5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 13

Nervous system disorders due to retroviruses (Level3)

Neuro-cognitive disorders due to HIV

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Neuro-cognitive disorders

due to HIV

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I declare that I have nothing to disclose

What this talk is about

HIV-associated neurocognitive disorder (HAND)
(synonyma: HIV-encephalopathy, HIV-encephalitis, HIV-associated dementia)

By necessity, about depressive disorders

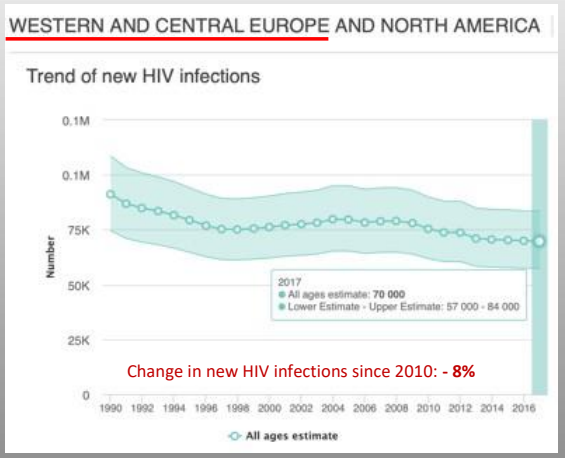
It is NOT about:

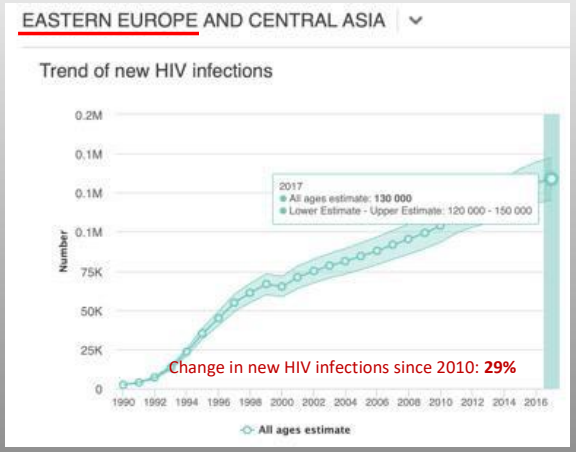
toxoplasmosis, PML, cryptococcosis, tuberculosis, CMV-encephalitis, primary CNS-lymphoma etc.

Content of the talk

- HIV infection of CNS
- way of Infection
- Infected cells in the CNS
- Histopathology
- Viral replication: its kinetics and where it takes place
- Association of viral load and viral kinetics with HIV dementia
- The clinical manifestation of HAND
- Pathogenesis of HAND
- Antiviral treatment of HAND
- The "new" era of highly active combination antiretroviral treatment
- HAND in the modern era
- Differential diagnosis to other forms of dementia

The AIDS and HIV-epidemic in Europe and the world





Source: UNAIDS.org (accessed June 2019)

HIV regularly infects the CNS („neurotropic virus“)

HIV detectable in the CSF within days or weeks after infection

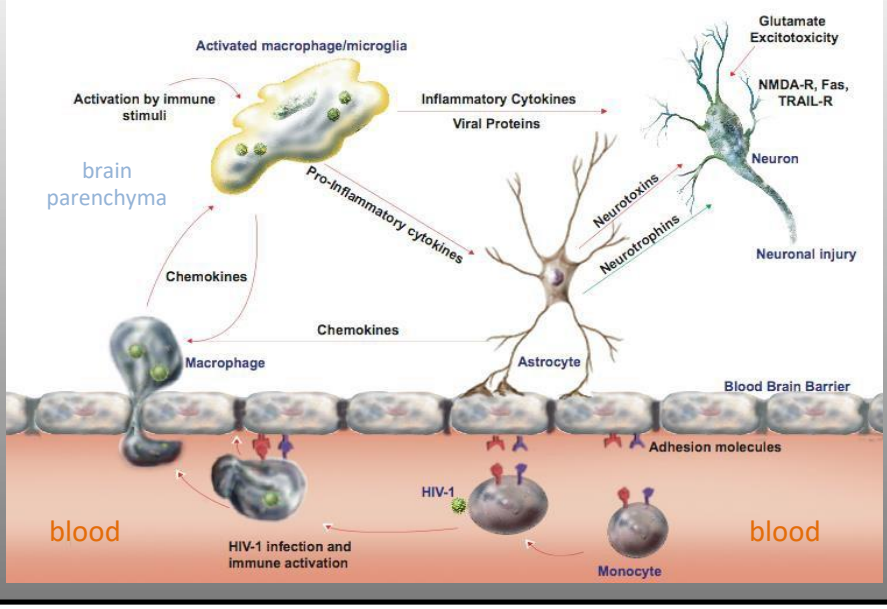
- Cultivation of HIV from CSF at seroconversion *(Ho 1985)*
- Histopathology of meningoencephalitis and detection of virus 15 days after iatrogenic infection *(Davis 1992)*

CSF findings suggestive of chronic infection present in some 100% of patients

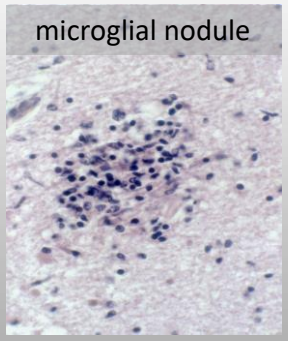
- mild mononuclear pleocytosis (lympho-, monocytes)
- autochthonous IgG production
- isolated oligoclonal bands in CSF

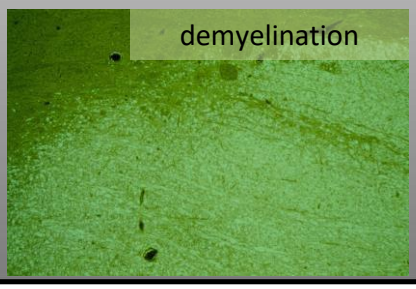
However, no correlation to clinical manifestations

HIV infects the brain via invading lymphocytes and monocytes/macrophages („trojan horse theory“)

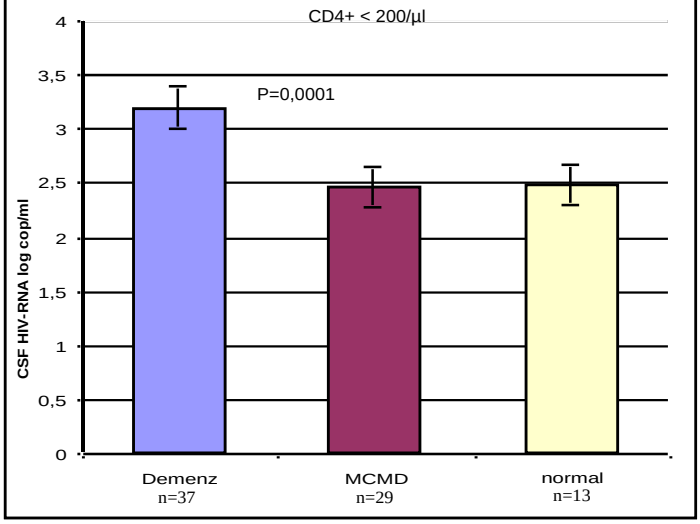


Histopathology of „classic“ full-blown HIV encephalitis





Virus Load and Dementia before the advent of cART: moderate but significant correlation



McArthur, Ann Neurol 1997;42:689

Brew, J Infect Dis 1997;175:963

Ellis, Ann Neurol 1997;42:679

Is the CNS an autochthonous compartment for viral replication?

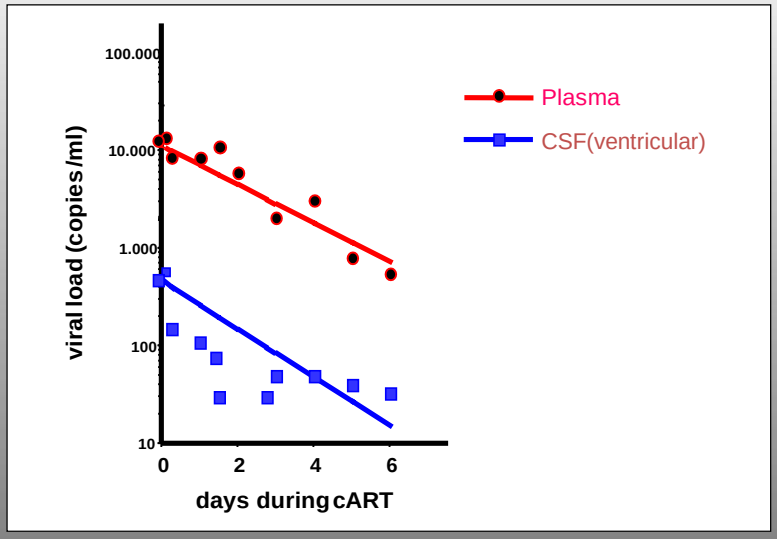
Pro

- no firm correlation between plasma and CSF viral load
- genetic segragation into different subpopulations
- elimination kinetics of the CSF virus during cART
- viral escape in the CSF (with suppressed plasma virus)
- ....

Contra

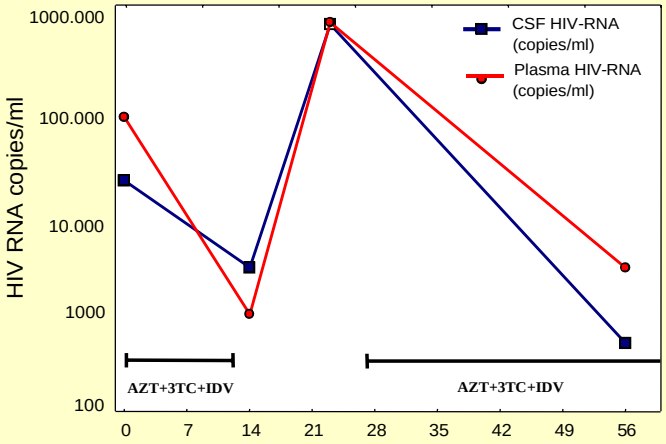
- some correlation of plasma/CSF viral load
- genetic sequence studies with similarities of CSF and Plasma virus
- elimination kinetics of the CSF virus during cART

Ventricular CSF and plasma in an individual with a ventricular drainage with introduction of cART



Eggers, C et al. Annals of Neurology 2000

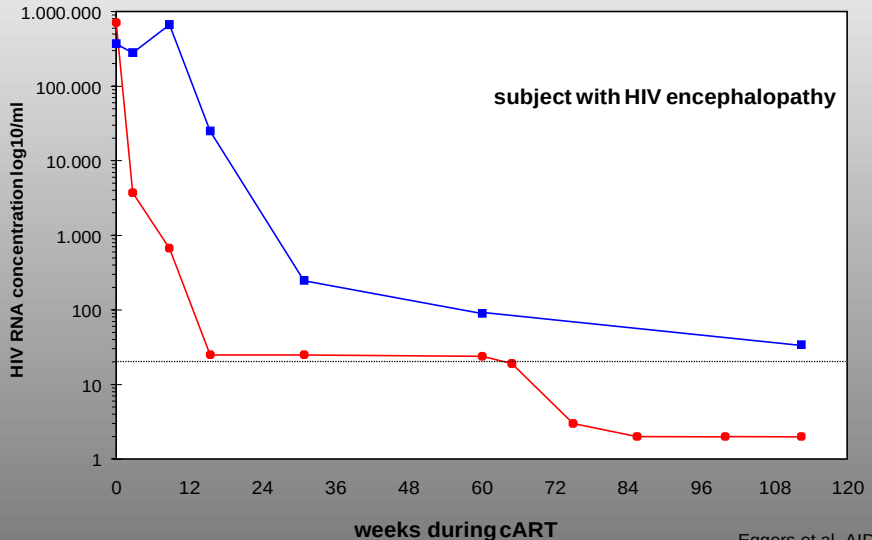
CSF- and plasma virus load on interruption and resumption of cART in an HIV-infected individual



Eggers et al, JAIDS 1999

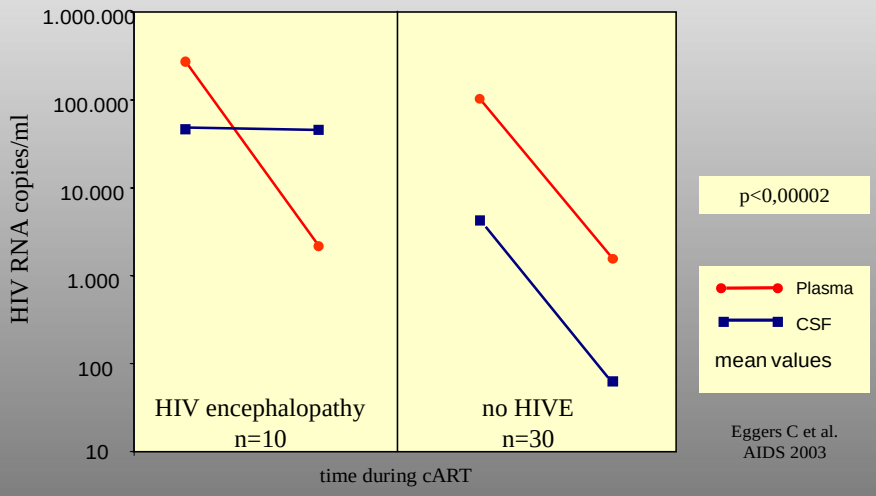
The CNS is an idependent compartment with (to some extent) autochthonous virus replication

Long term persistence of virus replication In the CNS



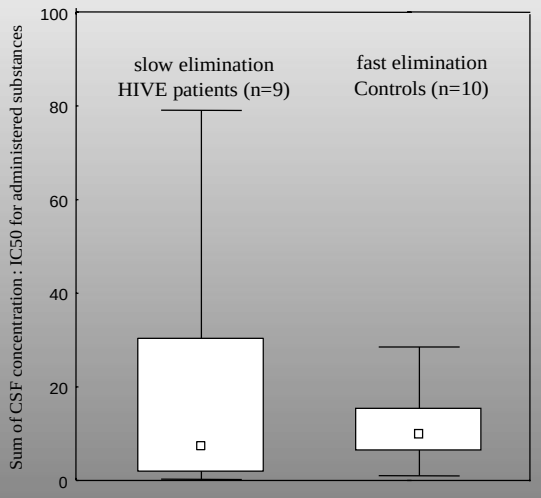
Eggers et al. AIDS 2003

Discordant evolution of virus load during cART in patients with HIV encephalopathy



Eggers C et al.
AIDS 2003

CSF levels of antiviral cART substances in patients with fast and slow CSF virus elimination under cART

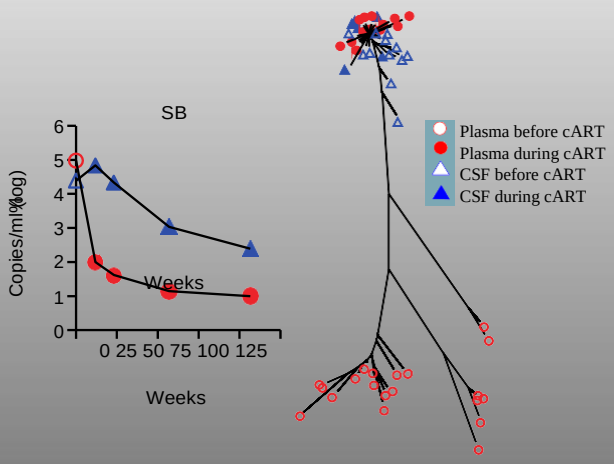


no viral resistances found in the CSF

Max
Min
75%
25%
Median

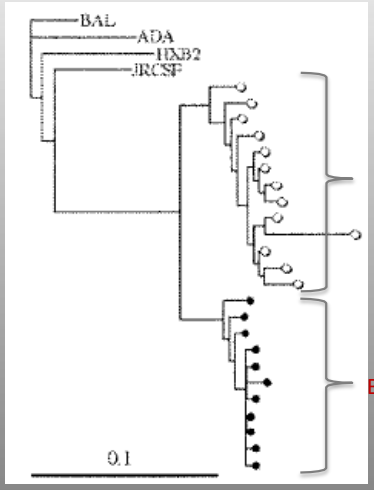
Eggers C et al. AIDS 2003

Plasma and CSF sequences before and during cART in a patient with HAND



Eggers et al. JNeuroVirol 2013

Plasma and CSF sequences in an untreated and cognitively impaired HIV-infected individual



Strain et al. JVirol 2005;79:1772

The clinical manifestations and diagnosis of HIV dementia

HIV dementia
history / *history by informant*

Behavioural/ Psychopathology

loss of social initiative, loss of libido,
emotional blunting, depressive appearance

Cognition

Disturbance and slowness of memory and concentration

Motor / autonomous

Instability of gait, urinary urgency,
erectile dysfunction

HIV dementia
Clinical findings on examination (1)

Psychopathology / Behaviour

no impairment of alertness (!), distractable
emotionally blunted
loss of drive and initiative
nor clear-cut signs of depression

Motor / Autonomous

gait disorder, disturbance of dexterity
Oculomotor disturbances (saccades)
muscle reflexes increased, potential Babinski‘s sign frontal disinhibition (palmo-mental-, glabella-, grasp reflexes)

HIV dementia
Clinical findings on examination (2)

Cognitive

“subcortical” dementia

vague responses (orientation, time sequences)

Psychomotor Speed
listing the months of the year, serial subtraction

Memory
encryption and reproduction of three words given to patient

Mental flexibility / Executive functioning
spelling backwards, Trail-making B

HAND = **H**IV-**a**ssociated **n**eurocognitive **d**isorder

Terminology from 2007 („Frascati criteria“)

HIV-associated asymptomatic neurocognitive impairment (ANI)	In neuropsychological cognitive testing, acquired impairment of ≥ 1.0 SD below the mean for age- and education-appropriate norms, involving ≥ 2 ability domains*. The cognitive impairment does not interfere with everyday functioning.
HIV-1-associated mild neurocognitive disorder (MND)	Results of cognitive testing as in ANI. At least some disturbance of daily functioning (e.g. reduced mental acuity, inefficiency at work, reduced social activities)
HIV-1-associated dementia (HAD)	Results of cognitive testing as in ANI, <u>but</u> with impairment ≥ 2 SD. Marked interference with daily functioning

* = cognitive domains include verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills

(Antinori et al. Neurology 2007;69:1789)

Diagnosis of HAND

A discernable cognitive dysfunction is a prerequisite

Subtle neurologic findings may co-exist but are not required for diagnosis
(e.g. clumsiness, impaired gait, oculomotor and pyramidal signs)

Similar to Mc Donald criteria for MS: *"... not better explained by other conditions."*

Search for psychiatric conditions such as major depression

Exclusion of other organic diseases by technical diagnostic steps:

- EEG
- MRI
- CSF including HIV viral load, search for other infectious pathogens
- Routine lab including thyroid status, Vit-B12 status, illicit drugs, ...

Depending on the age of the patient: Alzheimers, small vessel disease, Lewy-body dis. etc.

Pathogenesis of HIVE

HIV encephalopathy caused by HIV itself: it is not an opportunistic infection

HIV replicates in makrophages/ mikroglia and lymphocytes

much virus = much histopathology = much encephalopathy

much virus in the CSF = much virus in the brain parenchyma (quantitat. PCR)

Pathogenesis of HIVE (2)

Not every HIV infected subject will develop HAND,
and if so, this takes years – why?

virus

- quantity (virus load in CNS (CSF/parenchyma))
- type of virus (neurotropic/-virulent quasispecies, V3 sequence)
- place of replication (brain oder extracerebral)

Viral products

- gp120, gp41, tat, nef, rev, vpr, p24

Pathogenesis of HIVE (3)

Molecular pathogenesis

- molecules in the cascade leading to cellular dysfunction

  Cyto-/Chemokines (TNF-α, MCP-1 etc.),
  Complement,
  Matrix-metalloproteinases

- toxic products

  quinolinic acid, glutamate, arachidonic acid etc.

Host

- genetic factors

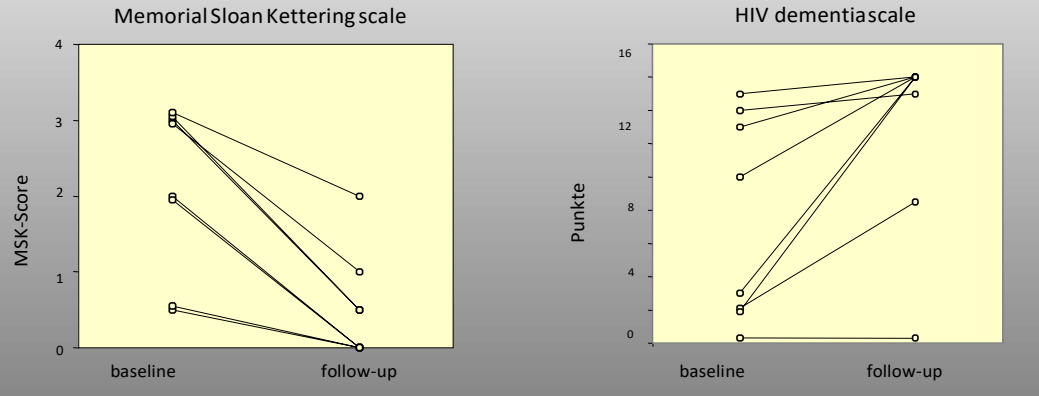
  polymorphisms for TNF-α, MCP1, CCR5, ApoE

- other factors

  age of pat., exposure to illicit drugs

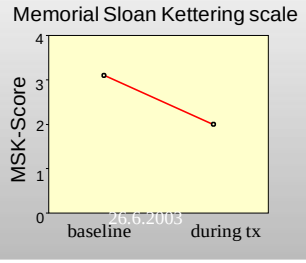
Whatever the pathogenesis - HIV dementia is treatable!

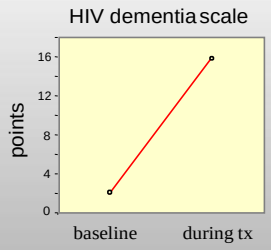
Evolution of clinical severity of HIV dementia during cART



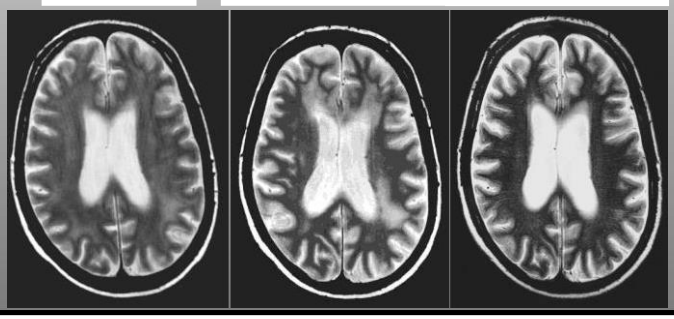
Eggers, unpublished

Severe dementia in an individual with leukencephalopathy: disease course during 21 months of cART





prior to cART | after 6 months of cART | after 21 months of cART



Licensed antiretroviral substances

Nucleoside-/Nucleotide analogues

AZT (Retrovir®)
ddC (Hivid®)
ddI (Videx®)
d4t (Zerit®)
3TC (Epivir®)
ABC (Ziagen®)
Tenofovir (Viread®)
Emtricitabine (Emtriva®)

Non-nucleoside reverse transcriptase inhibitors

Nevirapin (Viramune®)
Efavirenz (Sustivea®)
Rilpivirin (Edurant®)
Etravirin (Intelence®)

Fusion inhibitors
T20 (Fuzeon®)

Cytochrome P450 inhibitors
Cobicistat (Tybost®)
Ritonavir (Norvir®)

Protease inhibitors

Saquinavir (Invirase®)
Ritonavir (Norvir®)
Indinavir (Crixivan®)
Nelfinavir (Virazept®)
Amprenavir (Agenerase®)
Fosamprenavir (Telzir®)
Lopinavir / Ritonavir (Kaletra®)
Atazanavir (Reyataz®)
Tipranavir (Aptivus®)
Darunavir (Prezista®)
Tipranavir (Aptivus®)

Integrase inhibitors
Raltegravir (Isentress®)
Elvitegravir (in Stribild®)
Dolutegravir (Tivicay®)
Bictegravir (Bictarvy®)

CCR5 antagonists/entry inhibitors
Maraviroc (Celsentri®)

many different combinations

„Viral escape“

Discordance Between Cerebral Spinal Fluid and Plasma HIV Replication in Patients with Neurological Symptoms Who Are Receiving Suppressive Antiretroviral Therapy

Ana Canestri,[1,2] François-Xavier Lescure,[3] Stephane Jaureguiberry,[1] Antoine Moulignier,[3] Corinne Amiel,[4] Anne Geneviève Marcelin,[2,5,7] Gilles Peytavin,[5] Roland Tubiana,[1,7] Gilles Pialoux,[5,6] and Christine Katlama[1,5,7]

[1]Service de Maladies Infectieuses et Tropicales and [2]Laboratoire de Virologie, Hôpital Pitié-Salpêtrière, [3]Service de Maladies Infectieuses et Tropicales and [4]Laboratoire de Virologie, Hôpital Tenon, and [5]Service de Toxicologie, Hôpital Bichat-Claude Bernard, Assistance Publique–Hôpitaux de Paris, [6]Université Pierre et Marie Curie Paris, and [7]Institut National de la Santé et de la Recherche Médicale, U943, Paris, France

Clinical Infectious Diseases 2010; 50:773–778

- 11 pat. with stable cART, 8 of these with continuously suppressed plasma viraemia (<50 cop/ml), the rest had *„blips“*
- in all of these, the CSF contained virus (median 880 cop/ml)
- all patients were neurologically symptomatic (various focal symptoms)
- resistance mutations in the CSF were frequent (plasma HIV PCR below detectable)
- optimization of cAART according to resistance testing and the CPE score
  - ▸ Clinical improvement and suppression of CSF viral load in 8 of 9 pat.

„Viral escape“

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

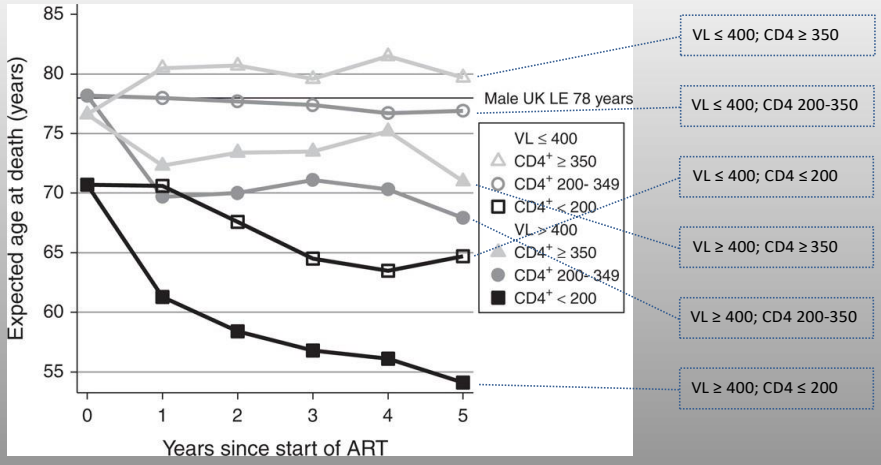
Michael J. Peluso[a], Francesca Ferretti[b], Julia Peterson[c], Evelyn Lee[c], Dietmar Fuchs[d], Antonio Boschini[e], Magnus Gisslén[f], Nancy Angoff[a], Richard W. Price[c], Paola Cinque[b] and Serena Spudich[a]

AIDS 2012, **26**:1765–1774

- 10 pats. with newly emerged neurological symptoms (sensory, motor, cognitive)
- under stable cART:
  10 with plasma viral load < 500 cop/ml for (median) 20 months
  5 with plasma viral load < 50 cop/ml for (median) 28 months
- all had detectable CSF virus (median 3900 cop/ml)
- median CD4-cell count 482/µl
- in 6 of 7 examined cases resistance mutations were found in the CSF (plasma HIV PCR below detectable)
- optimization of cART according to resistance testing and the CPE score
  - ▸ Clinical improvement and suppression of CSF viral load all

A new era?

Life expectancy with cART relative to virus load and CD4 cell count



May AIDS 2014; 28: 1193

∑: it is all about early start and continous treatment with antiviral drugs

Eradication of HIV on the horizon

2009: the „Berlin Patient“

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

2009; 360: 692

Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

Gero Hutter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Mugig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D , Ph.D.,J6rg Hofmann, Ph.D., Claudia Kucherer, M.D., Olga Blau, M.D., lgorW. Blau, M.D., WolfK. Hofmann, M.D., and Eckhard Thiel, M.D.

2019: the „London Patient“

nature
International journal of science

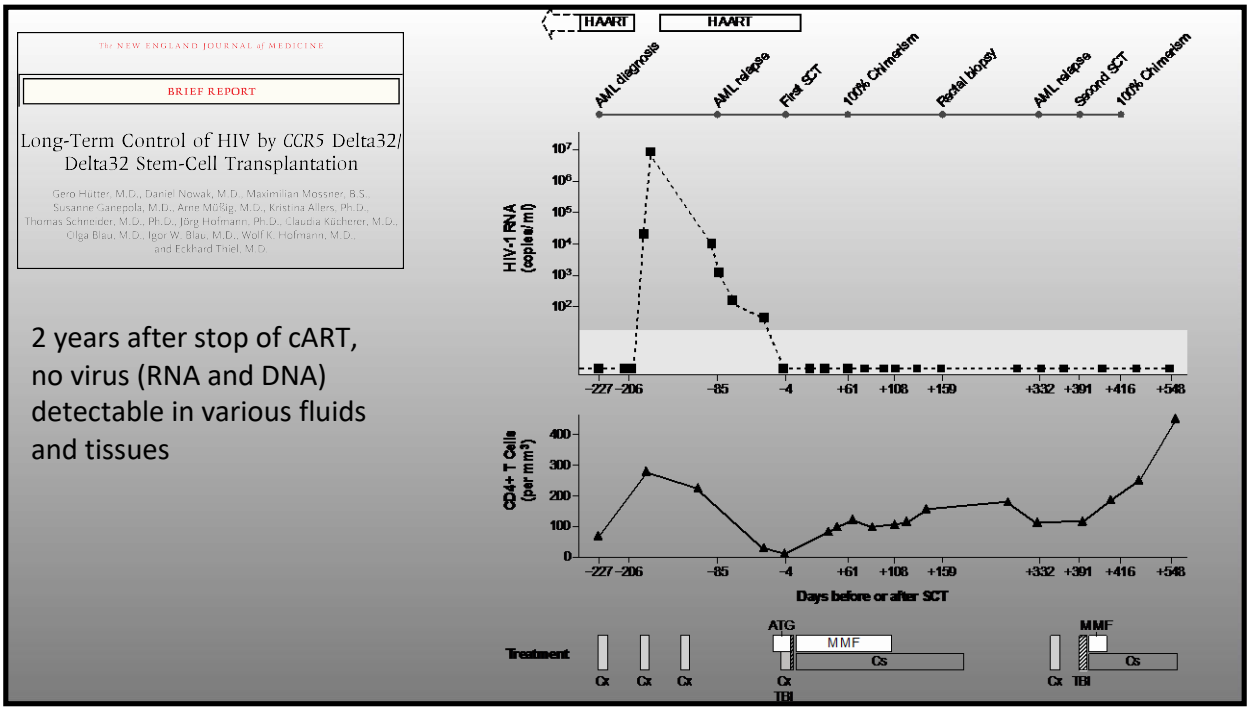
Letter | Published: 05 March 2019

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta, Sultan Abdul-Jawad, Laura E. McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M. J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew J. Innes, Luke Muir, Laura Waters, John Frater, Andrew M. L. Lever, Simon G. Edwards, Ian H. Gabriel & Eduardo Olavarria

Nature **568**, 244–248 (2019) | Download Citation

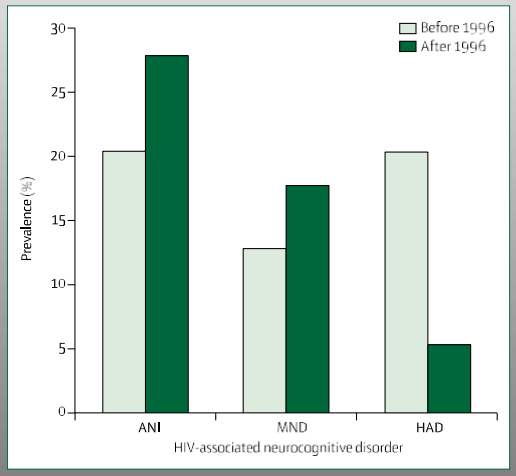
Both patients suffered from otherwise treatment-resistent hematological malignancies.
Both underwent myeloablative treatment (the „London-Pat“ without radiation) and consecutive transplantation of heterologous stem cells lacking a functional CCR5 receptor (due to homozygous deletion in the CCR5 gene)



HAND still exists

asymptomatic neurocognitive impairment (ANI) in the cART era: even more frequent

HAND before and after introduction of cART



Nightingale LancetNeurol 2014;13:1139

HAND still existent: 2019 in Alicante/Spain

Study with 84 pat. with long-term suppressed viral load:

Only „<u>healthy</u>“ pat. (exclusion of the following conditions: hypertension, cardiovascular disease, diabetes, chron. hepatitis, Depression, substance use, traumatic brain injury)

Comprehensive cgnitive testing
(7 domains according to Frascati criteria, corrected for age and education)

results:

neurocognitive impairment (NCI): **29,8**%

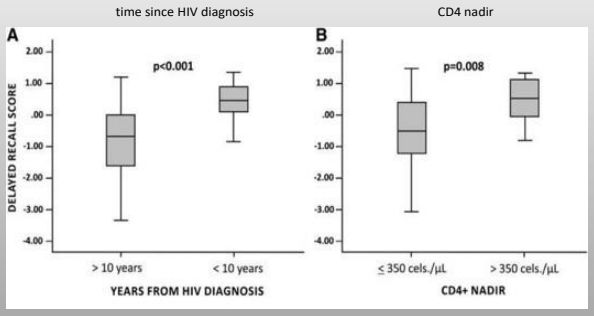
asympt. cogn. impairment (ANI): 19.0%

mild neurocogn. disorder (MND): 8.3%

HIV assoc. demenria (HAD) 2.4%

Risk factors for NCI:
longer time since HIV diagnosis
lower CD4 nadir
increased IL6 in plasma

memory function relative to



Portilla, AIDS Res Hum Retrov 2019

Risik factors from the literature

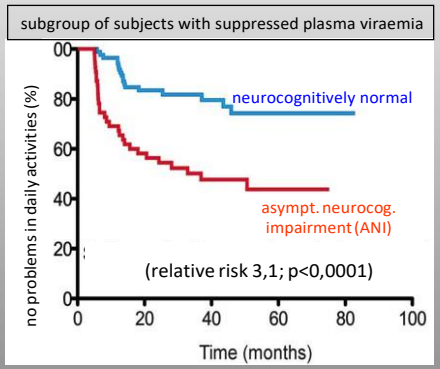
age	CD4 nadir
duration of HIV infection	cardiovascular risk factors
illicit drugs use	diabetes
depression	CPE score

Asymptomatic neurocognitive impairment (ANI) predicts transition in clinically relevant cognitive dysfunction

347 pat. of the CHARTER cohort

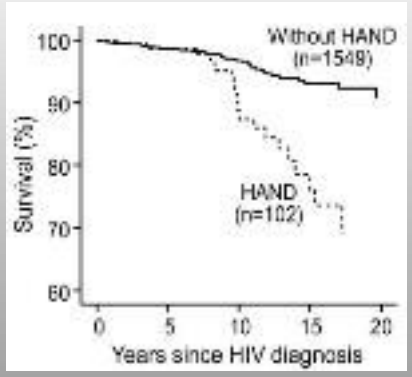
- comprehensive neurocognitive testing
- categorized into normal versus ANI at baseline
- observation over almost 4 years
- analyses adjusted for multiple confounding factors

- **result**: pat. with ANI converted earlier into clinically relevant cognitive dysfunction than normal subjects
- Predictors: depression, current CD4 count
- **not** predictive:
  - cART regime
  - viral load
  - CNS penetration effectivenes score (CPE) of the antiviral substances



Grant Neurology 2014

Life expectancy of HIV patients with and without HAND

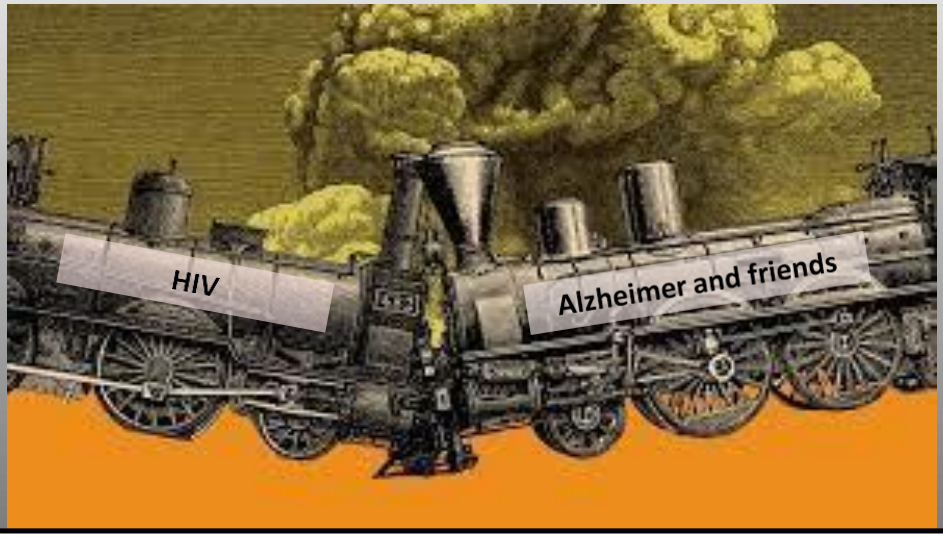


neurocognitive dysfunction → shorter survival

Power, Neurology 2010; Sevigny, ArchNeurol 2007

My patients is now 50 years of age.

What will be in 10 years time?



Increasing age of HIV infected people in Germany

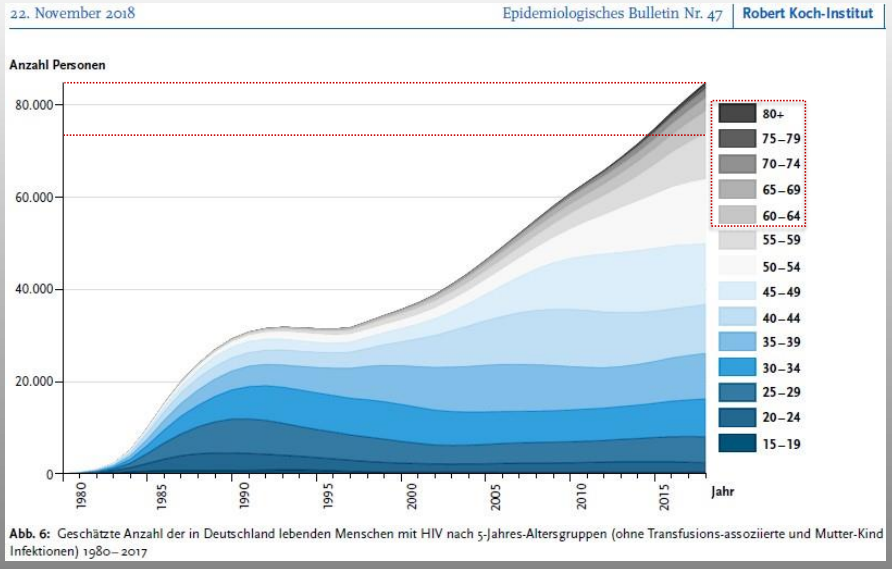
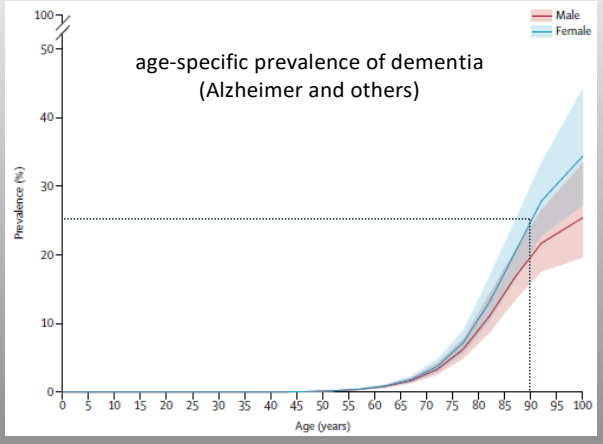


Abb. 6: Geschätzte Anzahl der in Deutschland lebenden Menschen mit HIV nach 5-Jahres-Altersgruppen (ohne Transfusions-assoziierte und Mutter-Kind Infektionen) 1980–2017

The prevalence of dementia increases with advancing age (Global Burden of Disease Study 2016)



The Global Burden of Disease Study 2016.
LancetNeurol 2019;18:88

various phenotypes of dementia

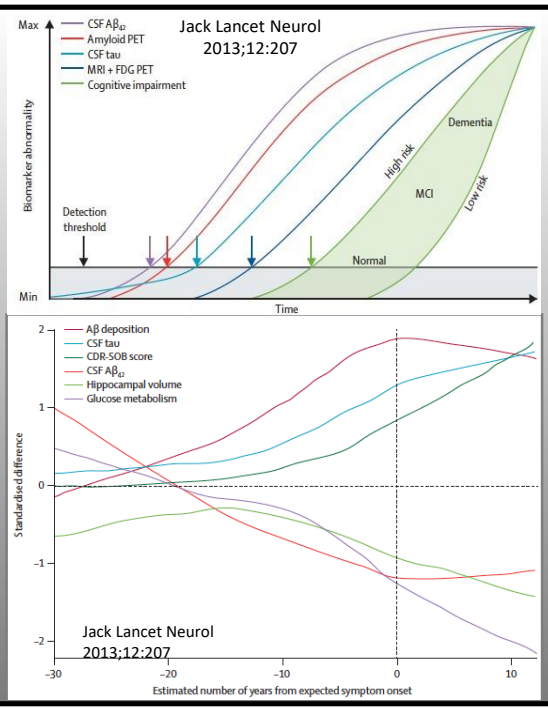
common features: progressive loss of cognitive functions und impairment in everyday functioning

disease / aetiology	important clinical features
M. Alzheimer	short term memory
vascular dementia (small vessel disease)	slowness, executive functions, decreased cognitive flexibility, non-cognitive signs (motor function)
frontotemporal dementia (M. Pick)	empathy, social behaviour, oppressiv-compulsive behaviour, disturbance of speech
dementia with Lewy bodies	slowness, memory, visual hallucinations, REM- sleep disorder, visuo-constructive dysfunction; later parkinsonian motor signs
normal pressure Hydrocephalus	Trias: dementia (slowing), gait disorder and micturition dysfunction
dementia with Parkinsons disease	attention disorder, executive functions, visuo-spatial functions, apathy, delusions, daytime sleepiness
Creutzfeldt-Jakob (CJD)	dementia, Myoklonus, Rigor, cerebellar signs, fasciculation of muscle
primary progressive aphasia (histol. tau, Aß42, TDP43, ...)	Speech: semantic and phonematic paraphasia, lack of speech comprehension, disturbance of grammar, logopenia, alexia und agraphia; later disorder of object recognition, apraxia, acalculia
others: Vit-B12 deficiency, syphilis, vasculitis, Hashimoto, autoimmune encephalitides, PSP, LATE, dementia mit argyrophilic bodies, Huntington, leukencephalopathies such as CADASIL etc.	

HAND and the most important differential diagnoses

Typical and early manifesting symptoms and signs

	HAND	vascular dementia small vessel disease/ Leukencephalopathy	Alzheimer
memory	+	+	+++
psychomotor slowing	+	++	-
executive functions	++	+++	+/-
affective / emotional	blunted	blunted, reduced flexibility	unaffectedt
behaviour	apathy	grumpy, possibly aggressiv	-
fine motor movements, gait and balance	+	++	-
oculomotor signs	++	++	+/-

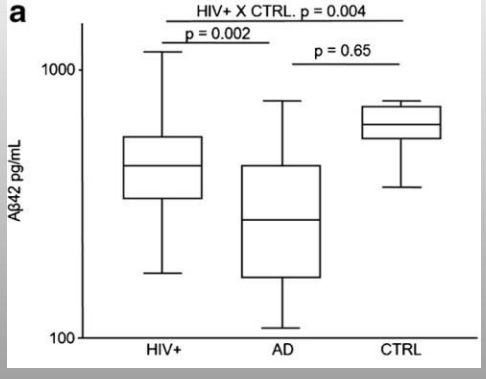


M. Alzheimer

time course of:

- amyloid
- tau
- structural damage
- early memory deficits
- full-blown dementia

Amyloid (Aß42) and *tau* metabolism in HIV-infected, HIV-**un**infected and Alzheimer patients



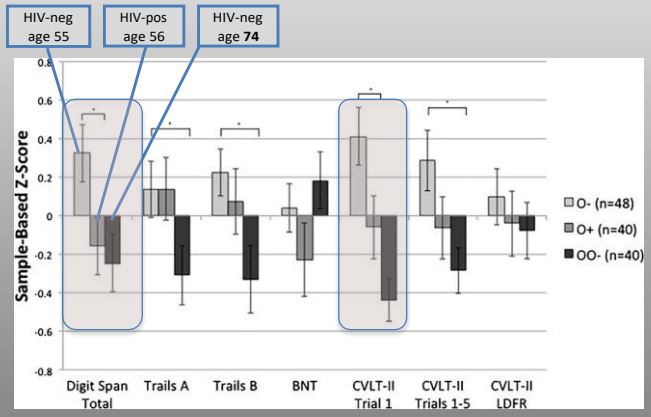
de Almeida „Amyloid Aß u tau i CSF i Alzheimer u HIV“
JNeuroVirol2018-24-28

... amyloid metabolism was influenced by HIV infection.

Cross sectional study:
HIV neg, 55 years, n=48
HIV **pos**, 56 years, n=40
HIV neg, **74** years, n=40
suppressed plasma virus in 85%

Result
the 56 year old HIV-positives were similarly impaired as the 74 year olds HIV-negatives;
this applied to the cognitive domains
memory span for digits (digit span) and early recall of memorized words
(both short term memory)

→ HIV accerates cognitive aging



Sheppard „Accelerated Cognitive Aging in HIV" JNeuroVirol 2017;23:492

Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study

Kaitl Goodkin, Eric N Miller, Christopher Cox, Sandra Reynolds, James T Becker, Eileen Martin, Ola A Selnes, David G Ostrow, Ned C Sacktor, for the Multicenter AIDS Cohort Study

LancetHIV 2017
Published Online
July 14, 2017
http://dx.doi.org/10.1016/S2352-3018(17)30098-X
See Online/Comment

Summary

Background The demographics of the HIV epidemic in the USA have shifted towards older age. We aimed to establish the relationship between the processes of ageing and HIV infection in neurocognitive impairment.

Methods With longitudinal data from the Multicenter AIDS Cohort Study, a long-term prospective cohort study of the natural and treated history of HIV infection among men who have sex with men in the USA, we examined the effect of ageing, HIV infection (by disease stage), and their interaction on five neurocognitive domains: information

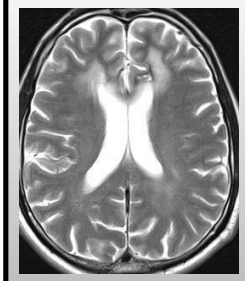
„A greater than expected effect of ageing on episodic memory and motor function with advanced HIV infection suggests ..... progression of neurocognitive impairment caused by ageing ...

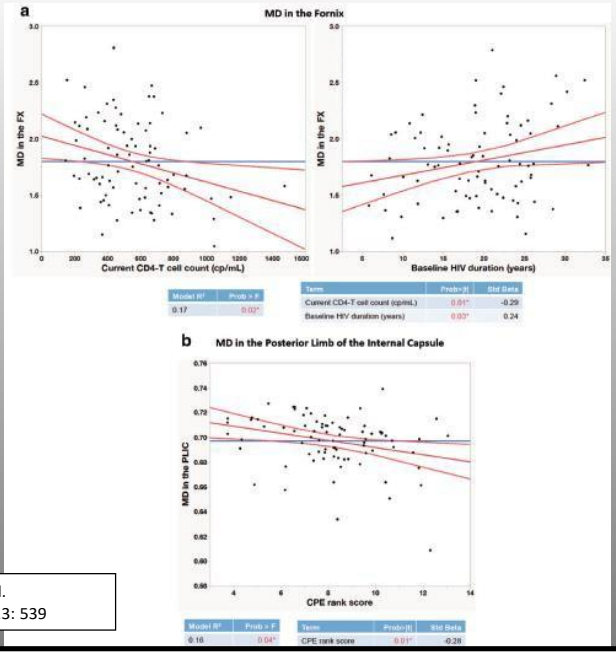
late-stage HIV disease progression on information processing speed (p=0·002), executive function (p<0·0001), motor function (p<0·0001), and working memory (p=0·001). Deleterious interaction effects were also noted in the domains of episodic memory (p=0·03) and motor function (p=0·02).

Interpretation A greater than expected effect of ageing on episodic memory and motor function with advanced stages of HIV infection suggests that these two domains are most susceptible to the progression of neurocognitive impairment caused by ageing in individuals with HIV. This deficit pattern suggests differential damage to the hippocampus and basal ganglia (specifically nigrostriatal pathways). Older individuals with HIV infection should be targeted for regular screening for HIV-associate neurocognitive disorder, particularly with tests referable to the episodic memory and motor domains.

Johns Hopkins School of Public Health, Baltimore, MD, USA (Prof C Cox PhD, S Reynolds MA); University of Pittsburgh, Pittsburgh, PA, USA (Prof J T Becker PhD); Rush University, Chicago, IL, USA (Prof E Martin PhD); Johns Hopkins School of Medicine, Baltimore, MD, USA (Prof O A Selnes PhD, Prof N C Sacktor M D); and

White matter lesions on MRT in 40 patients with suppressed plasma virus load





White matter damage measured by fractional anisotropy and mean diffusivity.

Results:

less white matter damage with:
- higher current CD4 count
- more recovery of CD4 count
- higher CPE score of cART

more white matter damage with:
- longer duration of HIV infection
- presence of neuro-cognitive impairment

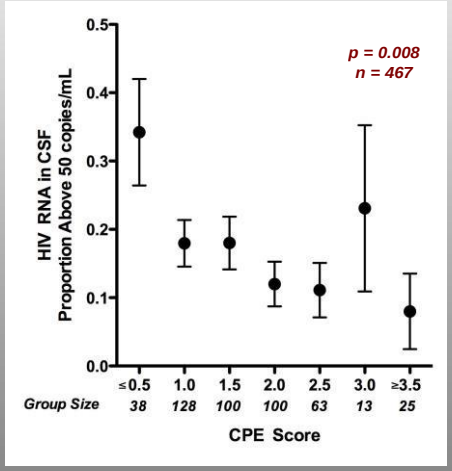
Cysique L, et al.
J NeuroVirol 2017; 23: 539

CNS Penetration-Effectiveness Score, 2010

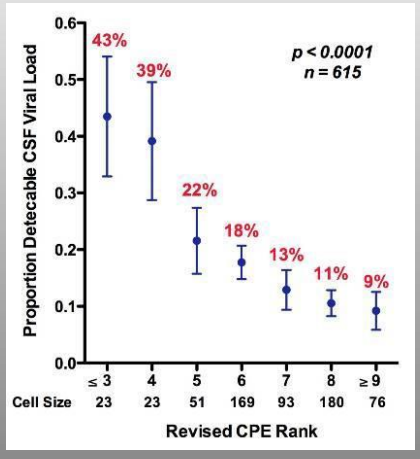
	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir	Nelfinavir
		Fosamprenavir-r	Atazanavir-r	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir-r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

Letendre et al, 17th CROI 2010, Abstract 172

penetration of antiviral compounds into the CNS
better penetration => lower CSF-Viruslast



Letendre S, et al. Arch Neurol 2008



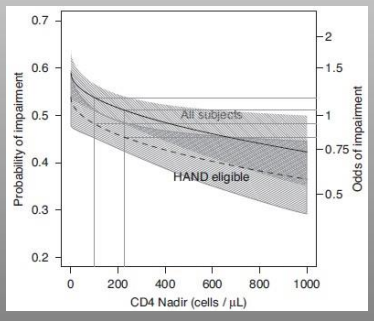
Letendre et al. 17th CROI 2010, Abstract 172

CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy

Ronald J. Ellis[a], Jayraan Badiee[a], Florin Vaida[a], Scott Letendre[a], Robert K. Heaton[a], David Clifford[b], Ann C. Collier[c], Benjamin Gelman[d], Justin McArthur[e], Susan Morgello[f], J. Allen McCutchan[a], Igor Grant[a], for the CHARTER Group

AIDS 2011, **25**:1747–1751

- 1525 pat. in the CHARTER-study (observational study)
- comprehensive cognitive testing
- thorough differential diagnostic procedures
- statistical adjustement for clinical and demographic factors (age, education, current CD4-count, plasma-VL, duration of HIV-Inf, HCV-coinfection)
- median CD4-count 172/µl
- **in pats. with plasma-VL <50/ml: significant association with CD4 nadir**



Neurocognitive impairment in patients with suppressed plasma virus
-
potential explanations

- Residual cerebral lesions from before start of cART
- continuous vira replication in the CNS despite viral suppression in plasma
  (Letendre CROI 2009 Abstract 484b)
- continuous immune activation in the CNS independent of viral replication
  (Eden JID 2007; Lackner JNI 2010)
- non-infectious neurologic diseases with cognitive dysfunction
  (Alzheimer, vascular dementia, major depression etc.)
- Toxicity of cART (Underwood AIDS 2015)

Chronic immune activation:
examplified by auto-antibodies against cerebral antigensv in the CSF
(myelin oligodendrocyte glycoprotein = MOG)

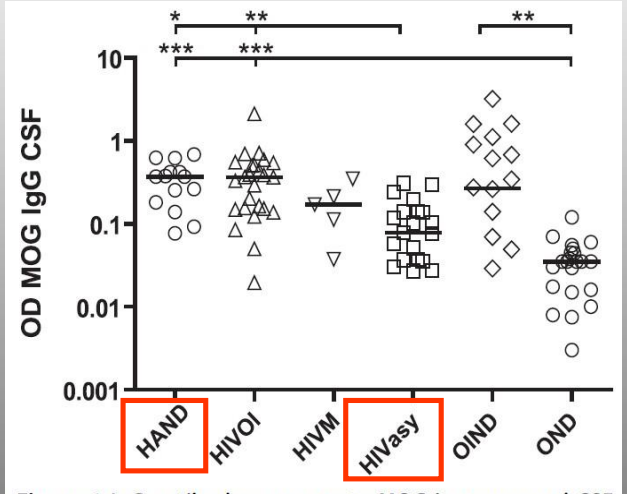


Figure 1 IgG antibody response to MOG in serum and CSF.

Lackner, Kuenz, Reindl, Schmutzhard, Morandell, Eggers.
Journal of Neuroinflammation 2010;7:79

To be kept in mind:

- the diagnosis of HAND requires the integration of many single findings
- HAND exists despite cART
- it all depends on whether the virus load is suppressed and the CD4 cells have recovered
- „viral escape“ in the CNS exists (although rare)
- the older the patient the more „competition“ with other forms of dementia
- Chronic immune activation and accelerated cognitive aging
- risk factors for HAND, vascular dementia and Alzheimers overlap
  ➔ management of risk factors
- Major depression interacts with HAND and is an important differential diagnosis

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Thank you for your patience