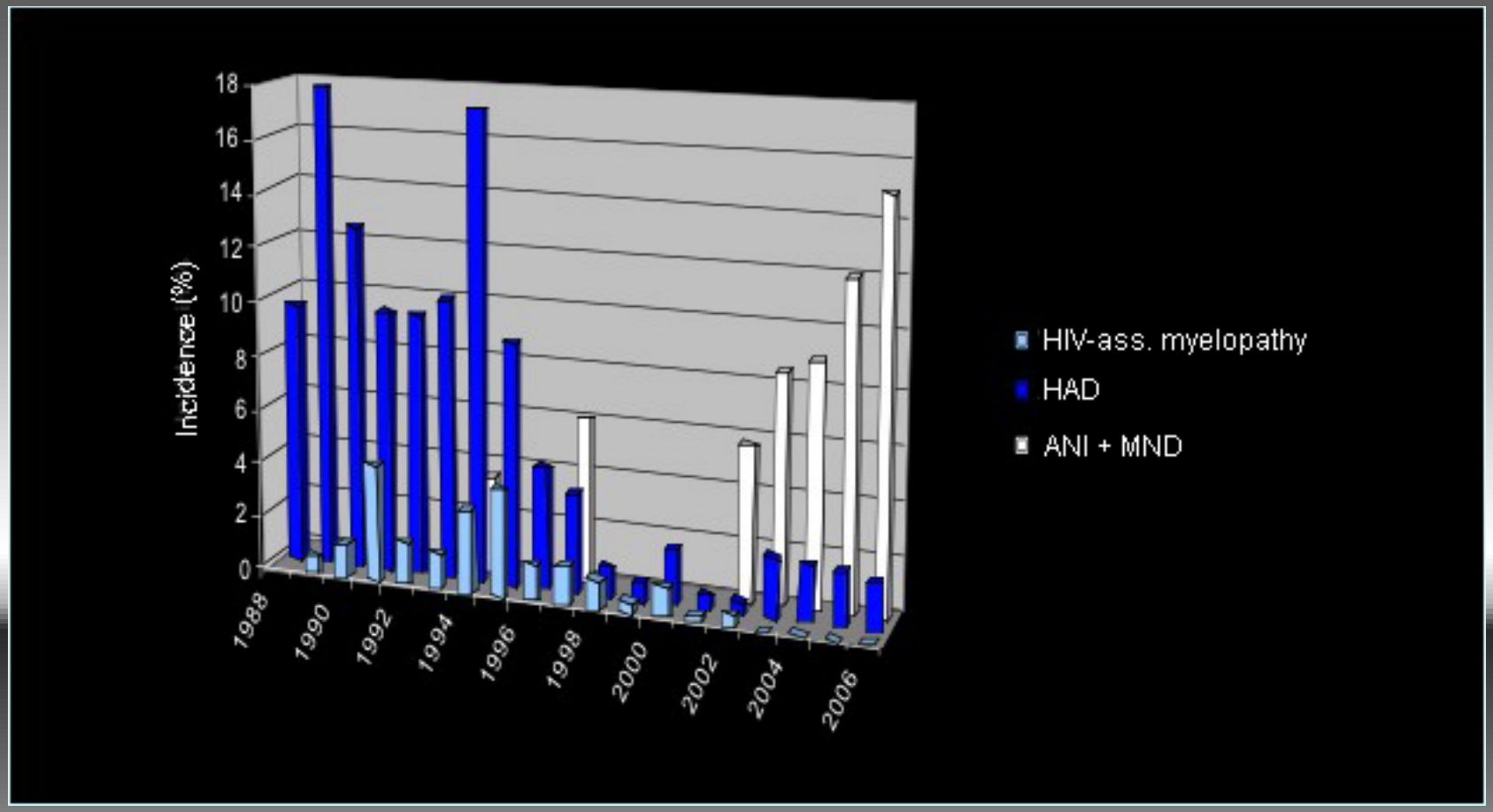
The Factors involved in Neuropsychiatric and neuropsychological Disorders in HIV-positive Patients

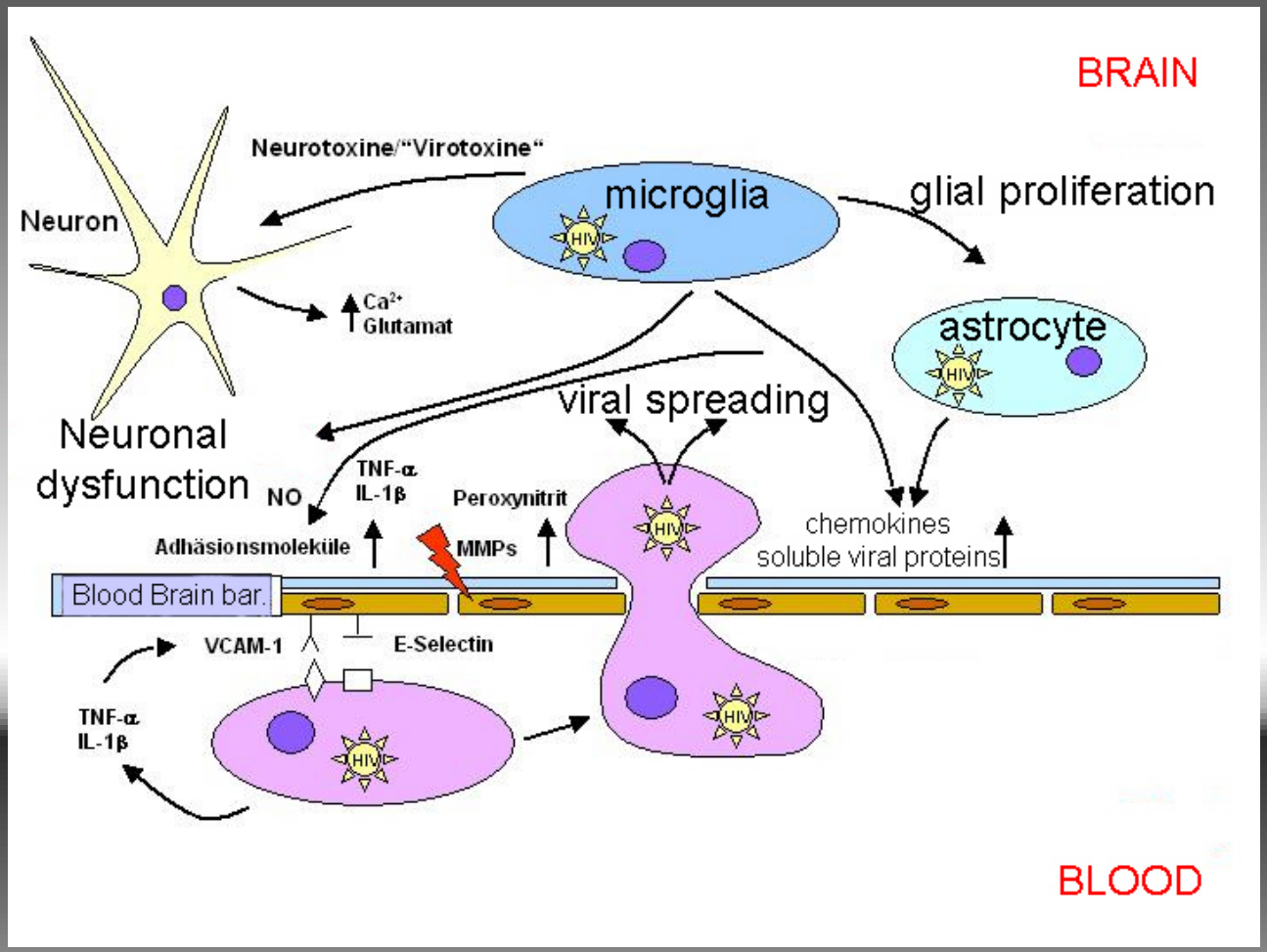
Gabriele Arendt

Department of Neurology, University Hospital of Duesseldorf (UKD)

Epidemiology: Duesseldorf 1988 - 2006



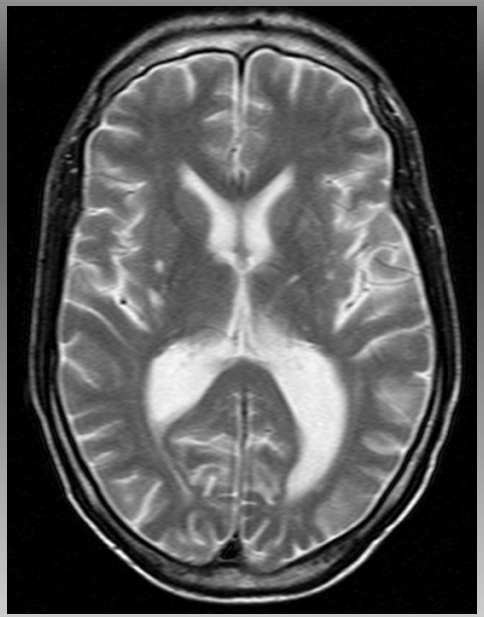
Pathophysiology of CNS infection by HIV (Kaul et al., 2001)

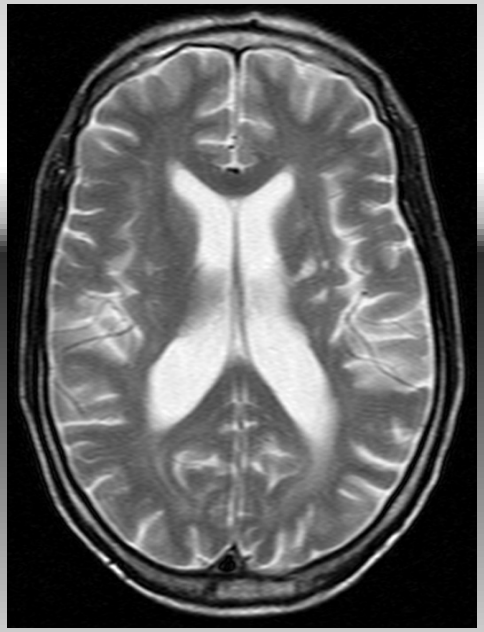


HIV-1-associated dementia

symptoms:

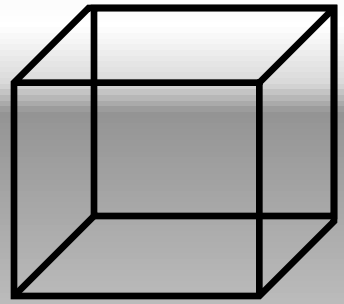
- motor impairment
- cognitive deficits
- personality changes
- depression





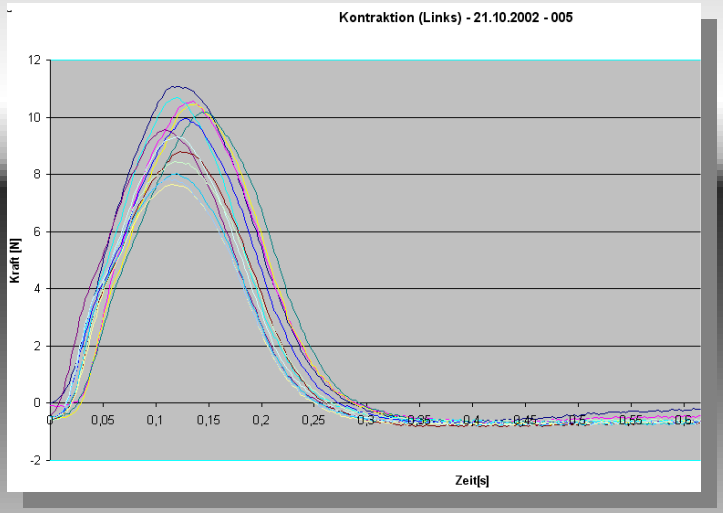
HIV-Dementia-Scale (Power et al., 1995)

- Memory:
  Try to remember four words (cat, trousers, yellow, banana).
- Attention:
  antisaccadic eye movments (20 commands)
- Psychomotor velocity (measurement):
  Write down the alphabet in capital letters!
- Memory:
  Which are the four words you were asked to remember?
- Construction:
  Copy the cube as fast as you can!



Measurement of MRC

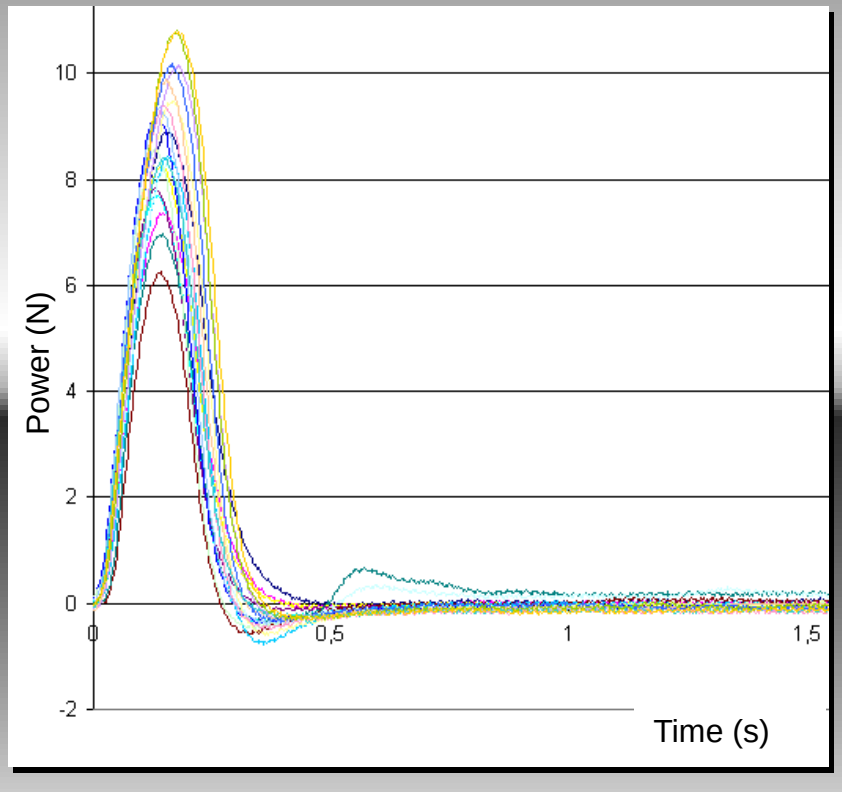
(most rapid voluntary isometric index finger extension)

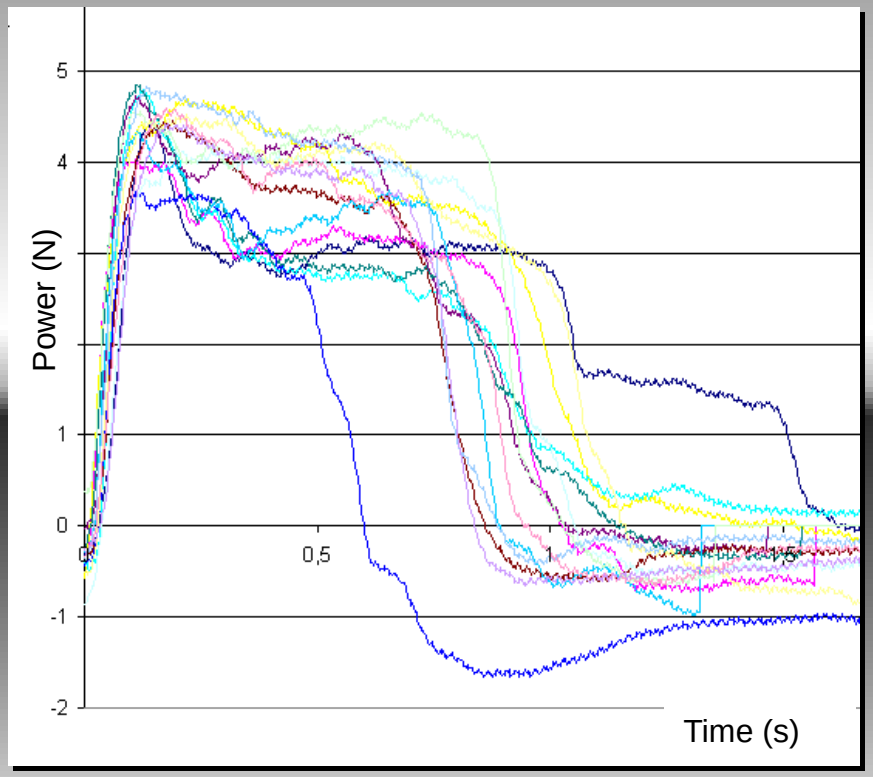


For isometric force measurement the patients´index finger is fixed with its middle and endphalange in a plastic ring of variable diameter, which is connected to a force transducer (KD-45-20 with double bars and resistive DMS, ME-technical systems, Hennigsdorf / Berlin). The patient is asked to respond as fast as possible with an index finger extension to an acoustical signal of 50 ms duration. In an off-line analysis reaction time = RT (time span between the beginning of the acoustical signal and the contraction) and contraction time = CT (time span between the beginning of the contraction and ist maximum), as well as force amplitude (AM) und the rate of rise of tension (RRT=AM/RT) are calculated.

Fine Motor Testing

- Most Rapid Index Finger Extensions (MRC):
  - Reaction time (RT)
  - Contraction time (CT)





MRT-Study

n = 743/2346	Age:	39,39 ± 10,34 a	Sex:	♂=677 ♀=66	Duration of infection:	3,76 ± 3,62	

Symptoms:

- Focal neurol. deficits n=206 ⇒ Opp. infection
- cognitive/motor deficits n=160 ⇒ HAD
- Headach, unspecific complaints n=422 ⇒ unsuspicious

Viral load (plasma):

- <1.000 n=644
- 1.000 - >10.000 n=36
- >10.000 n=63

Drugs:

- w/o therapy n=304
- monotherapy n=240
- Dual combination n=65
- HAART n=134

PET-Study

n = 15 Age: 42 ± 11 a Sex: ♂ Duration of infection: 4,8 ± 4,3 a

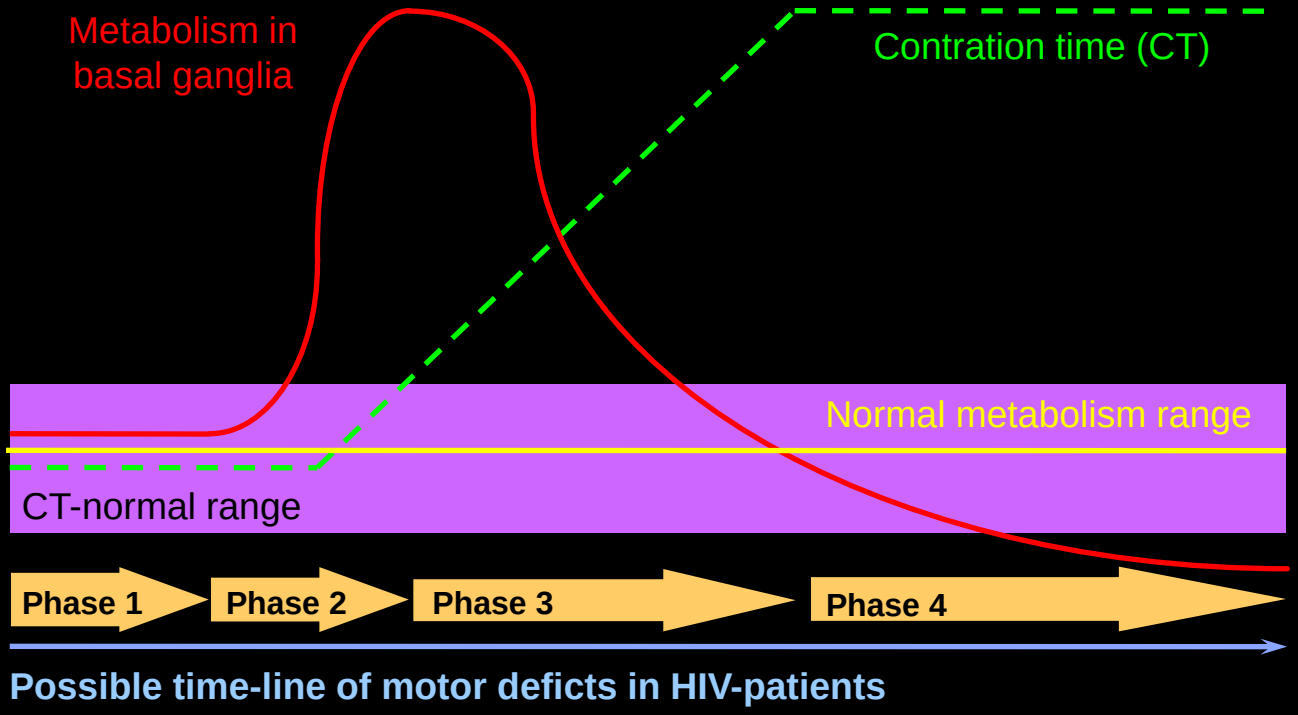
Symptoms: minor motor deficits (MMD)

Viral load:

- < LOD n=5
- <1.000 n=1
- 1.000-10.000 n=1
- 10.000-30.000 n=4

Drugs:

- w/o drugs n=3
- NRTIs n=7
- HAART n=9



Phase 1: Normal, metabolic and electrophysiological function

Phase 2: Elevated viral load. Penetration of HIV in basal ganglia; elevated blood flow and hypermetabolism, compensation of electrophysiological deficits

Phase 3: Secondary hypometabolism and beginnig of clinical deficits; beginning glial proliferation

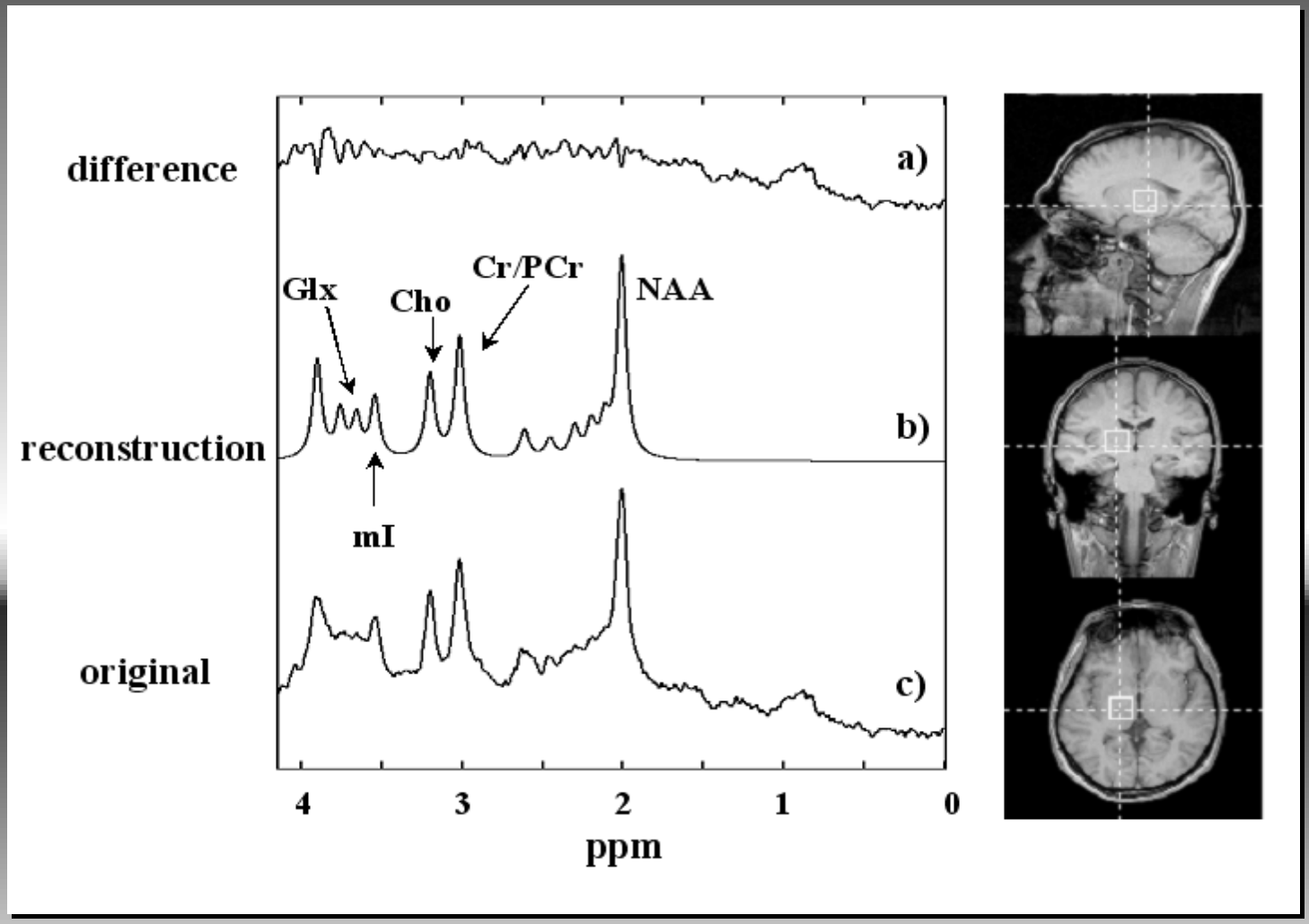
Phase 4: Progression of phase-3 modifications and beginning neuronal death

MRS-Study

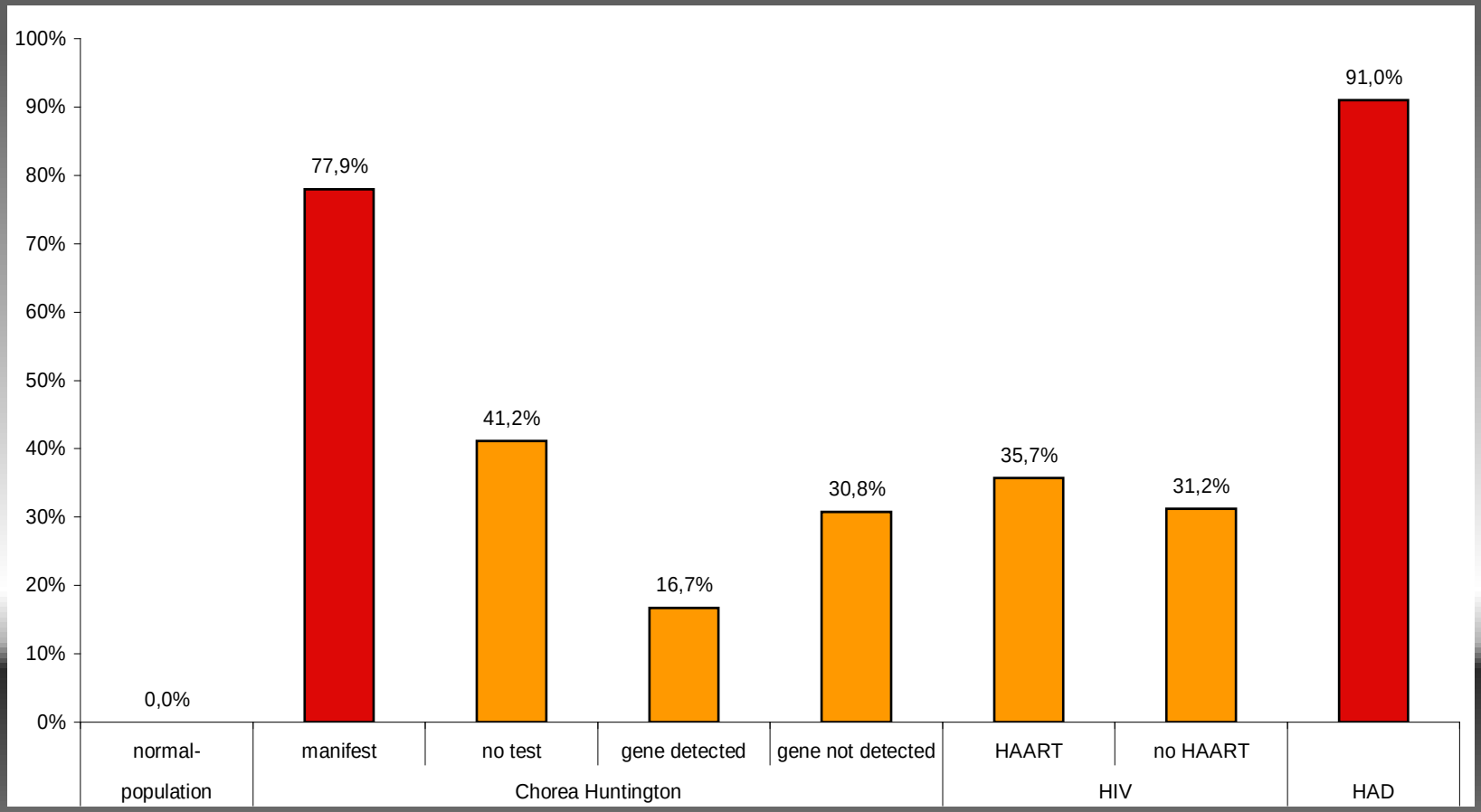
n = 32	Age	Sex: ♂	Duration of infection:
	a) 43,1 ± 11,1 a		a) 7,8 ± 5,6 a
	b) 38,2 ± 5,4 a		b) 8,3 ± 6,1 a
	c) 43,4 ± 10,4 a		c) 5,5 ± 4,5 a

Symptoms:	a) asymptomatic	n=10
	b) ANI	n=8
	c) MMD	n=14
Viral load:	a) 1.000 - >30.000	n=5
	b) 1.000 - >30.000	n=1
	c) 1.000 - 10.000	n=1
Drugs:	a) HAART	N=6
	b) HAART w/o	n=2
	c) NRTIs	n=13
	d) No thearpy	n=1

Kernspinspectroscopy (MRS)

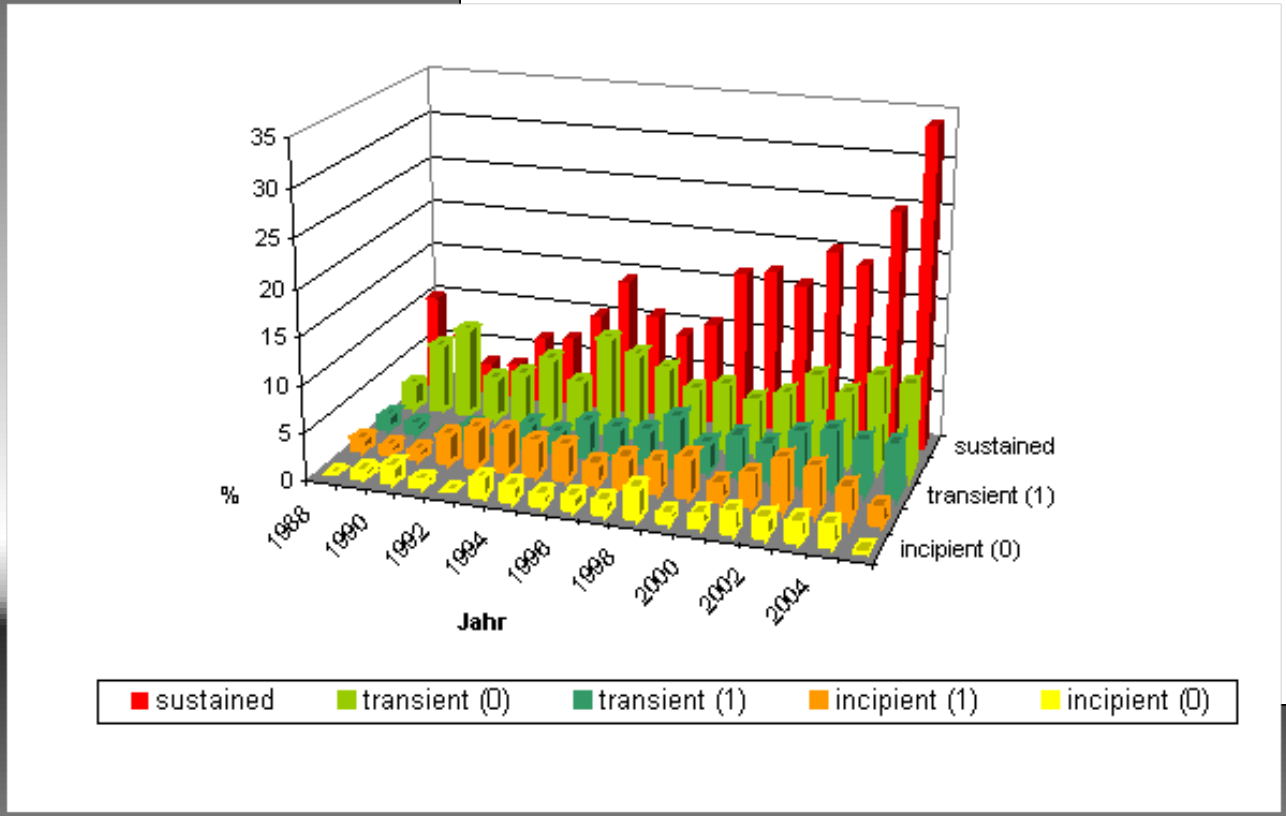


Contraction analysis in Chorea-Huntington and HIV-1-positive male adults against the healthy population



Pathological results (percent of the study population) detected in the first ever recorded contraction-test

Electrophysiological Test Results according to the Duesseldorf Classification



Abbreviations:

1. *Sustained:* electrophysiological pathologic despite HAART
2. *Transient(1) pathological:* transient improvement of electrophysiological results after initiation of HAART
3. *Transient(0) pathological:* transient improvement of elctrophysiological results after initiation of HAART followed by deterioration and again improvement after HAART correction
4. *Insipient(1) pathological:* beginning deterioration of pathological electrophysiological results
5. *Insipient(0) pathological:* beginning deterioration of electrophysiological results with normalisation after initiation of HAART

In 2004 American and Australian studies described changes in the clinical presentation of HIV-1-associated dementia.

As possible causes have been discussed:

- **Hormonal deficits**
- **Mitochondrial toxicity of highly active antiretroviral medication (HAART)**
- **Neprilysin-inhibition by „tat“**

New Aspects of HIV-associated CNS Disease in the HAART-Era

- changed phenotype: less severe dementia cases, more mild cognitive deficits
- neuropathology: neuronal cell death, gliosis, microglia-activation, persistant synapto-dendritic damage (proteosomics)
- in long-term survivors chronic immune activation (CCL3L1; MIP1alpha), during physiological aging, deposition of abnormal proteins in the brain
- rising importance of co-factors and co-morbidities, f. ex.,metabolic disturbances (insulin resistance), hypertension, alcohol and drug abuse, viral co-infections (HCV), mitochondrial toxicity of HAART

ANI = asymptomatic HIV-1-associated, neurocognitive impairment

1. **Acquired deficits in cognitive performance** (verbal fluency, executive functions, speed of information processing, attention, working memory, verbal and visual learning, visual information processing); results of at least **2 standardised tests range outside one standard deviation.**

2. **Deficits do not affect all days´ living.**

3. **Deficits persist more than one month.**

4. **Other reasons for ANI have been excluded, i.e., there should be no severe depression, psychosis and no active drug and alcohol abuse.**

MNCD = HIV-1-associated, mild neurocognitive deficits

1. Results of at least two **standardised tests range outside one <u>standard deviation</u>.**

2. **The cognitive deficits affect all days´ living.**
   i. Patients complain of reduced intellectual capacity, inefficiency in their profession + at home as well as of difficulties in social interaction
   ii. Confirmation or primary report of the above mentioned deficts by the patients´family and/or partner

3. **The deficits persist more than one month.**

4. **Other causes for the symptoms have been excluded** (psychiatric diseases, drug and/or alcohol abuse).

ANI and MNCD

Should clinical and/or neuropsychological improvement occur, the term „in remission“ is added to ANI/MNCD.

HAD = HIV-associated dementia

1. Marked cognitive impairment in at least two neuropsychological tests in different cognitive functions; test results have to range outside two standard deviations.

2. All days´ living can not be managed without support.

3. The deficits persist more than one month.

4. Other causes have been excluded.

ANI, MNCD and HAD

In diagnosing ANI, MNCD and HAD the following interfering variables have to be taken into account:

Primary variables:

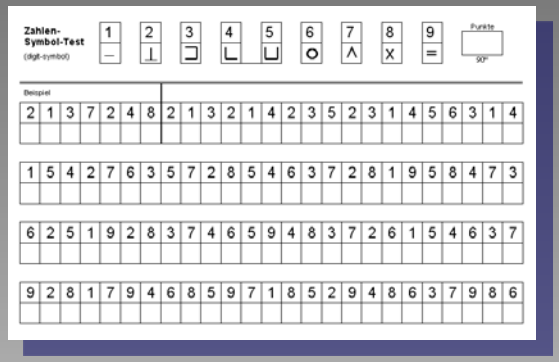
- age
- hepatitis C-co-infection
- vaskular or Alzheimer´s dementia
- psychiatric co-morbidity
- severe head trauma

Sekundary variables

- drug and/or alcohol abuse
- opportunistic cerebral infections

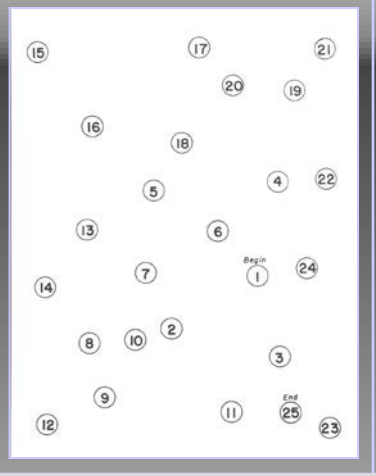
Cognitive / motor tests applied in patients with HIV-1-associated dementia and its precursor stages

Digit-Symbol-Test



Grooved-Pegboard-Test

Trail-Making-Test A + B



Motor Tests

Stroop Colour Test

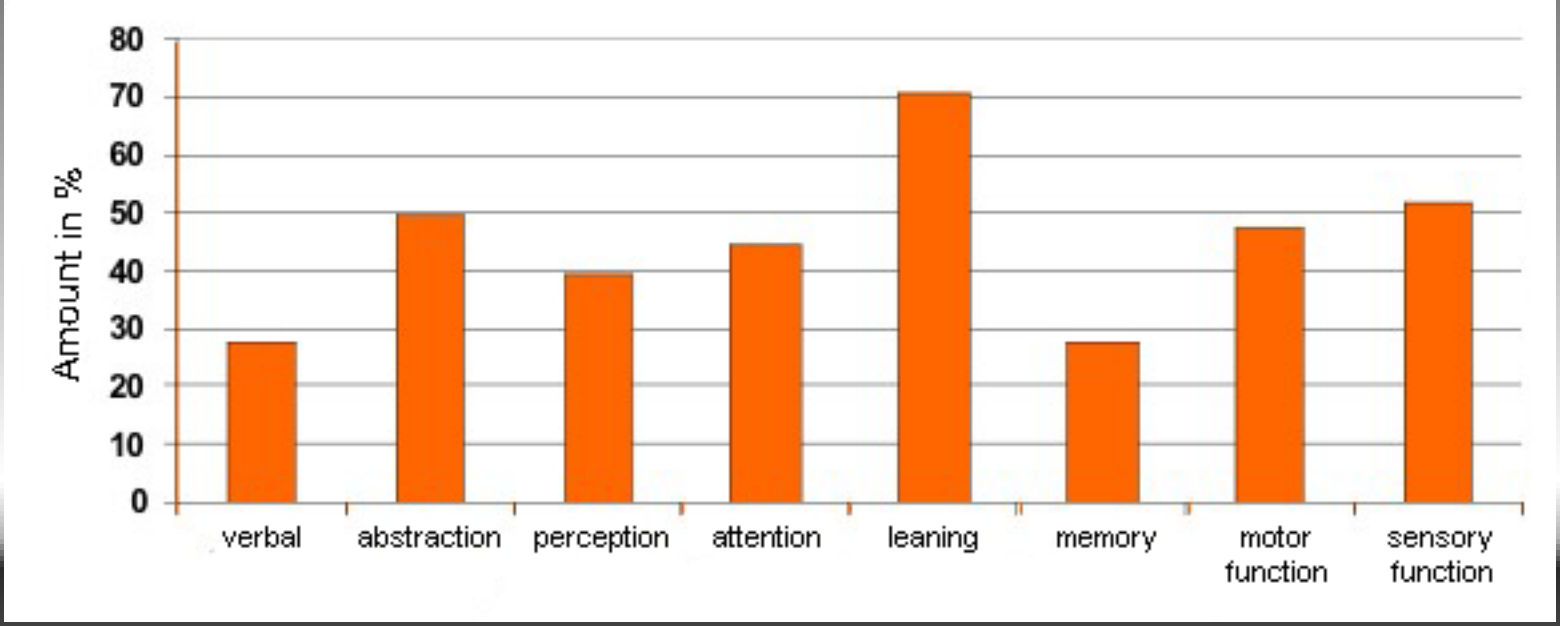
rot = red

grün = green

gelb = yellow

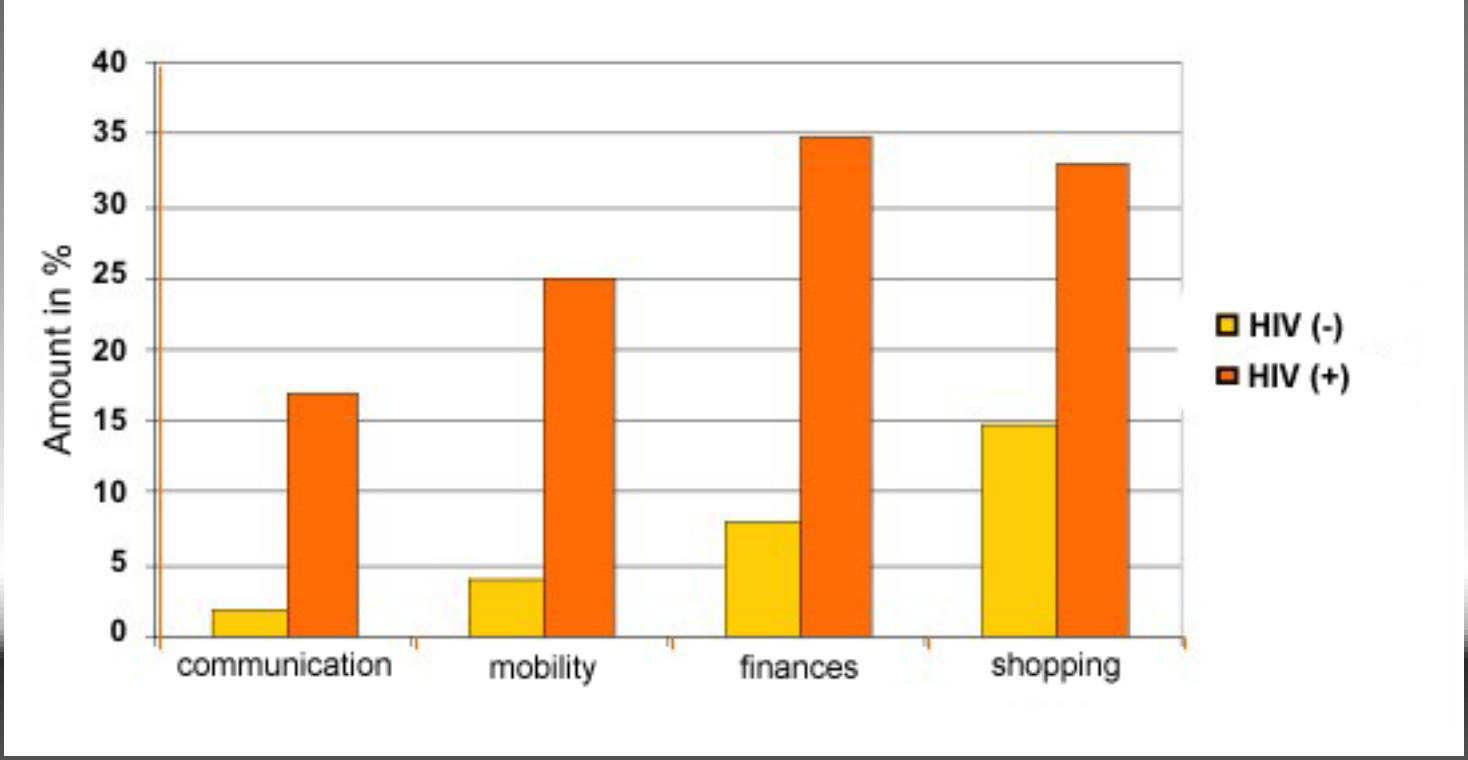
blau = blue

Pattern of HIV-associated neuropsychological Deficits



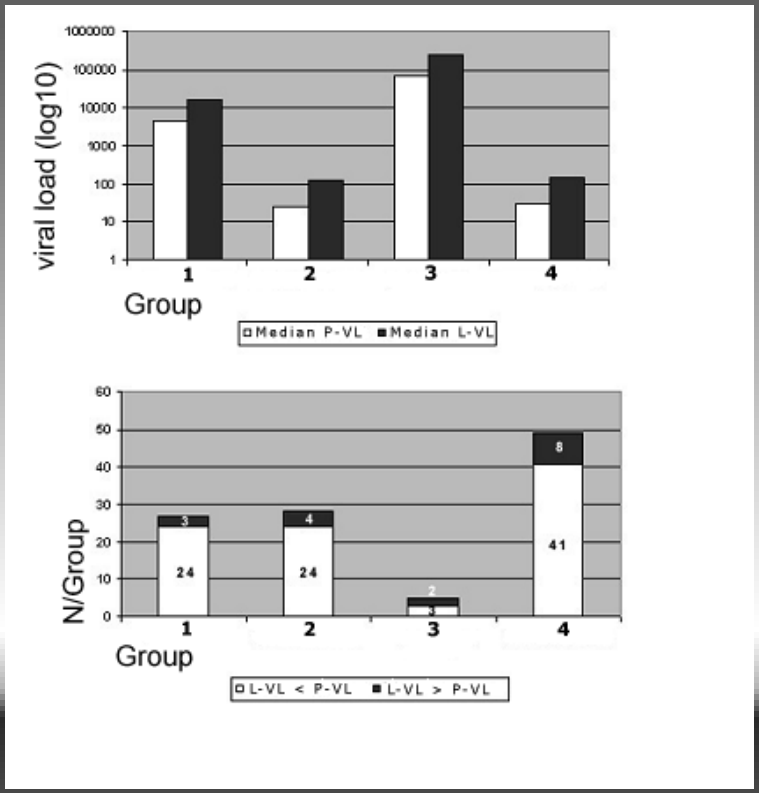
HIV Neurobehavioral research center (HNRC), San Diego, USA

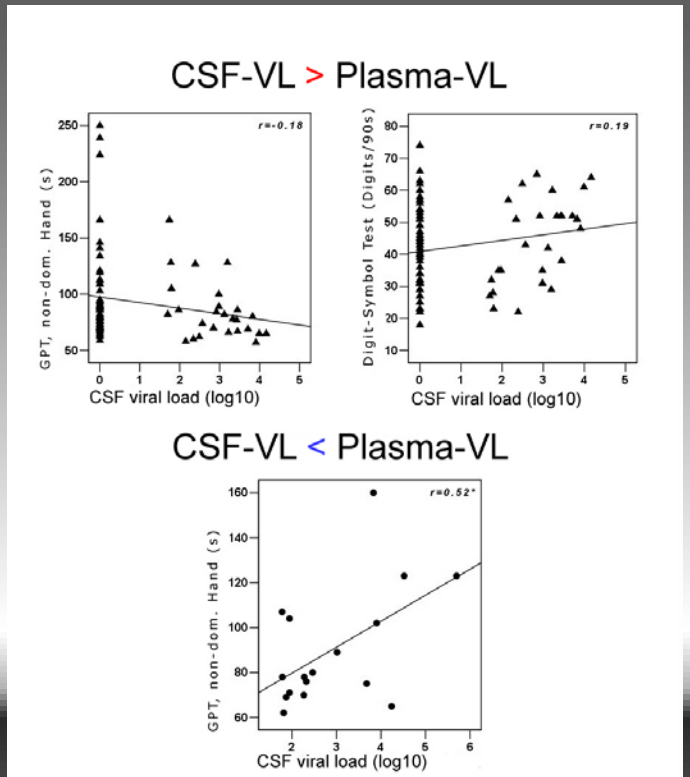
Impairment of all day´s living by HIV



HIV Neurobehavioral research center (HNRC), San Diego, USA

Arendt et al., JNV, 2007

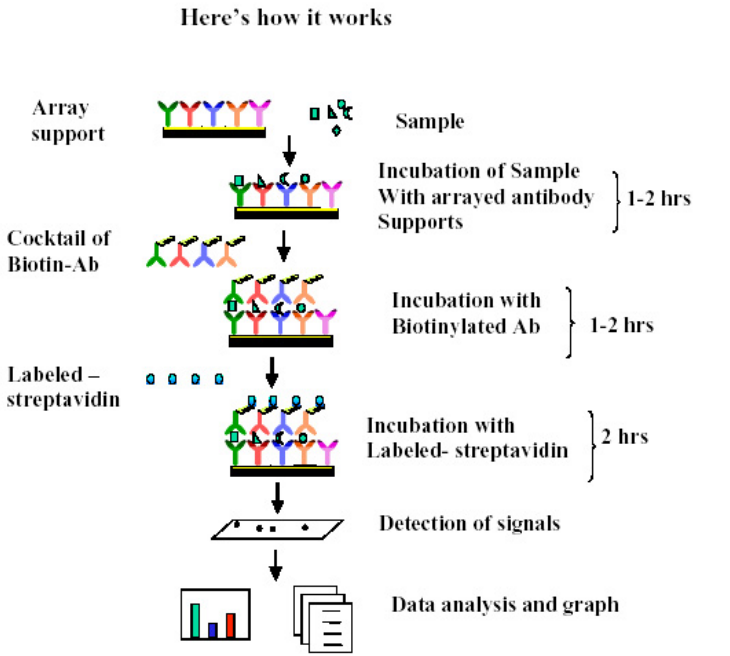


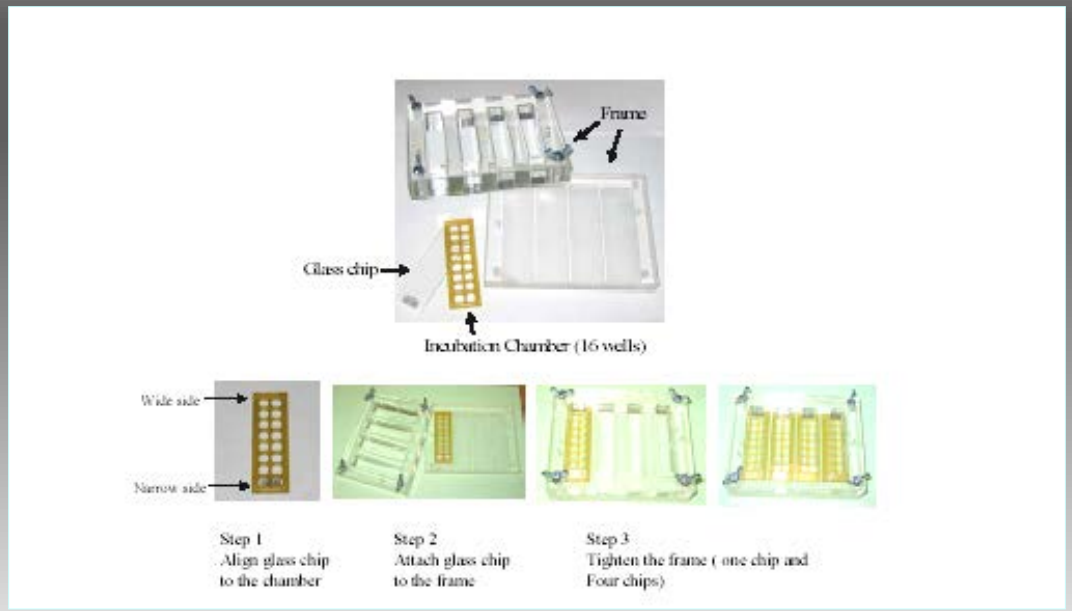


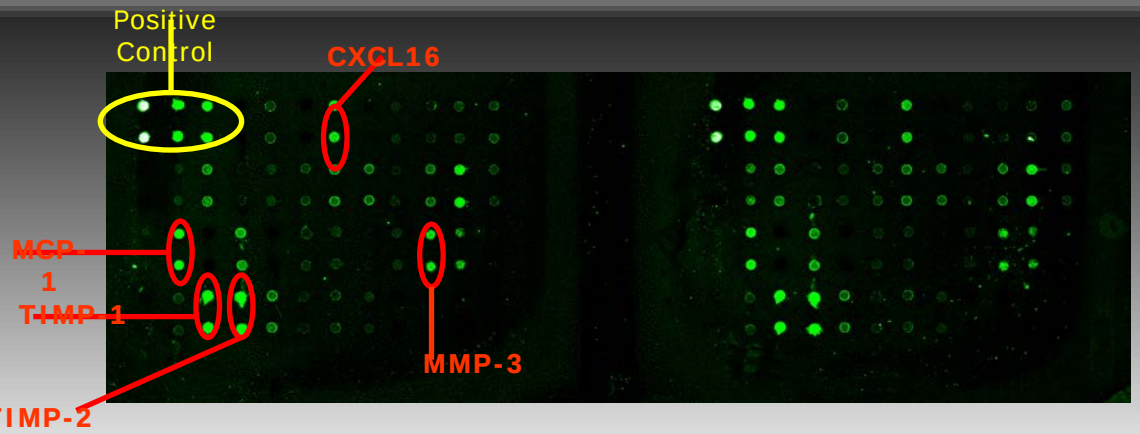
Correlations with CSF-VL (log)		Log_{10} VL blood	CSF: cells	CSF: protein	CSF: lactate	IgG-Index	CD4 count	HIV-duration
VL CSF > VL Plasma	Log_{10} VL CSF	0,890	0,618	0,643	0,416	0,629	- 0,459	-,328
VL Plasma > VL CSF	Log_{10} VL CSF	,789	,476	,289	,160	,381	-,197	-,275

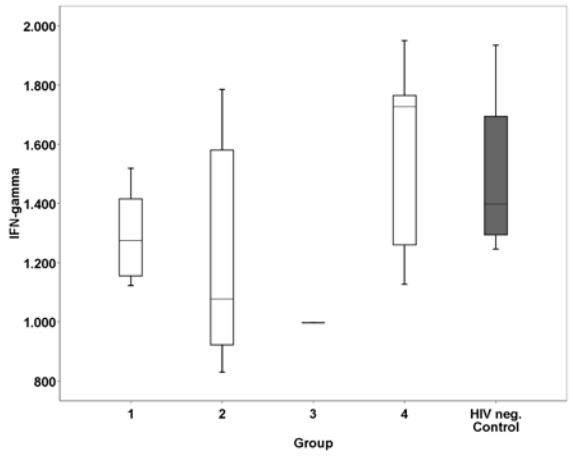
Correlations with CSF-VL (log)		CSF: MCP1	CSF: Gal3	CT right hand	CT left hand	HIV-demen. scale	GPT: domin. hand	GPT: non-domin. hand
VL CSF > VL Plasma	Log_{10} VL CSF	,791	,503	-,111	,047	,049	-,191	-,226
VL Plasma > VL CSF	Log_{10} VL CSF	,270	,287	-,229	-,273	-,245	,551	,528

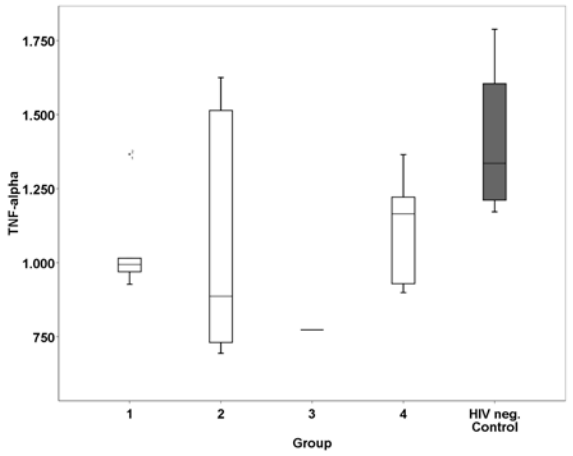
Cytokine-Array

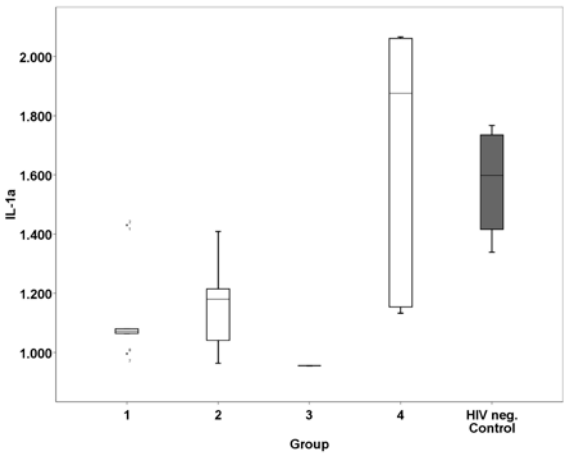


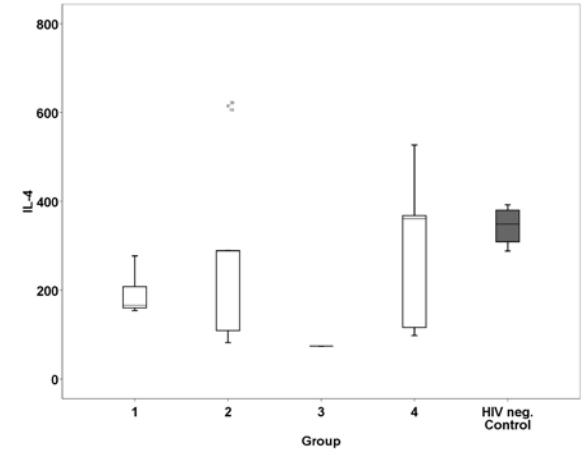


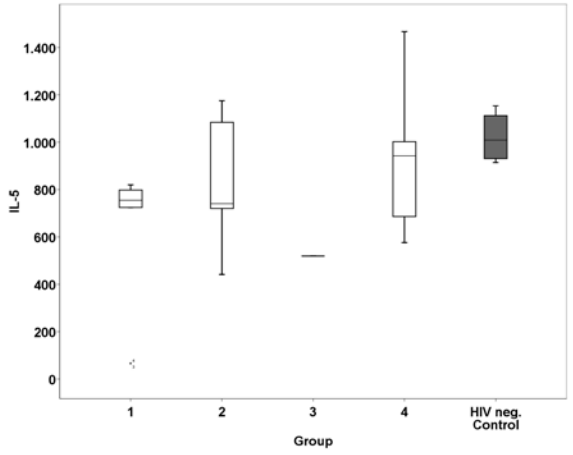


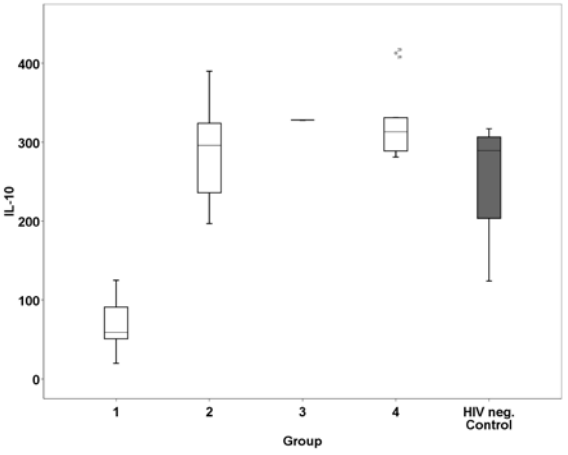

IFN-gamma
2.000
1.800
1.600
1.400
1.200
1.000
800
1
2
3
4
HIV neg. Control
Group

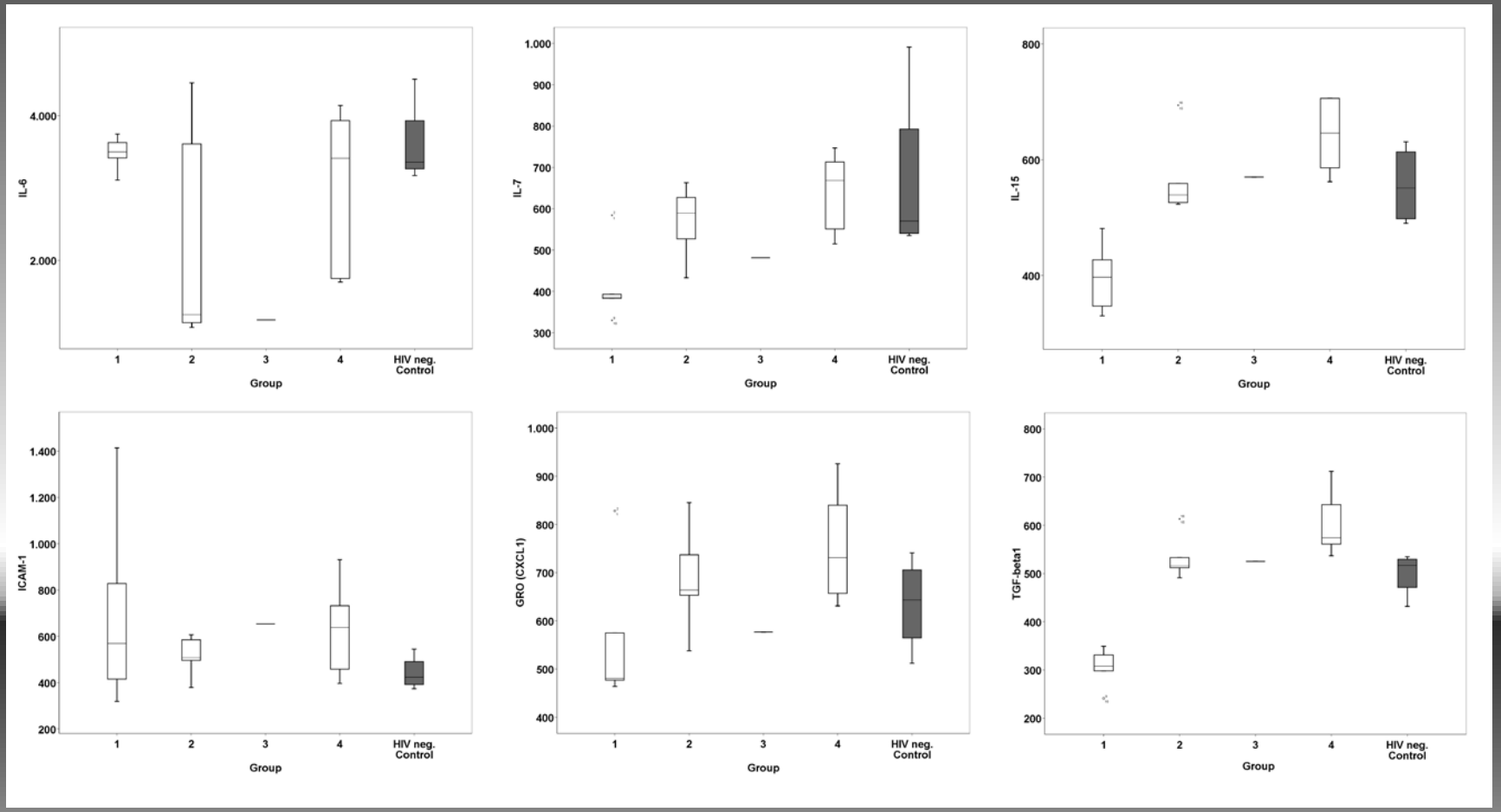

TNF-alpha
1.750
1.500
1.250
1.000
750
1
2
3
4
HIV neg. Control
Group


IL-1a
2.000
1.800
1.600
1.400
1.200
1.000
1
2
3
4
HIV neg. Control
Group


IL-4
800
600
400
200
0
1
2
3
4
HIV neg. Control
Group


IL-5
1.400
1.200
1.000
800
600
400
200
0
1
2
3
4
HIV neg. Control
Group


IL-10
400
300
200
100
0
1
2
3
4
HIV neg. Control
Group


IL-6
4.000
2.000
1
2
3
4
HIV neg. Control
Group
IL-7
1.000
900
800
700
600
500
400
300
1
2
3
4
HIV neg. Control
Group
IL-15
800
600
400
1
2
3
4
HIV neg. Control
Group
ICAM-1
1.400
1.200
1.000
800
600
400
200
1
2
3
4
HIV neg. Control
Group
GRO (CXCL1)
1.000
900
800
700
600
500
400
1
2
3
4
HIV neg. Control
Group
TGF-beta1
800
700
600
500
400
300
200
1
2
3
4
HIV neg. Control
Group

Biomarkers with relevance for HIV-associated CNS-disease

- Viral load in cerebrospinal fluid (CSF)
- Markers for oxidative stress (ceramide + DNA-metabolites)
- CXCL12 (SDF1) as protective marker
- Neurofilament light-chain-protein – marker for axonal degeneration
- Sialoadhesin as a marker for HIV-CNS-penetration
- Genotyp of the host: CCL3L1
- Mitochondrial haplotyps T42/6

HAART 2008

NRTIs *(Nukleoside-/Nukleotide-Reverse-Transcriptase-Inhibitors)*

Zidovudine AZT (Retrovir®)

Lamivudine 3TC (Epivir®)

AZT + 3TC (Combivir®)

Abacavir ABC (Ziagen®)

AZT + 3TC + ABC (Trizivir®)

3TC + ABC (Kivexa®)

Didanosine ddI (Videx®)

Zalcitabine ddC (Hivid®)

Stavudine d4T (Zerit®)

Tenofovir TDF (Viread®)

Emtricitabine FTC (Emtriva®)

FTC + TDF (Truvada®)

FTC + TDF + EFV (Atripla ®)

NNRTIs *(Non-Nukleoside-Reverse-Transcriptase-Inhibitors)*

Nevirapine NVP (Viramune®)

Efavirenz EFV (Sustiva®)

Delavirdine DLV (Rescriptor®)

TMC125 (Etravirine)

PIs *(Protease-Inhibitors)*

Saquinavir SQV (Invirase500®)

Indinavir IDV (Crixivan®)

Nelfinavir NLV (Viracept®)

Ritonavir RTV (Norvir®)

Fosamprenavir APV (Telzir®)

Lopinavir/Ritonavir LPV/r (Kaletra®)

Atazanavir ATV (Reyataz®)

Tipranavir TPV (Aptivus ®)

TMC 114 (Prezista ®)

Fusion-Inhibitors

Enfurvirtide T20 (Fuzeon ®)

Maturation-inhibitors

Integrase-Inhibitors

Raltegravir (Isentress)

GS-9137 (Phase I)

CCR5-Antagonists

Maraviroc (Celsentri)

CSF penetration

CHARTER study

- 347 patients on ART; plasma and CSF probes
- Antiretrovirals will be assigned to penetration rates (0; 0,5, 1) based on literature research
- High penetration scores are positively correlated to low viral load in CSF
- The correlation does not depend on plasma-VL, duration of therapy and kind of drugs

Letendre et al., CROI 2006

	Zunehmende Liquorgängigkeit →		
	0	**0.5**	**1**
NRTIs:	TFV ddI ddC	d4T 3TC FTC	ZDV ABV
NNRTIs:		EFV	DLV NVP
PIs:	NFV SQV SQV-r RTV TPV-r	APV f-APV ATV IDV	APV-r f-APV-r ATV-r IDV-r LPV-r
Fusions-inhibitoren:	T-20		

CSF penetration

	CSF penetrance index	*CNS penetrance index*
Zidovudine (500 mg)	0.6	0.8
Efavirenz (600 mg)	0.6	
Stavudine (80 mg)	0.5	0.34
Nevirapine (400 mg)	0.45	
Abacavir (600 mg)	0.2	
Indinavir (800–1200 mg)	0.14	0.18
Nelfinavir (2500 mg)	0.07	
Lopinavir (800 mg)	0.07	
Lamivudine (300 mg)	0.06	
Didanosine (400 mg)	0.05	0.05
Zalcitabine (225 mg)	0.03	0.19
Ritonavir (1200 mg)	0.02	
Saquinavir (2000 mg)	0.005	
Delavirdine (1200 mg)	0.001	
Amprenavir (2400 mg)	0.001	

Evers S. et al., 2004

New therapies with potential CNS-effectivity

- erythropoetine
- MCP-1-activating substances
- MDR-modulators
- lithium (to date proven effectivity in animal studies + *in-vitro*)
- minocycline
- cytokine-antagonists

Cofactors and Comorbi-dities

- Age
- Vascular disease
- Mitochondrial toxicity of HAART
- Psychiatric disease (esp. depression and drug abuse)
- Hepatitis virus C Coinfection
- Neurosyphilis

Psychiatric diseases

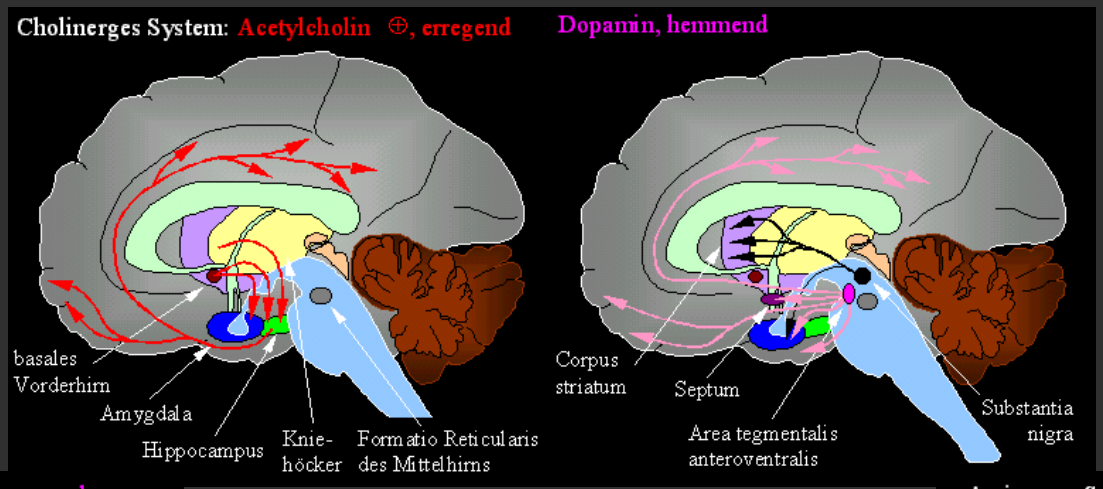
- Major and moderate depressive epsiodes
- Dysthymia
- Bipolar and schizophrenic psychosis
- Personality disorders

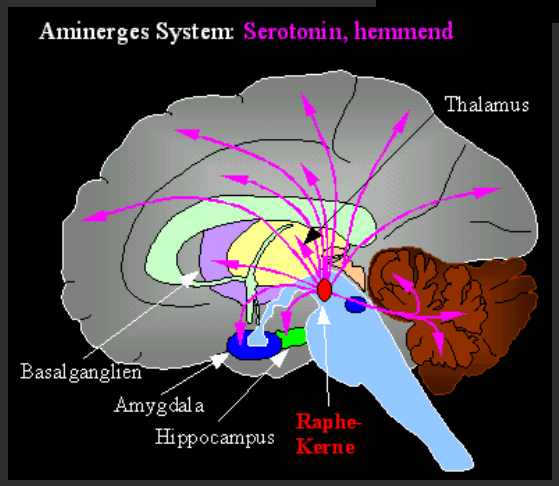
Depression

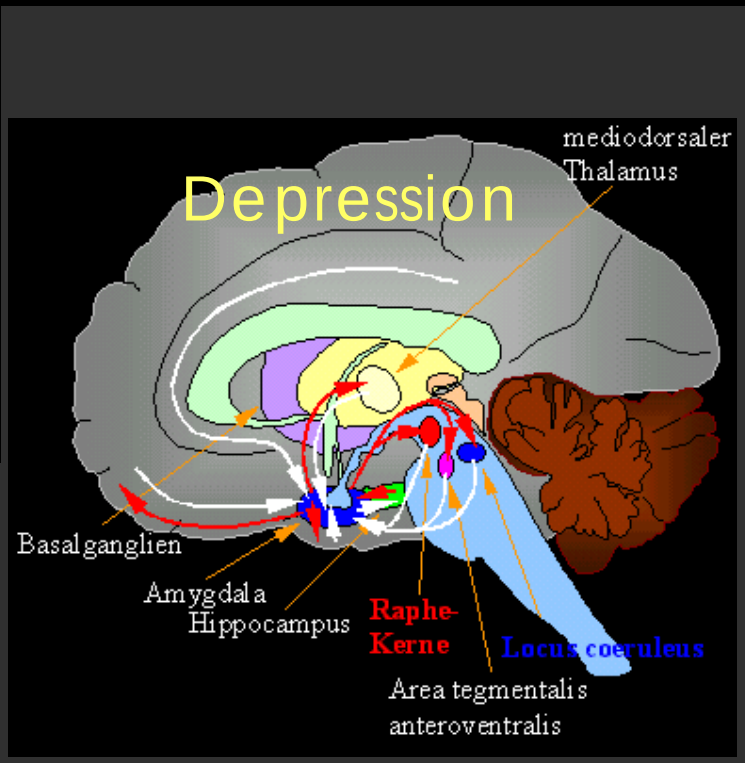
Life-time prevalence

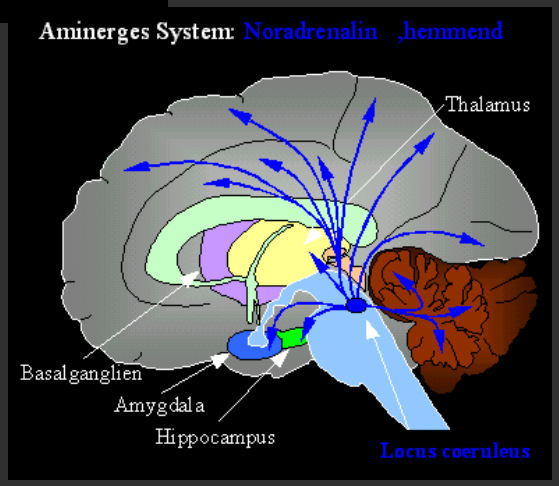
- Depression occurs in 22 - 45% of all HIV-positive patients !

Biopsychiatric Concept of pathogenesis of depression

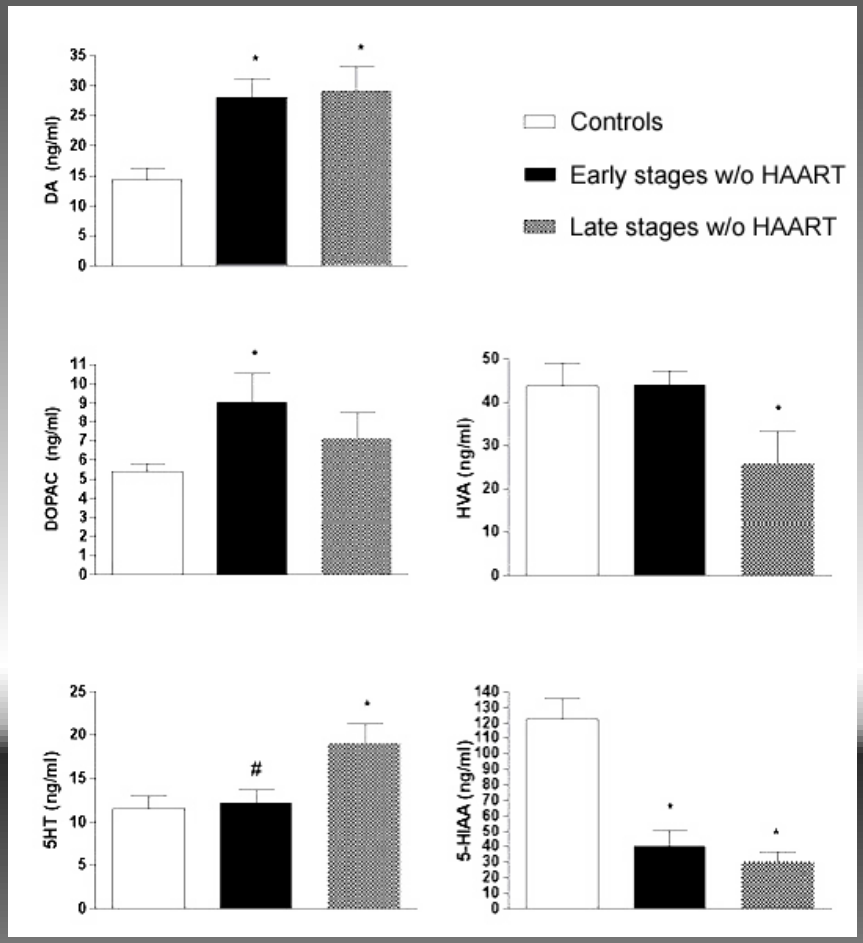


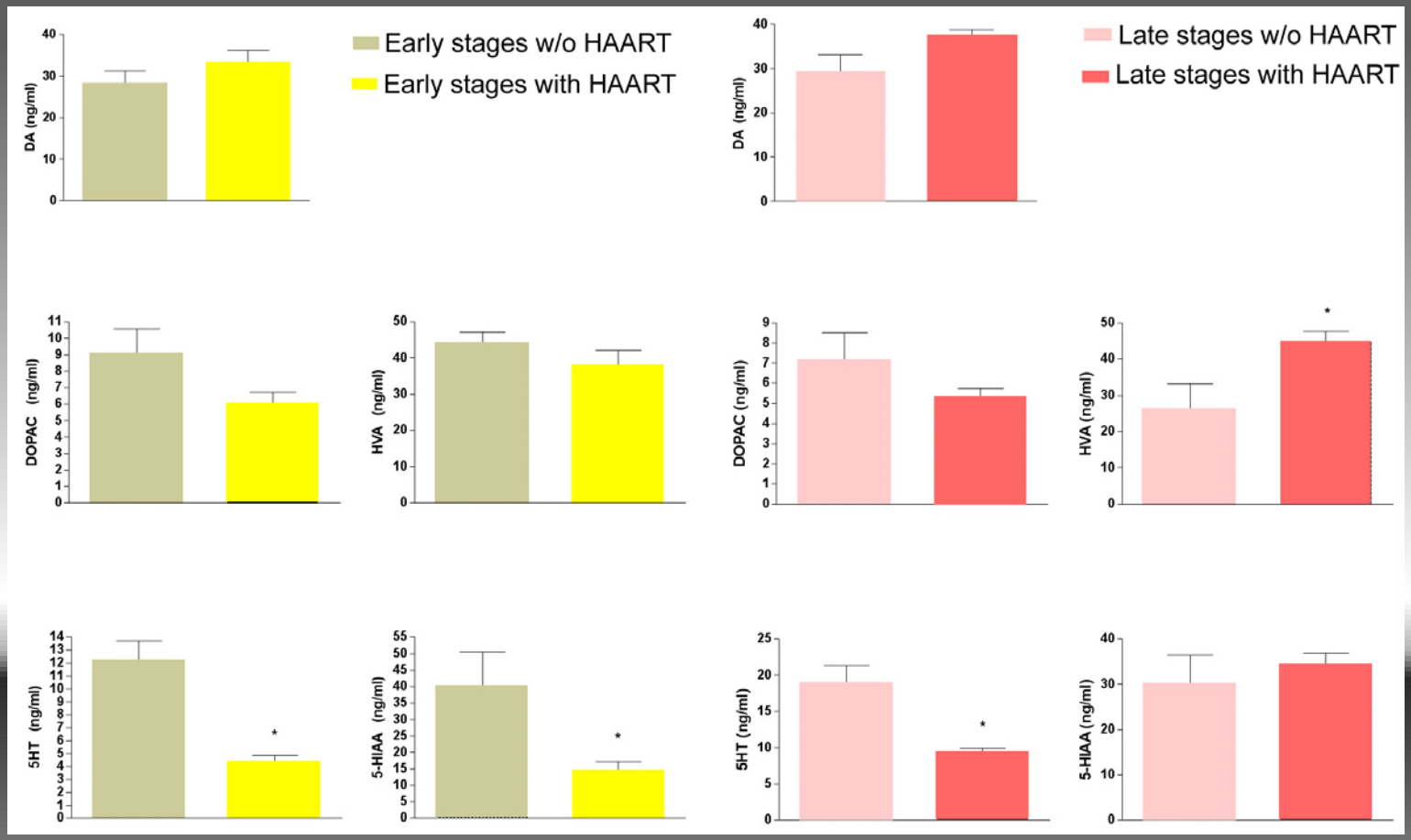






Depression negatively influences therapy adherence !


DA (ng/ml)
DOPAC (ng/ml)
HVA (ng/ml)
5HT (ng/ml)
5-HIAA (ng/ml)
Controls
Early stages w/o HAART
Late stages w/o HAART
*
#


Early stages w/o HAART
Early stages with HAART
Late stages w/o HAART
Late stages with HAART
DA (ng/ml)
DOPAC (ng/ml)
HVA (ng/ml)
5HT (ng/ml)
5-HIAA (ng/ml)
*

Drugs frequently used by HIV-positive patients worldwide

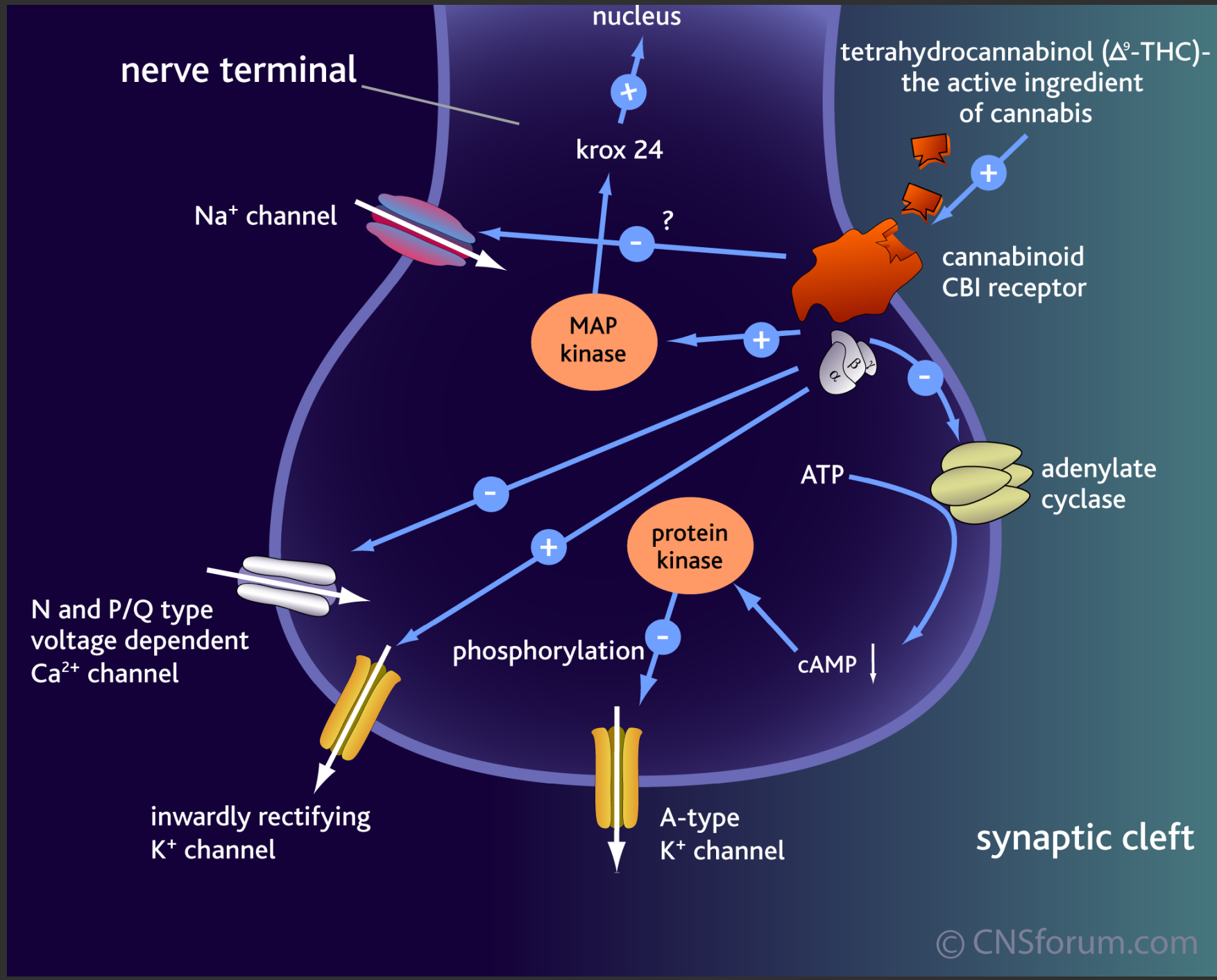
- Alcohol
- Cannabis (-derivatives)
- Amphetamine (-derivatives)
- Heroine

Alcohol effect in HIV-infection

Alcohol

- stimulates HIV-replication in infected cells
- influences cytokin-synthesis
- decreases CD8+-cell count
- decreases immune function (f.ex.macrophage function)
- increases permeability of the blood brain barrier
- has synergistic effects with neurotoxic HIV-proteins (inhibits N-methyl-D-aspartate-NMDA-receptor function as well as Na+/Ca++-exchange among others)

Mechanism of cannabis action in CNS

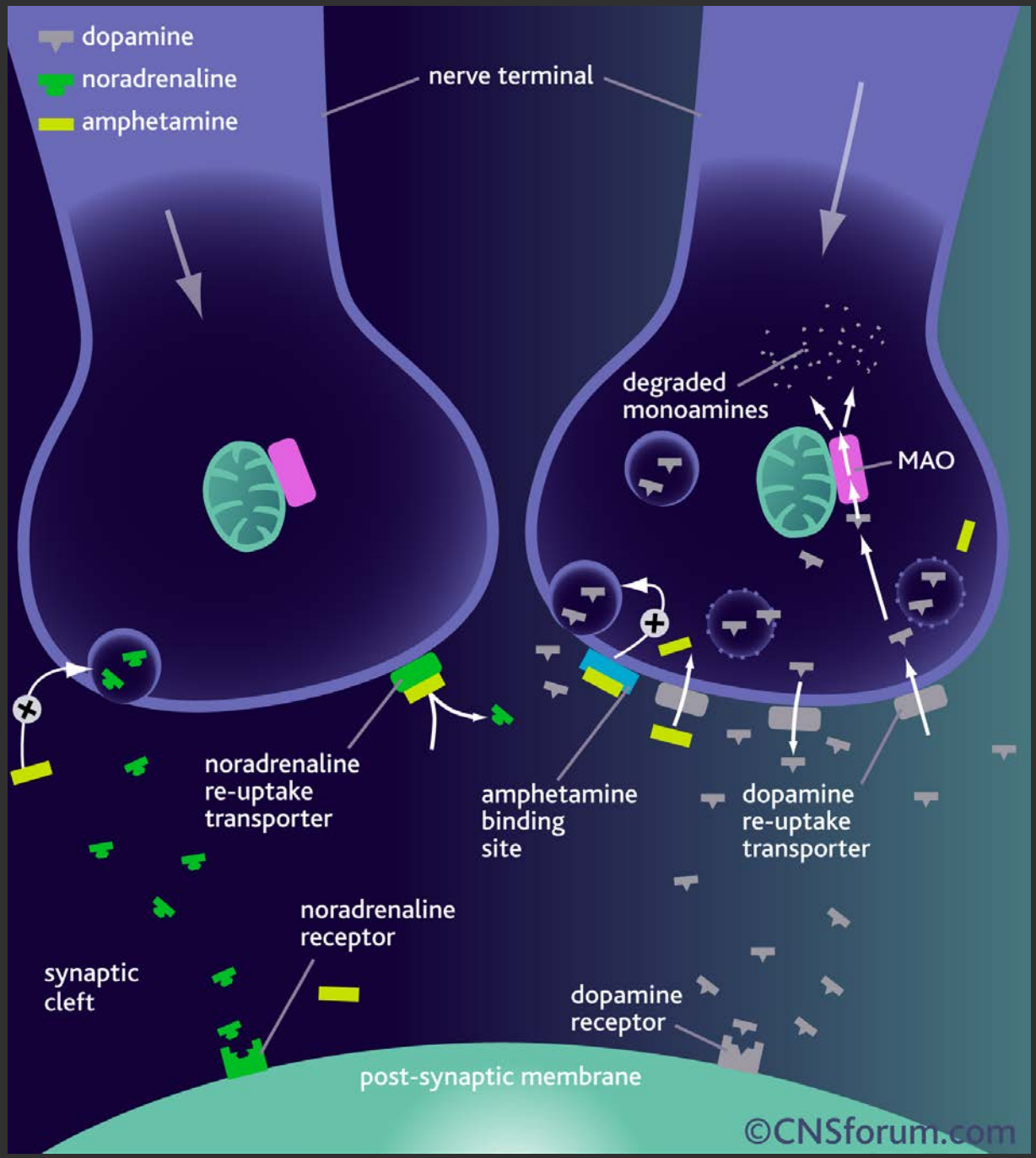


Cannabis and derivatives

- Negative influence on cognition
  and
- Negative influence on the immune system

- Important in AIDS-defined patients

Action of amphetamines wthin CNS



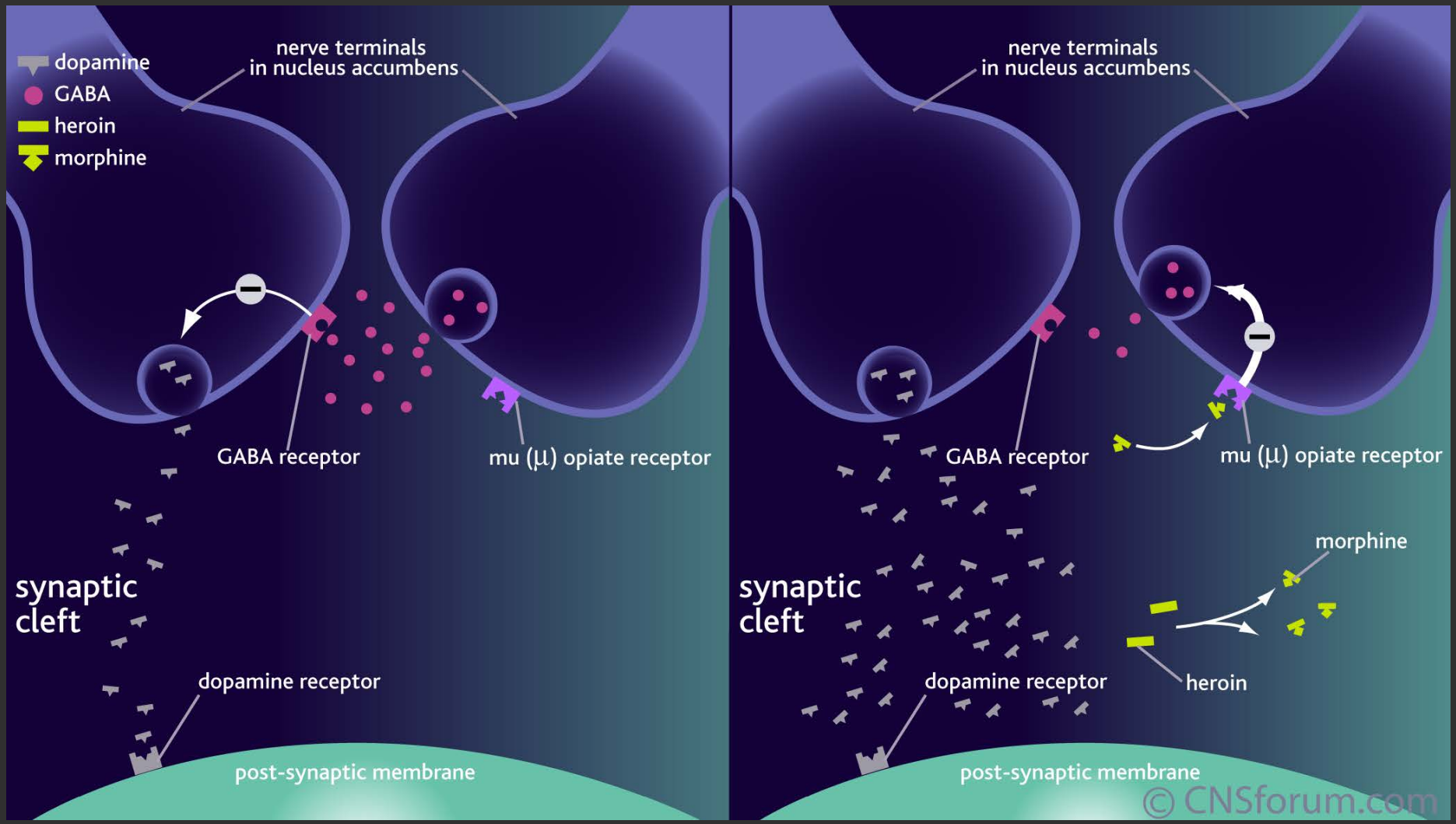
Methamphetamine

- Increases neuronal damage
- Elevates the risk of developing neuropsychological deficits in HIV(+)-patients
- Proven, selective damage of dopaminergic neurons esp. of the basal ganglia in animal studies
- Seems to be especially dangerous for HIV/HCV-co-infected patients
- Mitochondrial toxicity in combination with HIV-*tat*

Methamphetamine

- provokes neuronal damage
- increases the risk of neuropsychological deficits in HIV-patients
- leads in animal studies to selective damage of dopaminergic neurons in the basal ganglia
- is especially dangerous in HIV-HCV-co-infected patients
- acts synergistically with HIV-*tat with respect to* mitochondrial toxicity

Action of heroine within the CNS



Methadone substituted HIV(+)-patients showed extremely bad results in neuropsychological test batteries !

Rodriuez Salgado D, Rodriuez Alvarez M, Seoane Pesqueira G. Neuropsychological impairment among asymptomatic HIV-positive former intravenous drug users.Cogn Behav Neurol. 2006;19(2):95-104.

Hepatitis-Virus-C(HCV)-Coinfektion (modified after Soriano et al., in: Gendelman et al., 2005)

	HIV	HCV
Isolation of virus	1983	1989
Persons infected worldwide	40 Mio.	170 Mio.
Genetic structure	RNA	RNA
Genom length	10^4	10^4
Genetic variabilty	HIV-1- und HIV-2; 3 groups (M,N,O) multiple subtypes	6 major subtypes
Daily reproduction	10^9 virions	10^{12} virions
Virion half life span	4 hours	2,7 hours
Major target cell	CD4+-T-Lymphocyt	hepatocyte
Mode of transmission	sexual	parenteral
Chronification	100 %	75 %
Persons healed by therapeutic intervention	0 %	40 %
Asymptomatic period	10 years	30 years
Disease markers	CD4+count, viral load	fibrosis; co-factors, e.g. alcohol consumption
Pathogenicity	Cell death	Immune modulation
Therapy	Antiretroviral drugs	Immune modulators
Therapy Predictors	Viral load; CD4+count; Compliance; Resistency	HCV-Genotype; cirrhosis; Compliance; viral load

Neuro-Lues

Definite Neuro-Syphilis	Probable Neuro-Syphilis	Possible Neuro-Syphilis
Positive TPPA und FTA-Abs in blood and CSF	Positive TPPA und FTA-Abs in blood and CSF	Positive TPPA und FTA-Abs in blood and CSF
positive VDRL-reaction in blood and CSF	negative VDRL-reaction in blood and CSF	negative VDRL-reaction in blood and CSF
	lympho-monocytic pleocytosis and protein elevation	lympho-monocytic pleocytosis and protein elevation
	Neurological complication, e.g. stroke, severe headaches, facial palsy, hypacusis	Absence of neurological complications

Modified: Modified after Marra C et al., 1992, in Gendelman et al., 2005

www.neuro-hiv.de