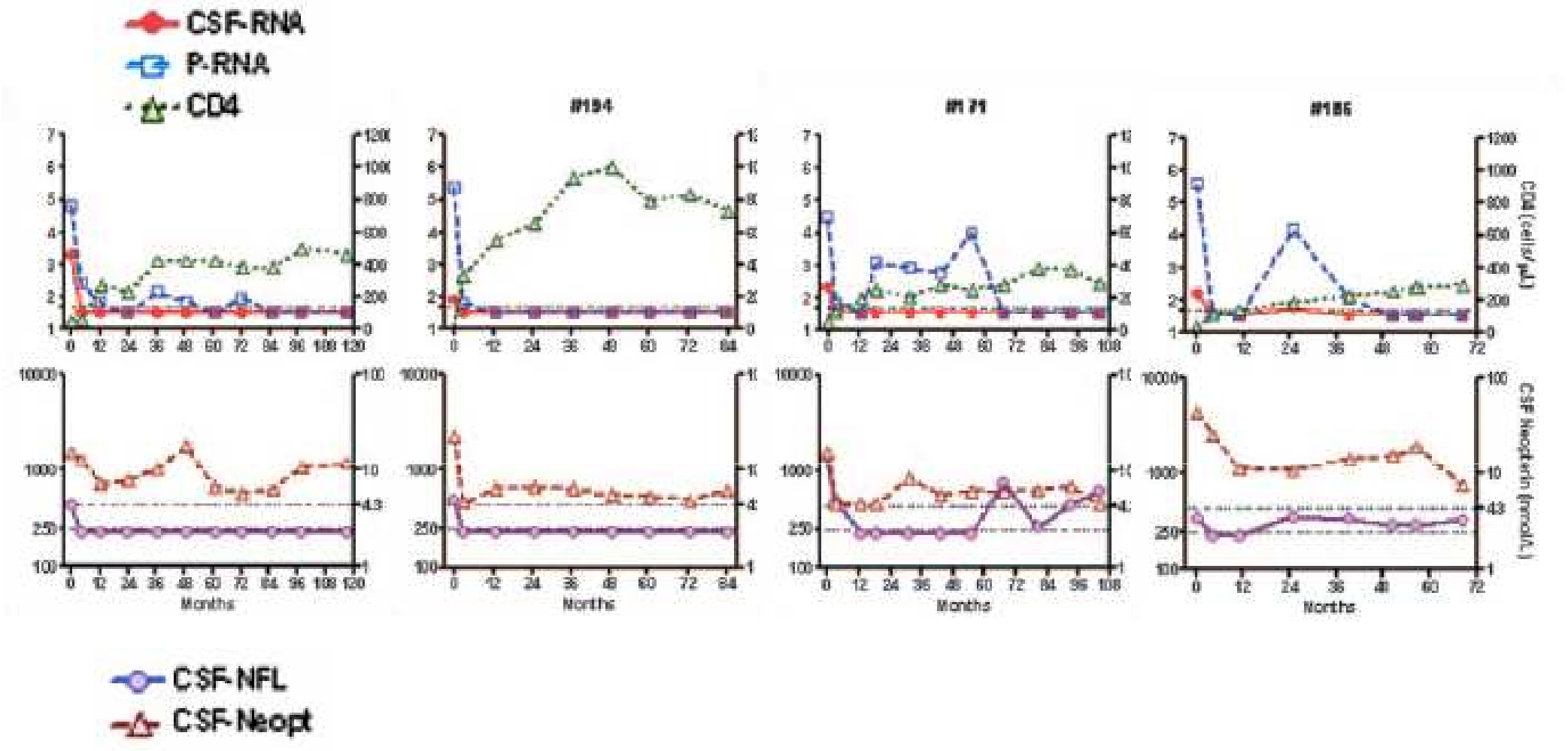
HIV in the CNS
as main cause of NCI in treated patients

- Active low-level replication
  - "CSF (or CNS) escape"
  - Below detection limit

- Established irreversible tissue damage, e.g., of neurons, astrocytes

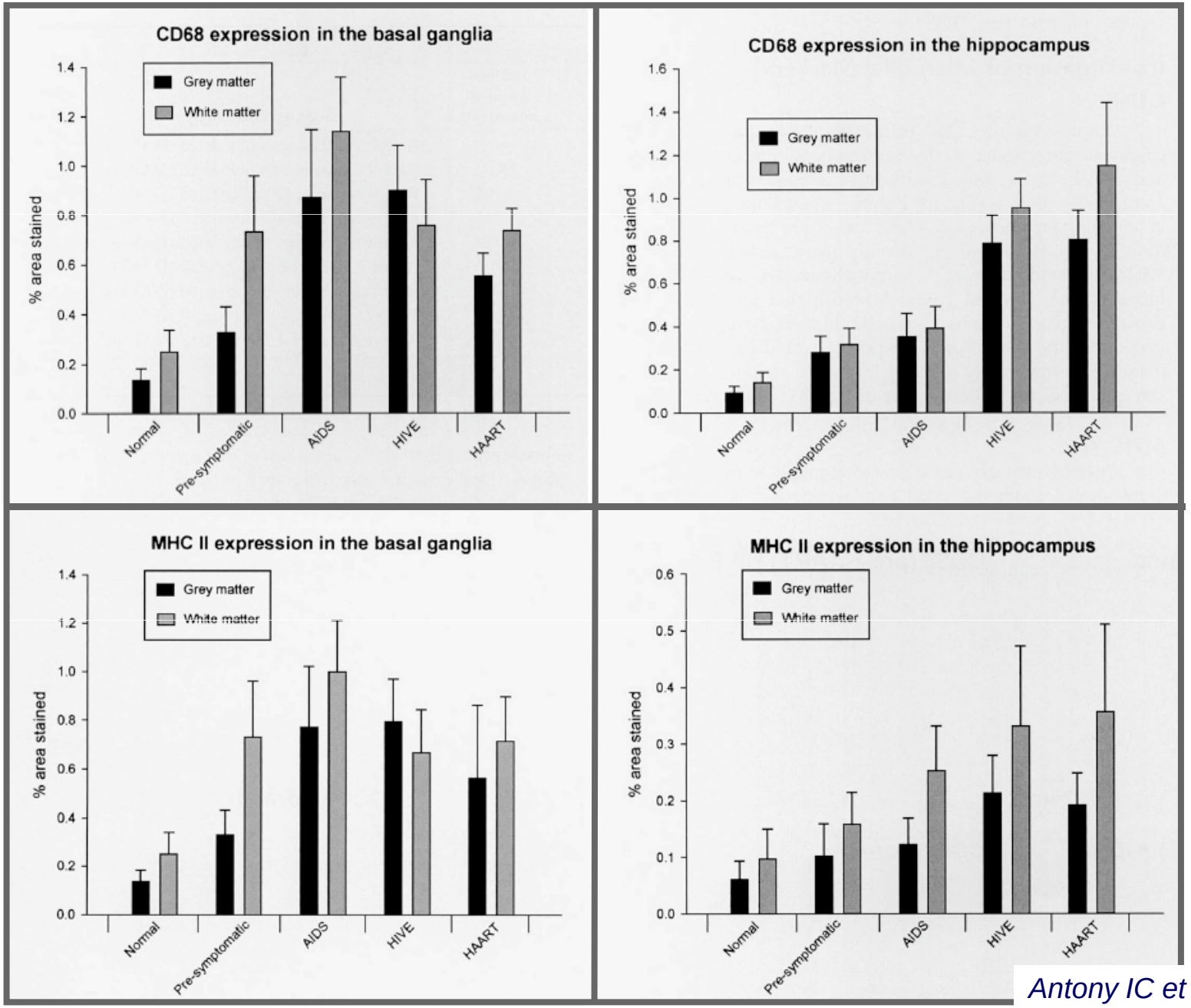
→ Intrathecal immuneactivation may persist in both cases

Persistent intrathecal immuneactivation despite cART



Mellgren A et al.,Neurology 2007

High degree immune activation in the brain of cART-treated patients



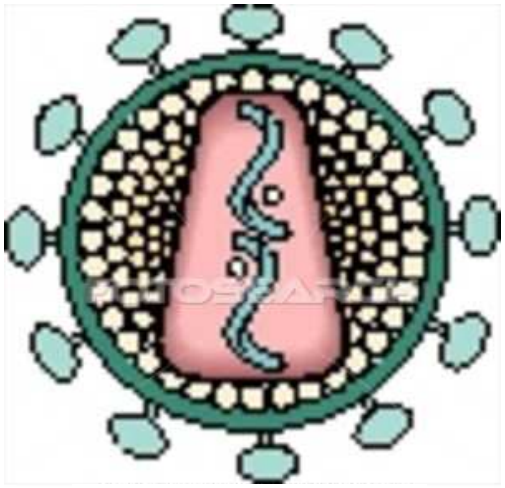
Antony IC et al. JNEN 2005

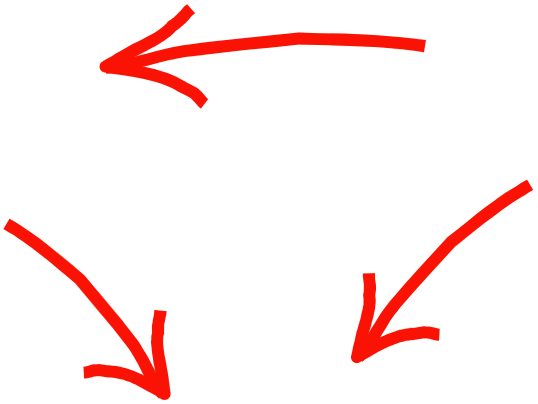
Risk factors and/or contributors of NCI in HIV-infected persons

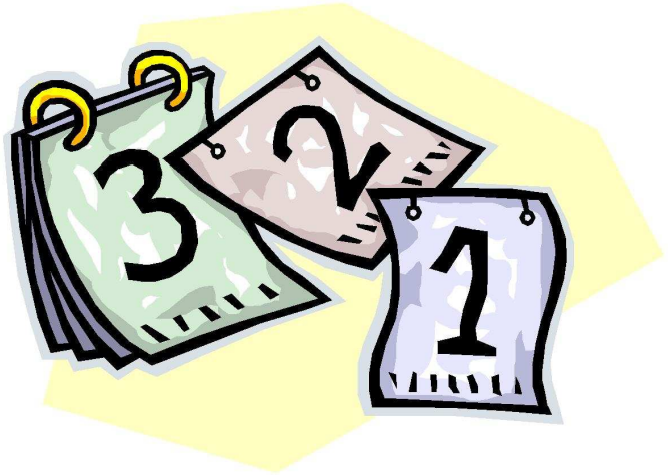
- Nadir CD4 < 200/µL
- "Physiological" aging
- Psychiatric disorders
- Drugs, alcool
- Alzheimer's and other neurodegenerative disease
- Cerebro-vascular disease
- HCV infection
- Others…

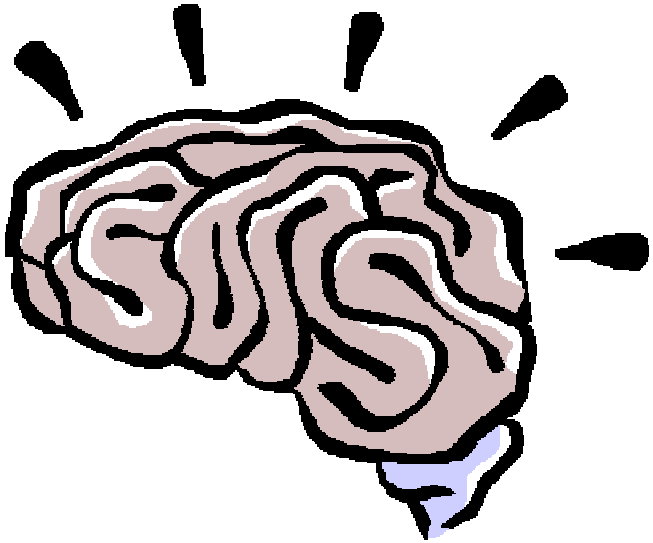
→ Again, intrathecal immuneactivation may mediate NCI in most of these cases

The brain, the virus and the advancing age

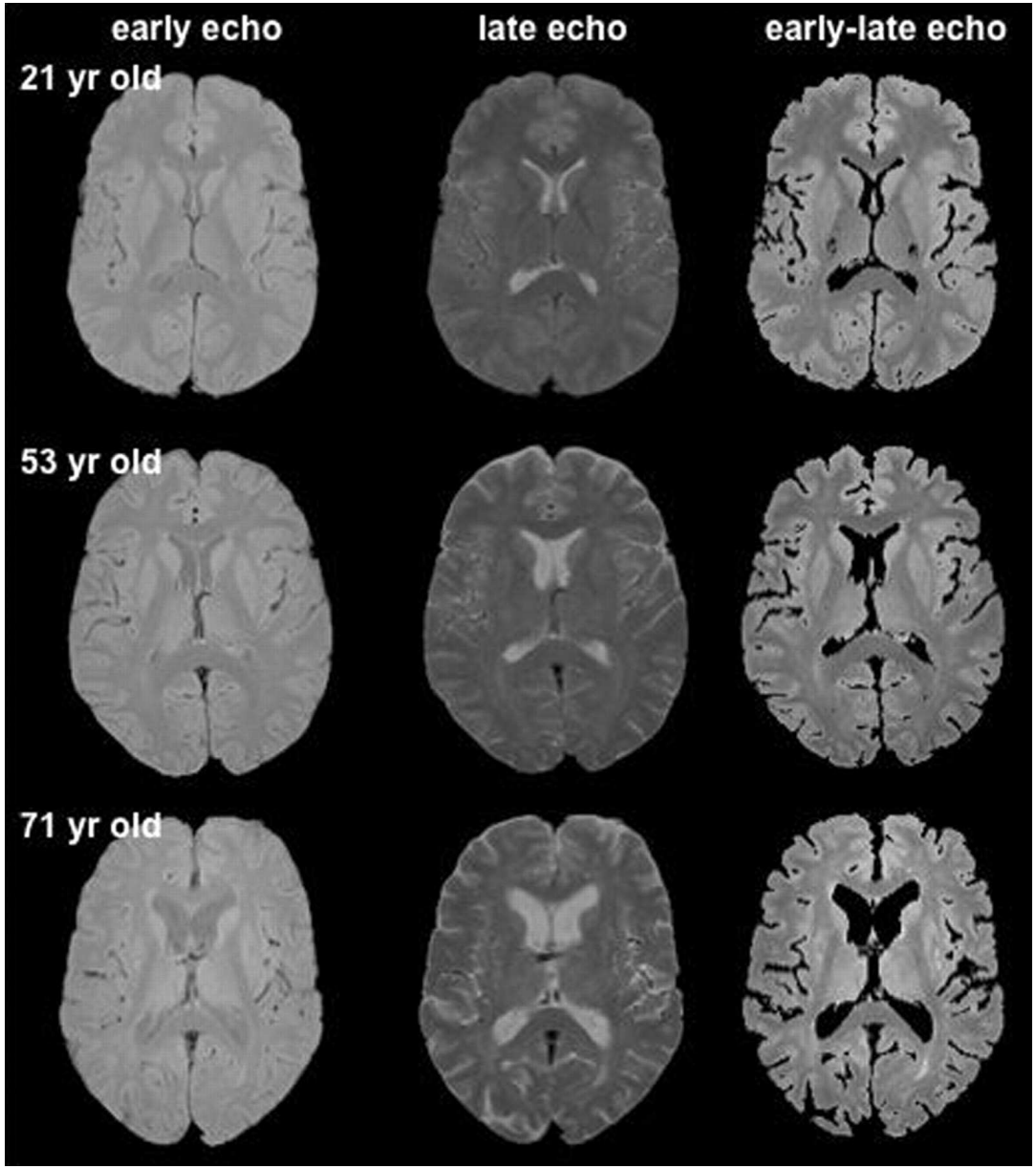








The aging brain: decrease of weight and volume

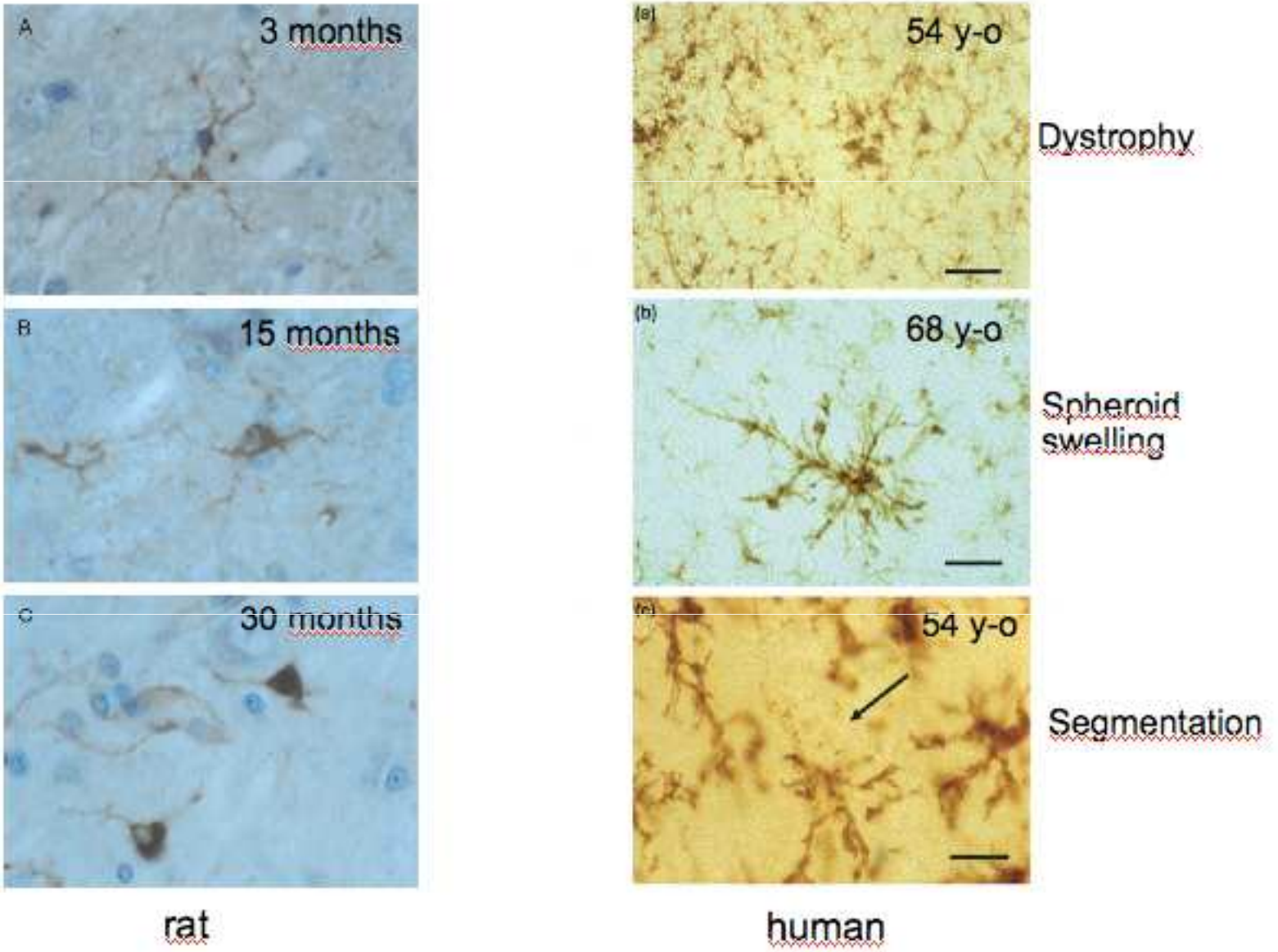


Sullivan EV, Br J Radiol 2007

The aging brain: structural changes

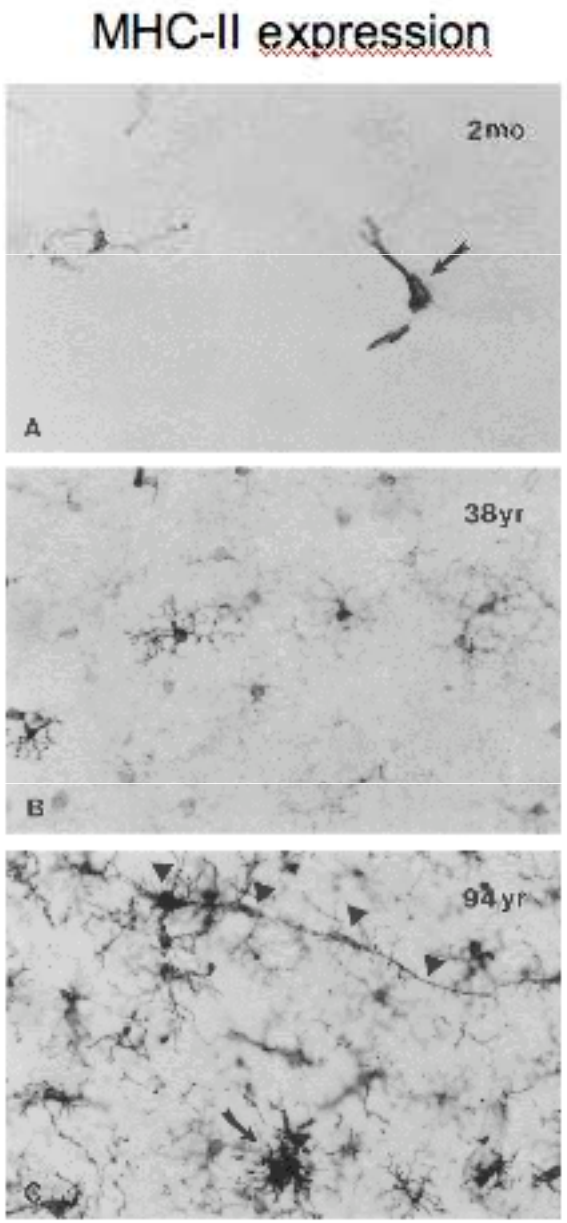
- Loss of neurons and demyelinated axons
- Increase of glial cells
  - Astrocytes
  - Microglial cells
- Deposition of proteic strutures (neurofibrillary tangles, senile plaques)

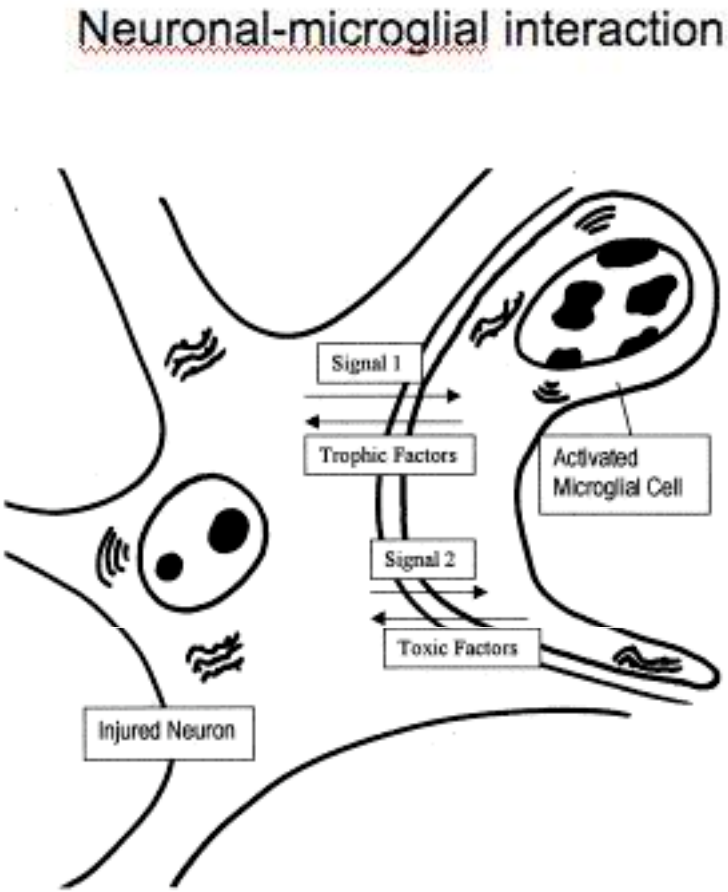
The aging brain:
morphological changes in microglial cells



Streit WJ, Trends Neurosci 2006

The aging brain:
phenotypic changes in microglial cells

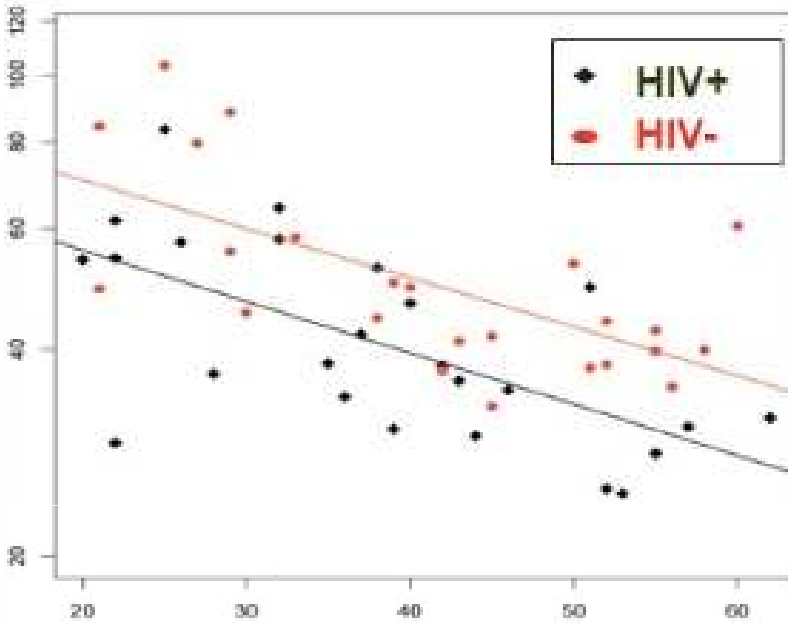




Streit WJ, Progr. Neurobiol 1999

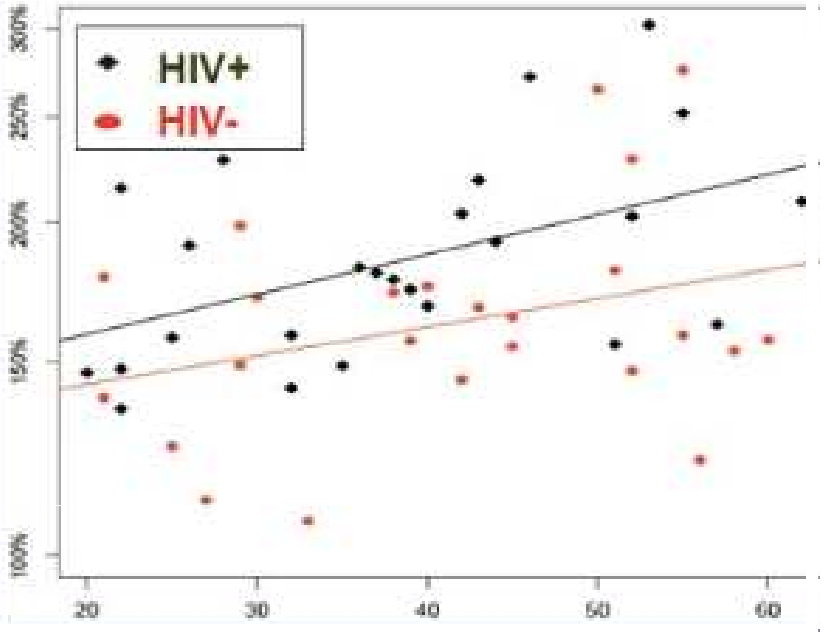
Additive effect of aging and HIV serostatus on cerebral blood flow (CBF)

- Baseline CBF



P<0.0001 (age)
P=0.0001 (HIV)

Functional CBF

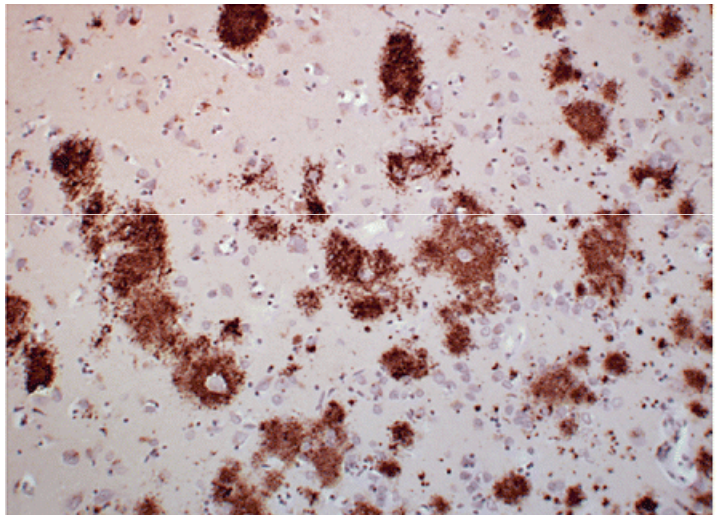


P=0.005 (age)
P=0.013 (HIV)

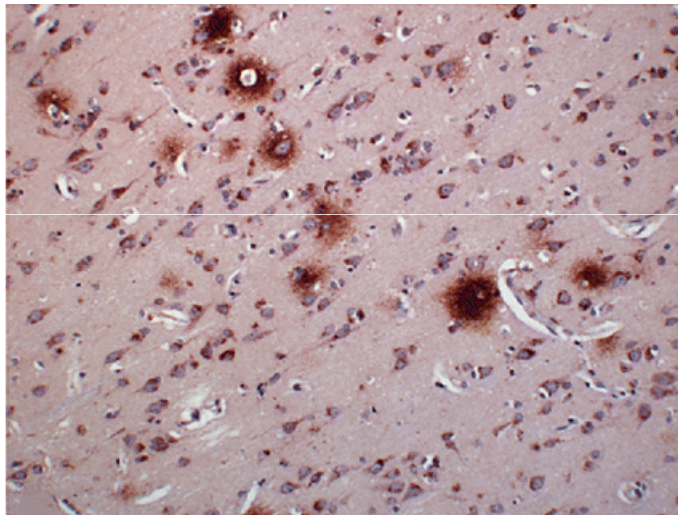
Ances B et al., CID 2009

β-amyloid deposition in AD and AIDS brain

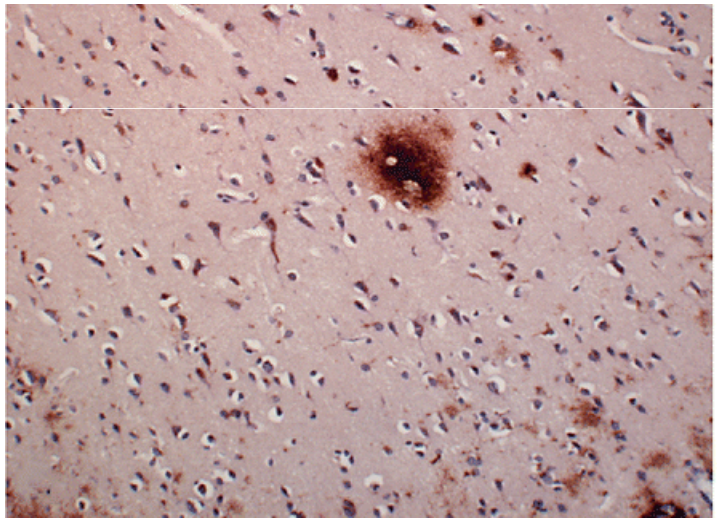
AD (extracellular plaques)



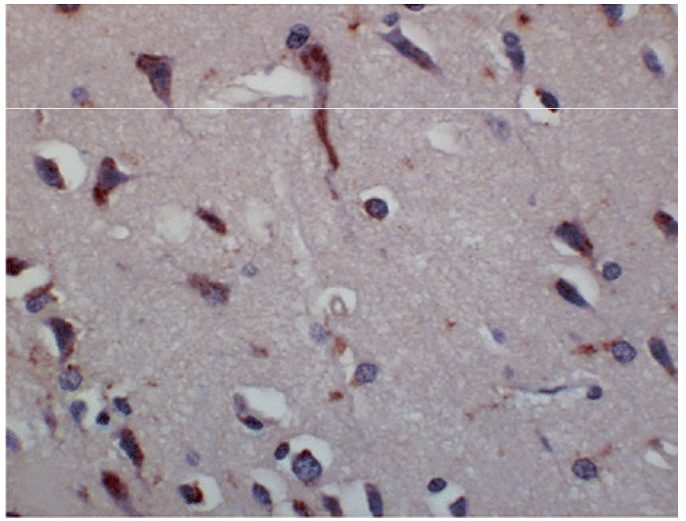
AIDS (extracellular plaques)



AIDS (extracellular and neuronal)

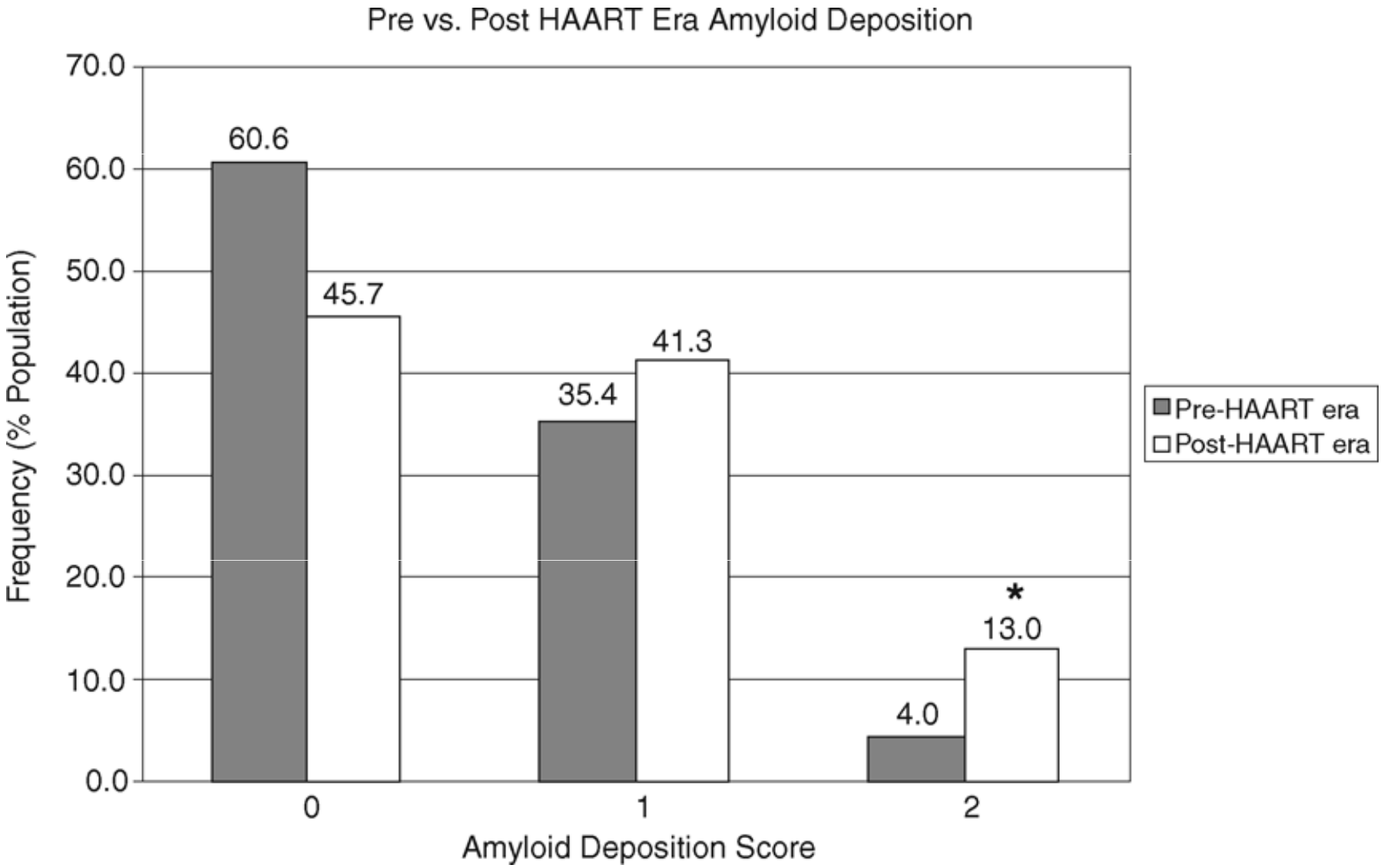


AIDS (neuronal)



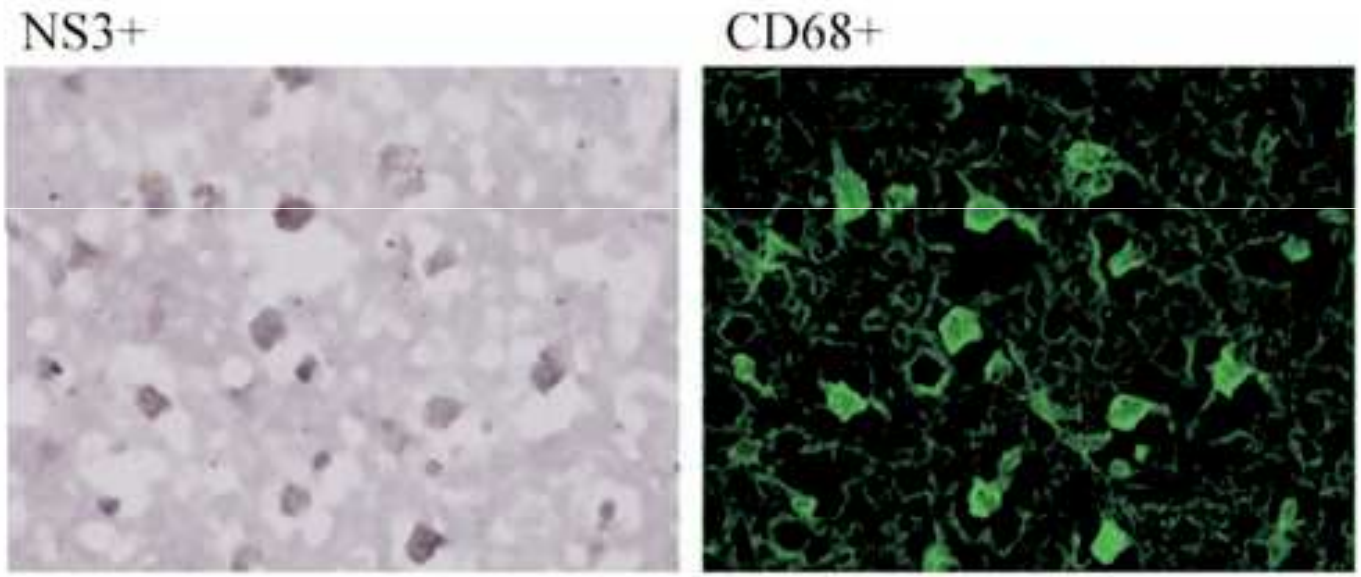
Green DA, AIDS 2005

β-amyloid deposition is increased in HAART-treated and older persons



Green DA, AIDS 2005

HCV infection, brain microglia and neurocognitive function



Wilkinson J et al., JV 2009

Neuropsychiatric symptoms reported in HCV and HIV-HCV co-infected patients, independently from decompensated liver functioning (*Clifford 2005*)

Magnetic Resonance Spectroscopy shows abnormal cerebral metabolism and cognitive impairment in HCV-positive patients *(Forton 2008)*

Conclusions

- Pathogenesis of NCI likely different end even more complex in treated than untreated infection

- Important role of **co-factors** in treated infection
  → which may contribute to HIV-related NCI

- Important role of **co-morbidities** in treated infection
  → which may contribute to NCI
  → but confound recognition of HIV-related NCI

Thanks to colleagues and collaborators

- Arabella Bestetti, Simona Bossolasco, Francesca Ferretti, Adriano Lazzarin; ID Dept. HSR, Milano
- Magnus Gisslen, Lars Hagberg; University of Goteborg, Sweden
- Serena Spudich, Dick Price; University of San Francisco, California
- Manuela Nebuloni; Pathology Dept., L. Sacco Universsity, Milano

FOURTH INTERNATIONAL MEETING on HIV Infection and the Central Nervous System

Treating the Brain in the HAART Era

Frascati (Rome), Italy

July, 15-16 2011