Co-Factors and Co-Morbidities in Neuro-AIDS

- **8th International Symposium on Neuropsychiatry & HIV, Barcelona, June, 2015**
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- Funding: Abbvie, ViiV Healthcare

Nomenclature of HIV associated neurocognitive disorders (HAND)

	Pre-existing Cause	Delirium Absent	Acquired Impairment in ≥ 2 Cognitive Abilities	Interferes with Daily Functioning
Asymptomatic Neurocognitive Impairment (ANI)	No	Yes	Yes	No
Mild Neurocognitive Disorder (MNCD)	No	Yes	Yes	Mild
HIV-Associated Dementia (HAD)	No	Yes	Marked	Marked

Antinori et al., Neurology, 2007, Simioni et al., AIDS, 2010

Cofactors

- 1. Demographic factors
- 2. HIV-related factors
- 3. Treatment associated factors
- 4. Biomarkers
- 5. Host and viral genetics
- 6. Others

Cofactors (1)

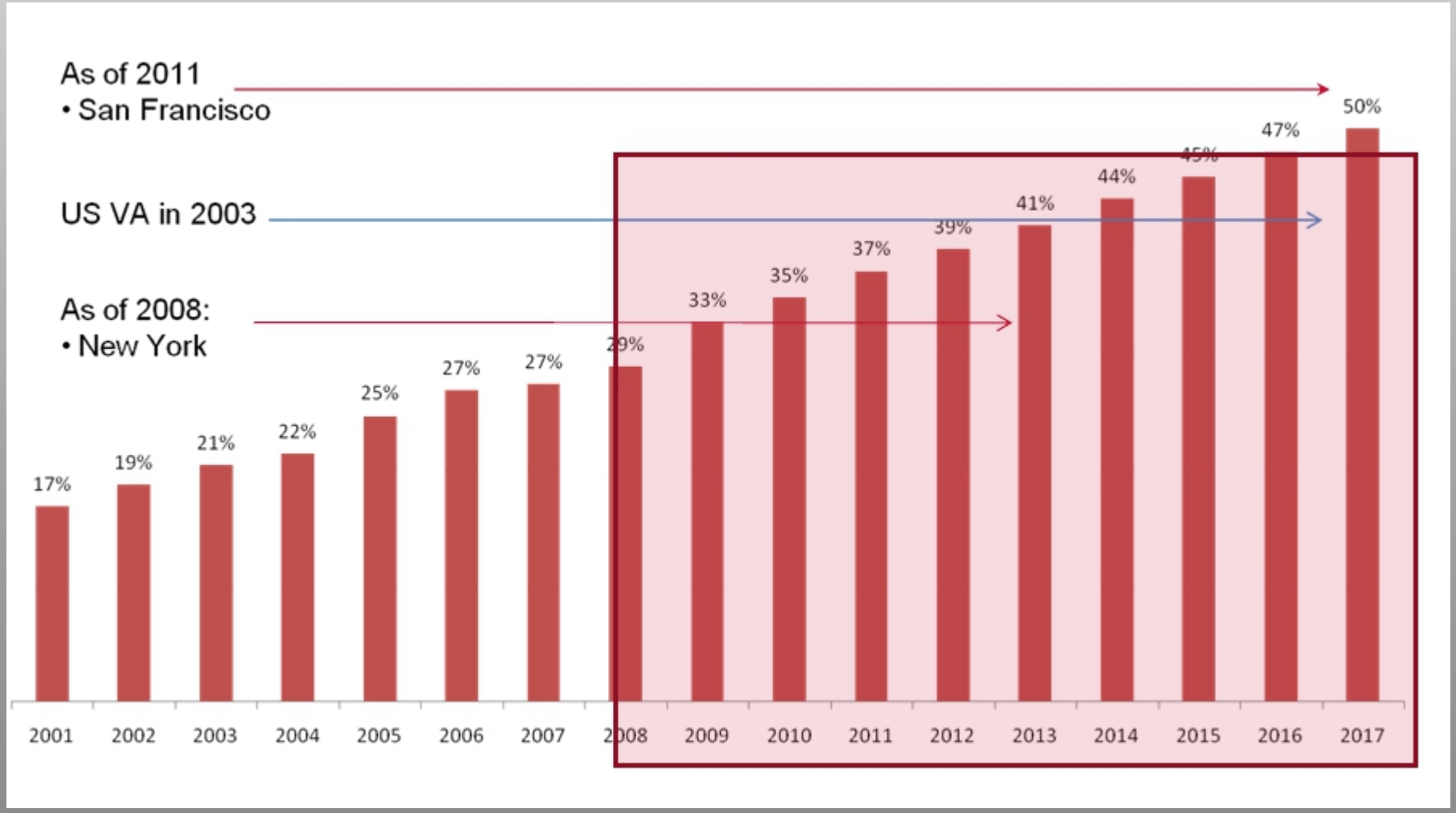
Demographic factors

- Age (Valcour et al., 2004)
- Neurodegenerative disease
- Low educational level (Mindt et al., 2011)
- Socio-economic status
- No access to standard care (Gupta et al., 2001)

Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes OA, Grove J, Liu Y, Abdul-Majid KB, Gartner S, Sacktor N. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. J Neuroimmunol. 2004;157(1-2):197-202.

Robbins RN, D'Aquila E, Morgello S, Byrd D, Remien RH, Mindt MR. Cultural Influences on Antiretroviral Therapy Adherence Among HIV-Infected Puerto Ricans. J Assoc Nurses AIDS Care. 2012

Gupta SB, Dingley SD, Lamagni TL, Mortimer JY, Evans BG. The national CD4 surveillance scheme for England and Wales. Commun Dis Public Health. 2001;4(1):27-32.



*Data from 2008, onward projected based on 2001-2007 trends (calculated by author), 2001-2007 data from CDC Surveillance Reports 2007. New York from their Departments of Public Health. SF from IAS 2011

Braithwaite *S. IAS 2011. Presentation MOWS0305*

Aging (A)

- Valcour et al., 2004 found a three times higher likelihood of developing HAND in people older than 50 years with extrapyramidal motor signs exacerbated by aging.

Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes OA, Grove J, Liu Y, Abdul-Majid KB, Gartner S, Sacktor N. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. J Neuroimmunol. 2004;157(1-2):197-202.

Aging (B)

- The brain undergoes in every human being physiological aging – HIV (*tat*) blocks neprilysine and thus, accelerates the physiological aging process !

Cofactors (2)

Directly HIV-infection related factors

- Longer duration of HIV-positivity
- Low CD4+-nadir (Heaton et al., 2011)
- High viral load in plasma and CSF (Rackstraw, 2011)
- Low current CD4+-cell count (Heaton et al., 2011)
- History of HIV-related CNS disease (Cysique et al., 2010)

Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I; CHARTER Group; HNRC Group. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011;17(1):3-16.

Rackstraw S. HIV-related neurocognitive impairment--a review. Psychol Health Med. 2011;16(5):548-63.

Cysique LA, Murray JM, Dunbar M, Jeyakumar V, Brew BJ. A screening algorithm for HIV-associated neurocognitive disorders. HIV Med. 2010;11(10):642-9.

Cofactors (3)

Treatment-associated factors

- Low therapy adherence (Becker et al., 2011)
- Non-optimal cART regimen (Cysique et Brew, 2009)
- cART interruption (Cysique et Brew, 2009)
- Treatment failure shortly after initiation (Cysique and Brew, 2009)
- Lower central nervous system penetration efficiency (Letendre et al., 2008)
- Potential neurotoxicity (Schweinsburg et al., 2005)

Becker BW, Thames AD, Woo E, Castellon SA, Hinkin CH. Longitudinal change in cognitive function and medication adherence in HIV-infected adults. AIDS Behav.2011;15(8):1888-94.

Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review. Neuropsychol Rev. 2009 Jun;19(2):169-85.

Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Gelman BB, McArthur JC, McCutchan JA, Morgello S, Simpson D, Grant I, Ellis RJ; CHARTER Group. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol. 2008;65(1):65-70.

Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ, Letendre S, Videen JS, McCutchan JA, Patterson TL, Grant I; HNRC Group. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol. 2005 Aug;11(4):356-64.

cART Adherence, Structured Treatment Interruption (STI) and Potential Neurotoxicity

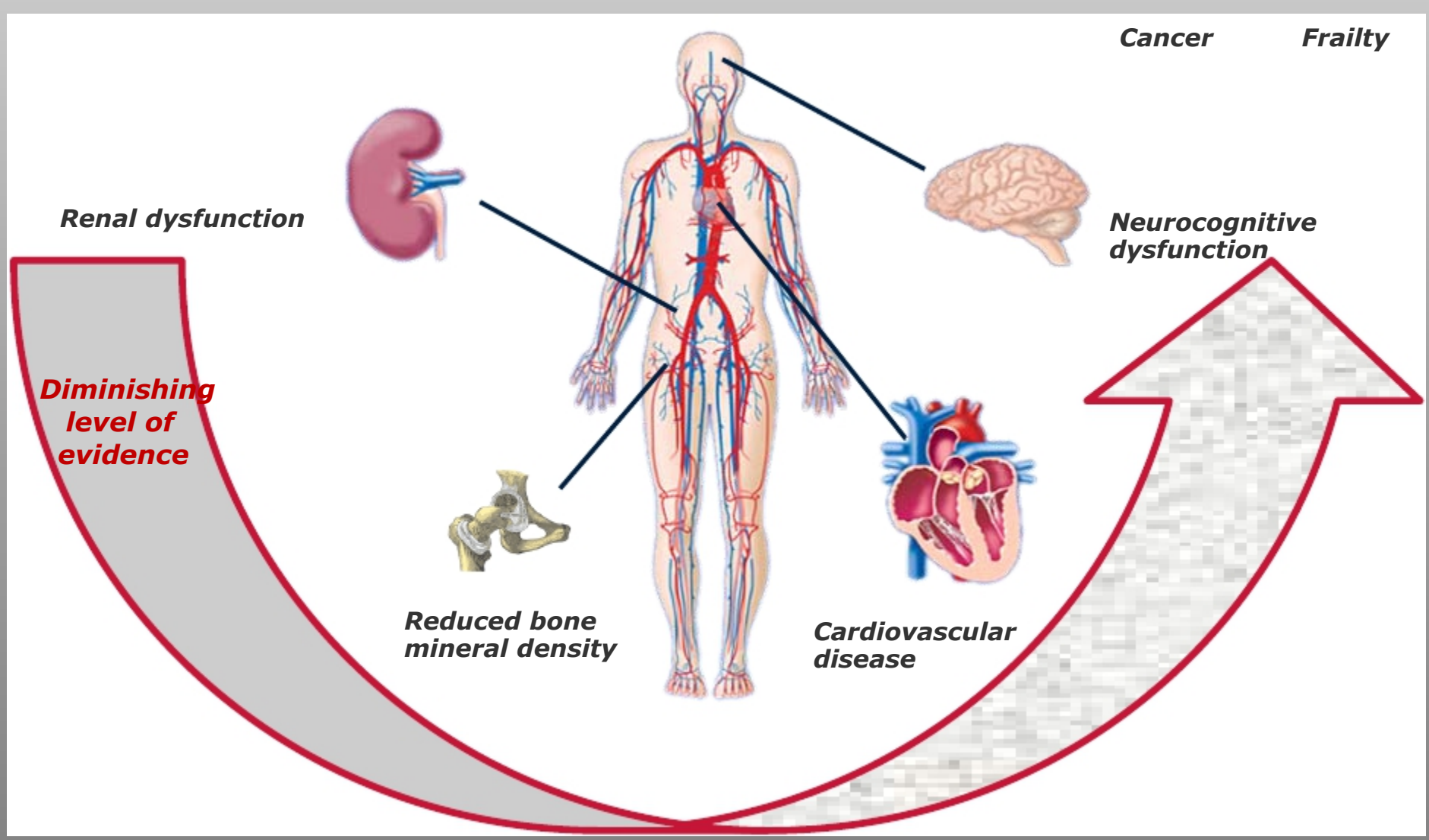
- Poor adherence leads to viral rebound and immune system impairment (Cysique and Brew, 2009), both risk factors for HAND.
- Vice versa, cognitive decline leads to poor adherence (Becker et al., 2011).
- One study showed significant cognitive improvement in 167 HIV-positive individuals with stable immune function and STI over almost 2 years.
- There is one MRS-study on 18 individuals (Schweinsburg et al., 2005) showing a neurotoxic long-term effect of cART; but almost all treatment combinations contained d4T and ddI, drugs which aren´t merely given anymore because of their mitochondrial toxicity.

Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ, Letendre S, Videen JS, McCutchan JA, Patterson TL, Grant I; HNRC Group. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol. 2005 Aug;11(4):356-64.

Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review. Neuropsychol Rev. 2009 Jun;19(2):169-85.

Becker BW, Thames AD, Woo E, Castellon SA, Hinkin CH. Longitudinal change in cognitive function and medication adherence in HIV-infected adults. AIDS Behav.2011;15(8):1888-94.

Toxicity of ART



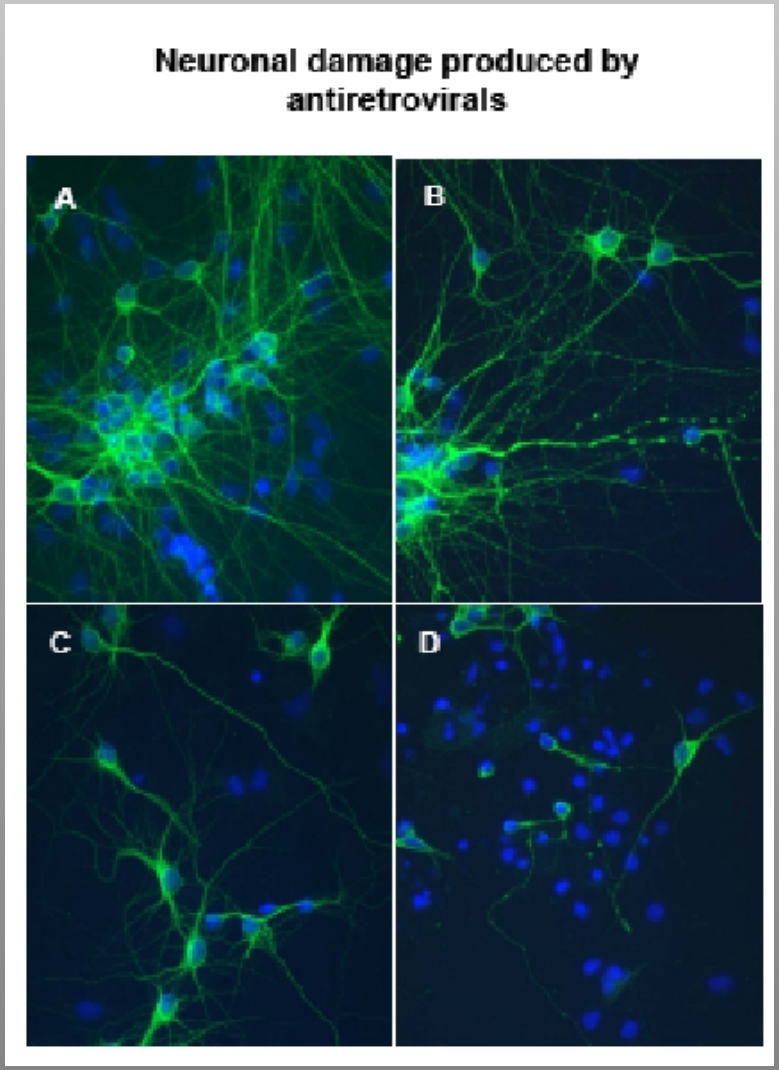
Modified according to A.Winston, HANSA, 2012

Evidence for antiretroviral toxicity

Drug Class	Class Toxcities	Specific Toxcities
NRTIs	• Mitochondrial toxicity	• Cardiovascular disease • Renal disease
NNRTIs	• Neuropsychiatric events	• Neuropsychiatric events • Depression
PIs	• Effects on lipids • Enzyme inhibition	• Cardiovascular
Entry Inhibitors		• Postural hypotension • Injection site reactions
Integrase Inhibitors		• Cerebellar ataxia • Depression • Psychomotor agitation

Modified according to A.Winston, HANSA, 2013

Neuronal damage and ART



Neurons stained for microtubule-associated protein-2 (MAP-2):

- (A) normal untreated cultures
- (B) dendritic beading
- (C) pruning of dendrites
- (D) loss of neuron density

Following 6 days exposure to ARVs at reported plasma concentrations:

- (B) and (C) cultures treated with atazanavir
- (D) maximal damage seen with efavirenz

Robertson K, J Neurovirol. (2012) 18:388-399

DHHS 2015 Guidelines

Recommended Regimen Options in Treatment-Naïve Adults (AI*)

Recommended regimens are those studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

CLASS	REGIMEN		LIMITATIONS
Integrase Inhibitor	EVG/COBI/FTC/TDF		pre-ART CrCl ≥70 mL/min
	DTG/ABC/3TC†		HLA-B*5701 negative
	DTG	FTC†/TDF	
	RAL (BID)	FTC†/TDF	
Boosted Protease Inhibitor	DRV + RTV	FTC†/TDF	

* All ARV regimens in this table have a rating of AI, which indicates strong data from randomized controlled trials
† 3TC may substitute for FTC or vice versa

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. April 8, 2015. Available at: http://www.aidsinfo.nih.gov/Guidelines

DHHS 2015 Guidelines
Alternative Regimen Options in Treatment-Naïve Adults

Effective and tolerable but have potential disadvantages, limitations for use in certain patient population, or less supporting data than Recommended regimens. An Alternative regimen may actually be the optimal regimen in a specific patient.

CLASS	REGIMEN		LIMITATIONS	RATIONALE
NNRTI	EFV/FTC*/TDF		-	Tolerability concerns, especially high CNS toxicity rates, possible suicidality association†
	RPV/FTC*/TDF		pre-ART HIV RNA <100,000 c/mL & CD4 count >200 cells/mm^3	Has limitations for use in certain patient population
Boosted Protease Inhibitor	ATV + COBI	FTC*/TDF	pre-ART estimated CrCl ≥ 70 mL/min	Cobicistat added to alternative category
	ATV + RTV	FTC*/TDF	-	Greater toxicity rate vs. DRV+RTC or RAL plus FTC/TDF (A5257)
	DRV + RTV/COBI	ABC/3TC*	HLA-B*5701 negative	Cobicistat added to alternative category
	DRV + COBI	FTC*/TDF	pre-ART estimated CrCl ≥ 70 mL/min	Cobicistat added to alternative category

* 3TC may substitute for FTC or vice versa
† Observed in one analysis of 4 clinical trials – Mollan KR, et al. Ann Intern Med 204;161(1):1-10

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. April 8, 2015. Available at: http://www.aidsinfo.nih.gov/Guidelines

Cofactors (4)

- **Biomarkers hypothesized to correlate with HAND**
- High CSF neopterin (Price and Spudich, 2008)
- High neurofilament light chain protein (NFL) (Price and Spudich, 2008)
- High monocyte chemoattractant protein 1 (MCP-1) (Arendt et al., 2007, Price and Spudich, 2008)
- High serum osteopontin (Brown et al., 2011)
- High IL-1, IL-6, TNF-alpha (Nolting et al., 2012)
- High plasma HIV DNA (Valcour et al., 2010)

Brown A, Islam T, Adams R, Nerle S, Kamara M, Eger C, Marder K, Cohen B, Schifitto G, McArthur JC, Sacktor N, Pardo CA. Osteopontin enhances HIV replication and is increased in the brain and cerebrospinal fluid of HIV-infected individuals. J Neurovirol. 2011;17(4):382-92.

Nolting T, Lindecke A, Hartung HP, Koutsilieri E, Maschke M, Husstedt IW, Sopper S, Stüve O, Arendt G; and the German Competence Network HIV/AIDS. Cytokine levels in CSF and neuropsychological performance in HIV patients. J Neurovirol. 2012

Price RW, Spudich S. Antiretroviral therapy and central nervous system HIV type 1 infection. J Infect Dis. 2008;197 Suppl 3:S294-306.

Valcour VG, Shiramizu BT, Sithinamsuwan P, Nidhinandana S, Ratto-Kim S, Ananworanich J, Siangphoe U, Kim JH, de Souza M, Degruttola V, Paul RH, Shikuma CM; Southeast Asia Research Collaboration with the University of Hawaii 001 protocol team. HIV DNA and cognition in a Thai longitudinal HAART initiation cohort: the SEARCH 001 Cohort Study. Neurology. 2009;72(11):992-8.

Cofactors (5)

- **Host genetics**
- Host candidate genetic variants for cognitive decline are located in:
- CCR2 and CCR5, MCP-1, TNF-alpha, mannose binding lectin-2 (MBL2), stromal cell-derived factor (SDF-1), interleukins and apolipoprotein E (APOE) and APOE e4 allele.
- In a prospective study in China (Spector et al., 2010) only APOE e4 and MBL2 were associated with cognitive decline over time.
- **Viral genetics**
- Candidate genes for cognitive decline are:

  Variants in CD4-binding site of env (Dunfee et al., 2007), Tat and Vpr as well as LTR sequence diversity (Jayadev and Garden, 2009)

Spector SA, Singh KK, Gupta S, Cystique LA, Jin H, Letendre S, Schrier R, Wu Z, Hong KX, Yu X, Shi C, Heaton RK; HNRC Group. APOE epsilon4 and MBL-2 O/O genotypes are associated with neurocognitive impairment in HIV-infected plasma donors. AIDS. 2010;24(10):1471-9.

Dunfee RL, Thomas ER, Wang J, Kunstman K, Wolinsky SM, Gabuzda D. Loss of the N-linked glycosylation site at position 386 in the HIV envelope V4 region enhances macrophage tropism and is associated with dementia. Virology. 2007;367(1):222-34.

Jayadev S, Garden GA. Host and viral factors influencing the pathogenesis of HIV-associated neurocognitive disorders. J Neuroimmune Pharmacol. 2009;4(2):175-89.

Viral DNA levels and viral subtypes

- Viral subtype B (Australia, Europe, USA) and C (South Africa, India) seem to provoke the same percentage of HAND.
- There are contradictory results with respect to subtype A and D (Uganda).
- There are no studies directly comparing subtypes A, B, C and D.

Cofactors (6)

- **Others**
- History of higher grade traumatic brain injury (Heaton et al., 2010)
- Vitamin or hormone deficiency
- Vascular risk factors

Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I; CHARTER Group; HNRC Group. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011;17(1):3-16.

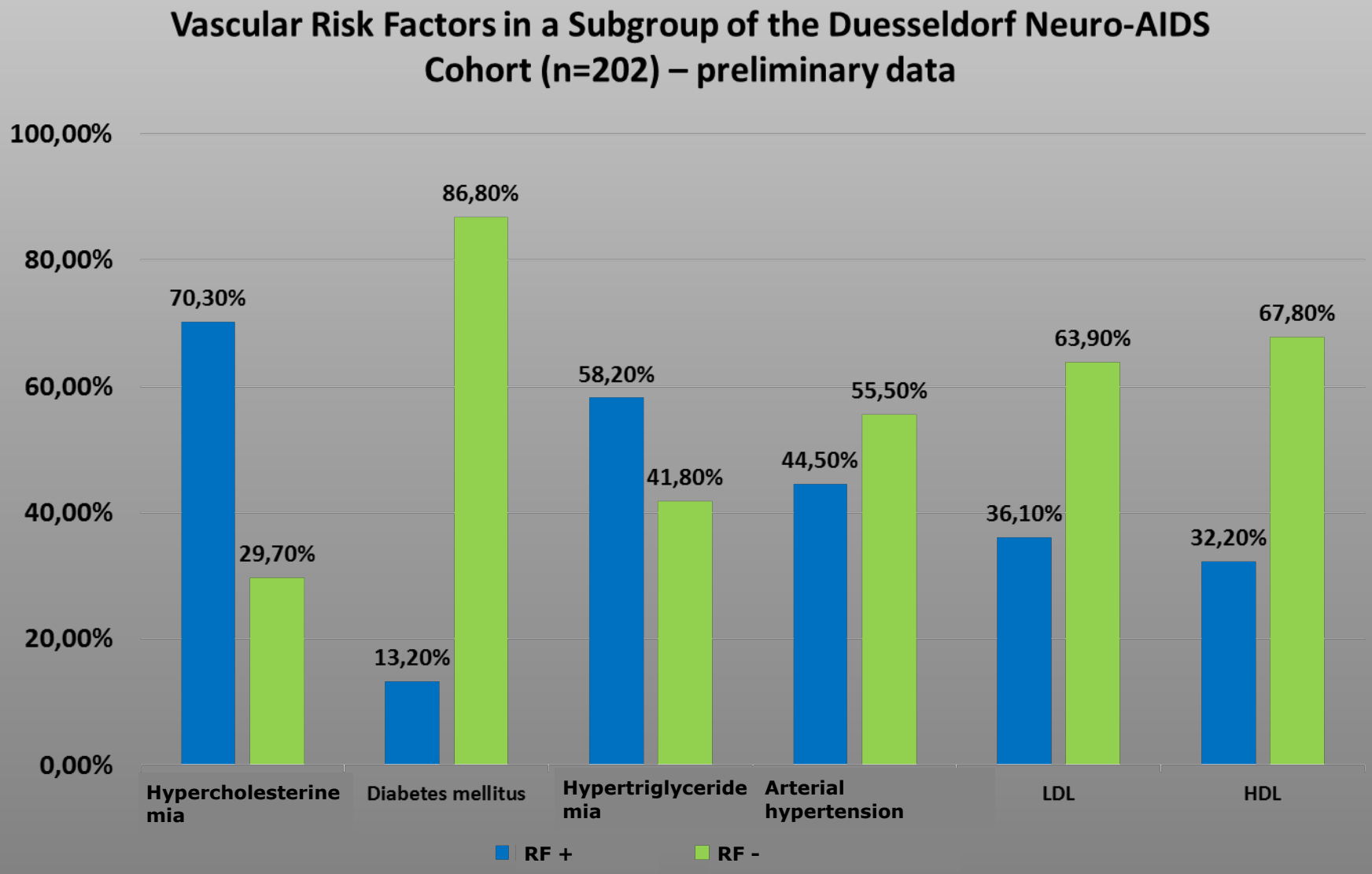
Vascular Risk Factors (1)

- Overweight (-)
- Smoking (+++)
- Diabetes (++)
- Arterial Hypertension (+)
- Hypercholesterinemia/Hypertriglycerid-emia (+++)

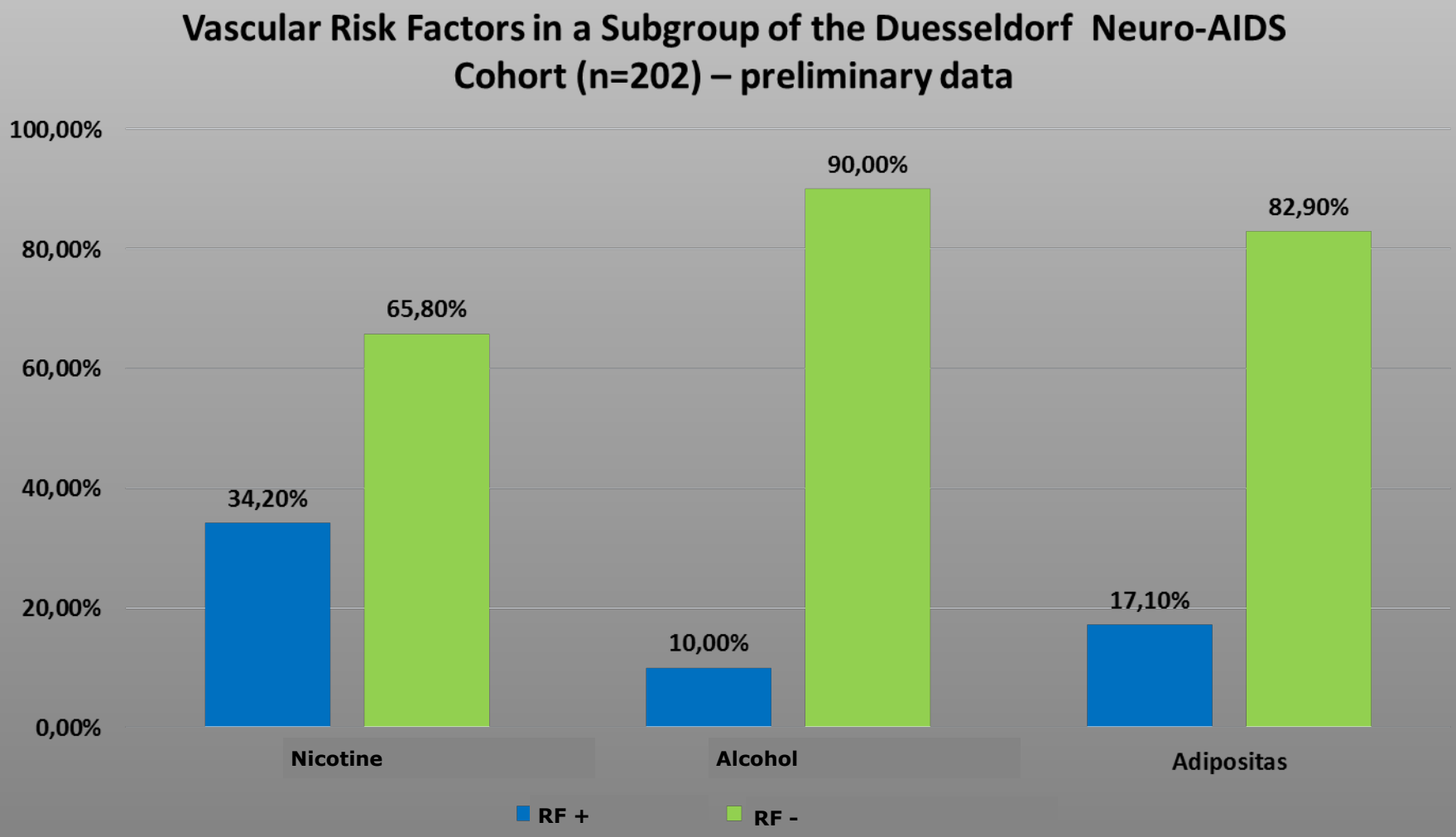
= metabolic syndrome

- Alcohol abuse (+)

Vascular Risk Factors



Vascular Risk Factors



Comorbidities

- Psychiatric Diseases
- Drug- und Alcohol Dependency
- **Hepatitis-Virus-C-Co-Infection**
- **Syphilis**

Hepatitis Virus C-Co-Infection(1)

- Chronic liver disease among HIV-infected patients is rising in incidence and prevalence (Thio et al., Lancet, 2002).
- Hepatitis-virus B (HBV)- und C (HCV) provoke – as HIV – nervous system diseases.
- Study results regarding „addition" of viral effects on the nervous system are contradictory.
- **No additive effects**: Hilsabeck et al., Hepatology, 2005, Perry et al., AIDS, 2005, Thein et al., AIDS, 2007
- **Additive Effects**: Letendre et al., J Neurovirol/Suppl, 2002, Martin et al., J Internat Neuropsychol Soc, 2004, von Giesen et al., J Neurpsychiatry Clin Neurosci, 2004, Ryan et al., Neurology, 2004

Hepatitis Virus-C-Co-Infection (2)

- Hepatitis Virus B (HBV) causes nervous system damage by:
- Metabolic disease
- Co-existing alcohol and/or drug abuse

- Hepatitis virus C (HCV) causes nervous system damage by:
- Neurotropism
- Vasculitis
- Metabolic disease
- Co-existing drug abuse

Hepatitis Virus C-Co-Infection (3)

- HCV is an enveloped, positive strand RNA virus of the Flaviviridiae family.
- HCV infects both hepatic and lymphatic cells.
- Associated disorders are: renal, endocrine, dermatological, cardiovascular, rheumatologic and ***central nervous system*** diseases.
- CNS symptoms do not correlate with the severity of liver disease and are independent from hepatic encephalopathy.
- HCV RNA has been found in CNS tissue and there are reports on viral sequence diversity between brain and liver suggesting independent evolution in both organs.

Hepatitis Virus C-Co-Infection (4)

- Human brain endothelial cells express functional receptors that support HCV entry and replication (Fletcher et al., *Gastroenterology*, 2012).

- HCV genomic sequences have been detected in the cerebrospinal fluid (CSF) of HIV-patients which raises the possibility that the CNS may act as a reservoir also for HCV (Morsica et al., *J Med Virol*, 1997)

Hepatitis Virus C-Co-Infection (5)

- HCV immunoreactivity was detected in astrocytes and macrophage-microglial cells.
- Hypothesis: HCV traffics into the HIV-infected brain where it might lead to a productive coinfection.
- Letendre et al., *J Infect Dis*, 2005

Hepatitis Virus C-Co-Infection (6)

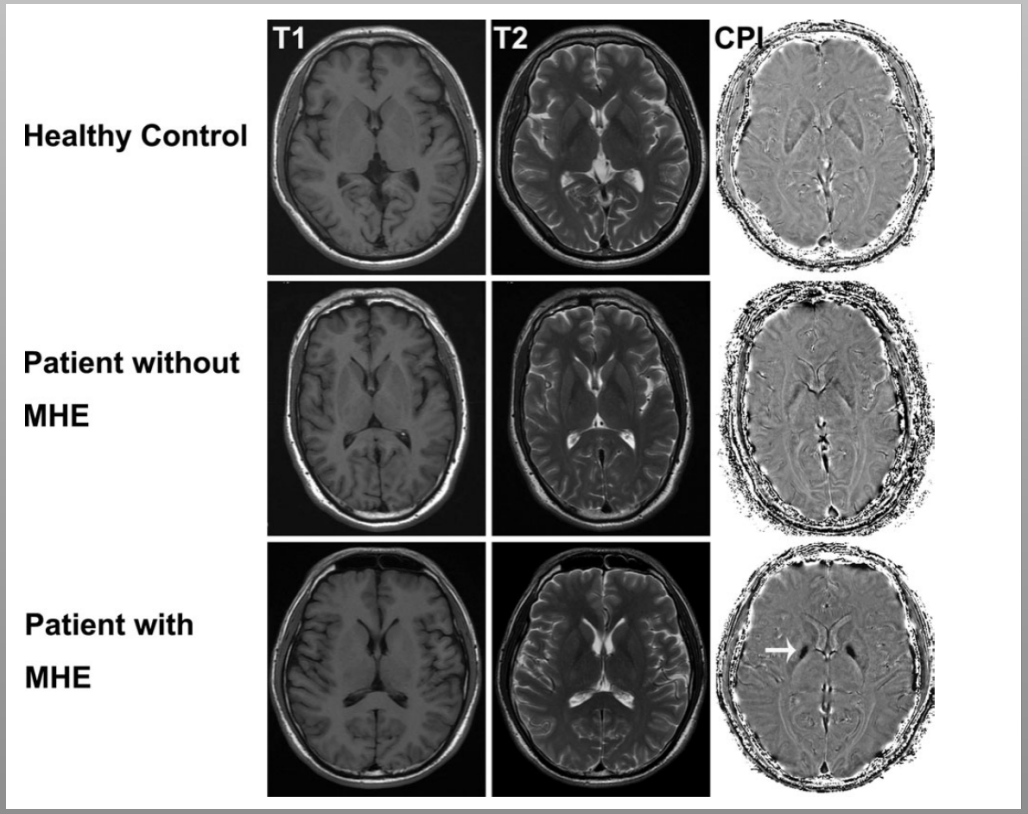
- The HCV core protein is neurotoxic.
- HCV leads to a sustained activation of the extracellular signal-related kinase (ERK)
- It is hypothesized that HCV core protein neurotoxicity may be mediated by the sustained activation of ERK and the signal transducer and activator of transcription (STAT3) via toll-like receptor 2 (TLR2)-signaling pathway.
- Paulino et al., *J Neurovirol,* 2011

Hepatitis Virus C –Co-Infection (7)

- HCV is one of the major causes of cryoglobulins, causing systemic cryoglobulinemic vasculitis.
- Main associated factors are: female gender, alcohol intake > 50 g/day, extensive liver fibrosis and steatosis.
- Cryoglobulinemic vasculitis is associated with older age, longer duration of infection and characteristics of cryoglobulins (type II, IgM kappa).
- Cacoub et al., *Clin Rev Allergy Immunol*, 2008

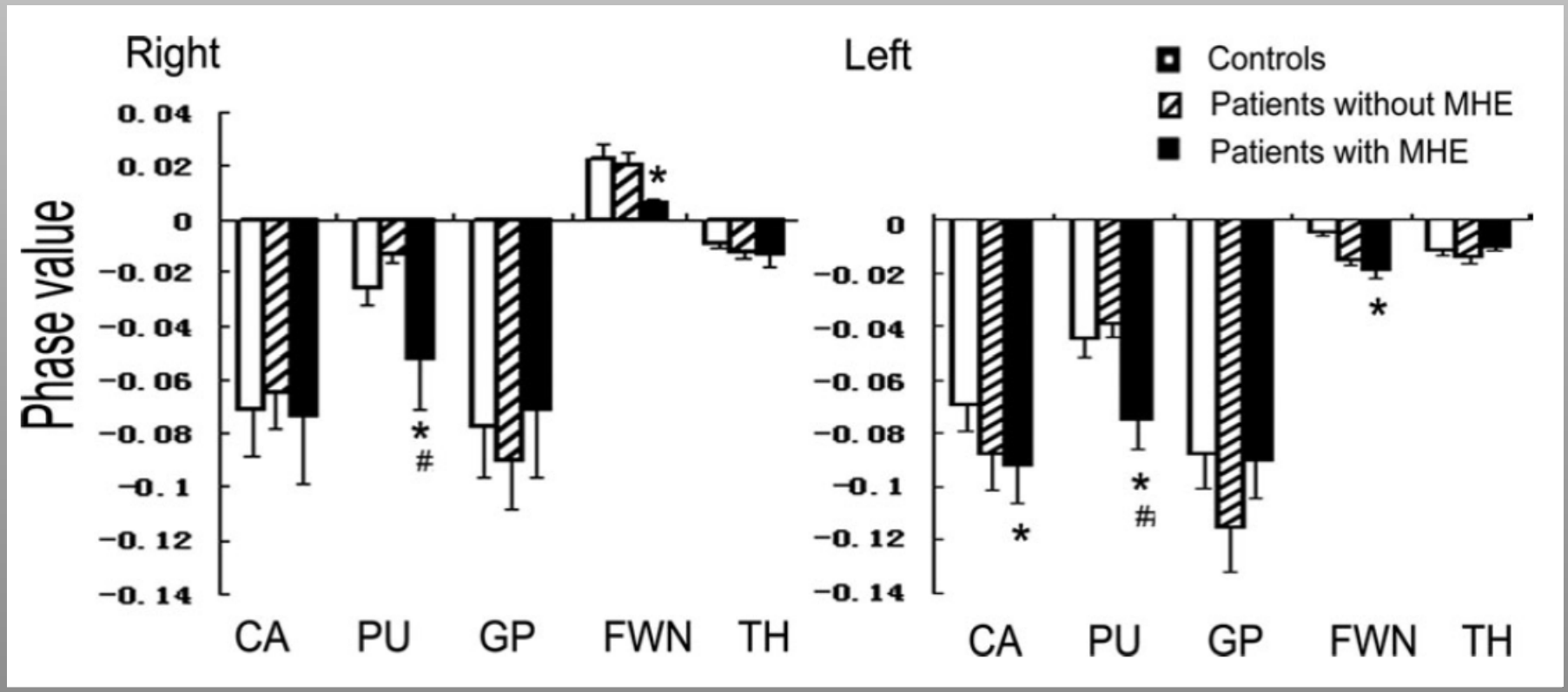
Hepatitis Virus C-Co-Infection (8)

Figure 1. MRI images in patients with minimal hepatic encephalopathy (MHE), without MHE and a healthy control. Representative images of T1-weighted, T2-weighted, and corrected phase image (CPI) of the frontal–basal ganglia–thalamocortical circuits from a 47-year-old healthy control (upper raw), a 47-year-old cirrhotic patient without MHE (middle raw) compared with a 50-year-old cirrhotic patient with MHE. No signal changes were found among three individuals on both T1 weighted and T2 weighted images. Significant iron deposition (arrow, globus pallidus) could be found only on the CPI image in patient with MHE.



T2* MRI of Minimal Hepatic Encephalopathy and Cognitive Correlates In Vivo Liu J-Y.et al., J Magn Res Imaging, 2013, Vol. 37, 179-186

Hepatitis Virus C-Co-Infection (9)



T2* MRI of Minimal Hepatic Encephalopathy and Cognitive Correlates In Vivo
Liu J-Y.et al., J Magn Res Imaging, 2013, Vol. 37, 179-186

HCV Eradication Treatment and Cognition (11)

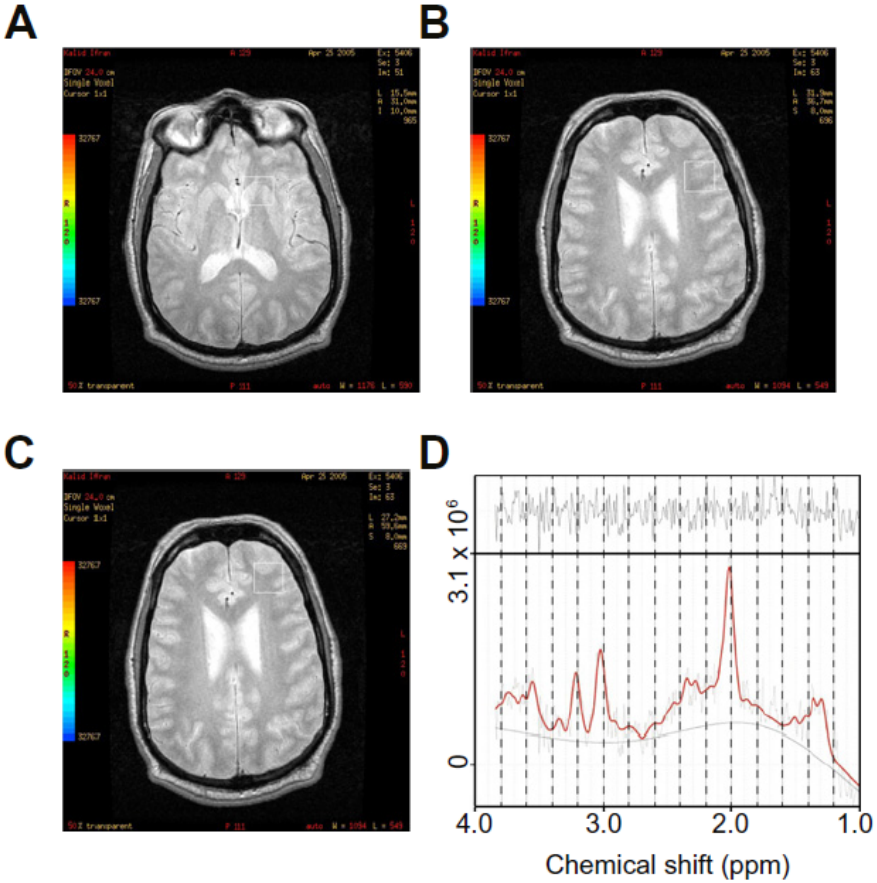


Fig. 1. MRS showing voxel positioning in the basal ganglia (A), left frontal cortex (B), left dorsolateral prefrontal cortex (C) and spectral analysis (D).

Byrnes, Valerie et al.: Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition J Hepatol 2012, vol 56:549-556

HCV Eradication Treatment and Cognition (12)

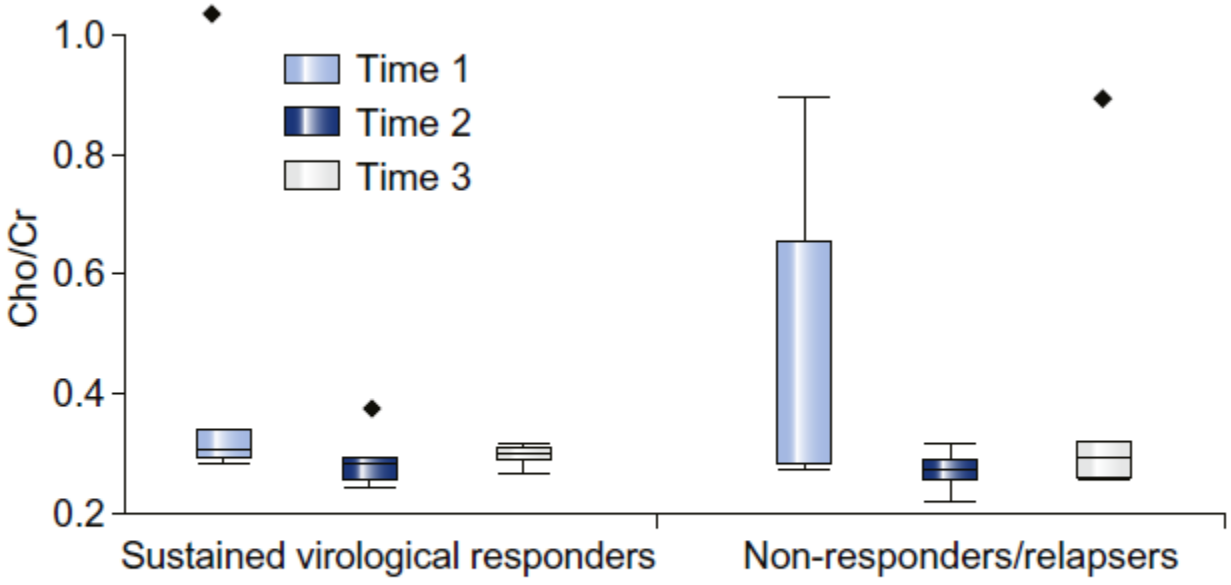


Fig. 2. MRS showing basal ganglia choline/creatine ratios across study time points for sustained virological responders and non-responders/relapsers.

Byrnes, Valerie et al.: Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition J Hepatol 2012, vol 56:549-556

HCV Eradication Treatment and Cognition (13)

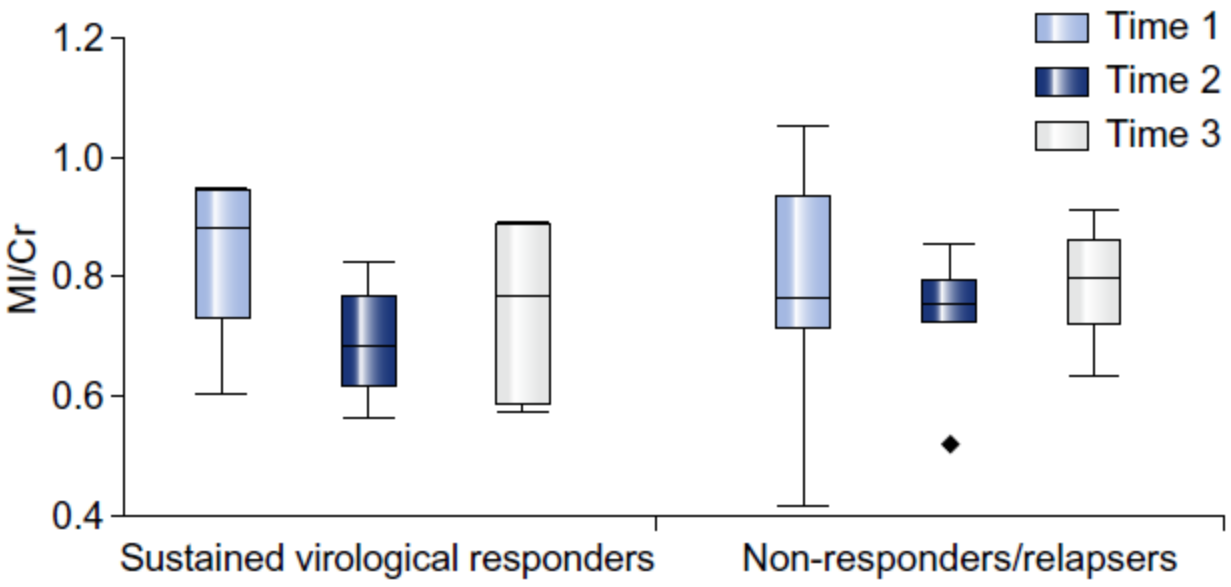


Fig. 3. MRS showing basal ganglia myo-inositol/creatine ratios across study time points for sustained virological responders and non-responders/ relapsers.

Byrnes, Valerie et al.: Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition J Hepatol 2012, vol 56:549-556

Hepatitis-Virus C-Co—Infection (10)

- HCV eradication has a beneficial effect on cerebral metabolism and selective aspects of neurocognitive function and is an important factor when contemplating antiviral therapy in HCV.

Byrnes V et al., J Hepatol, 2012

Hepatitis Virus C-Co-Infection (14)

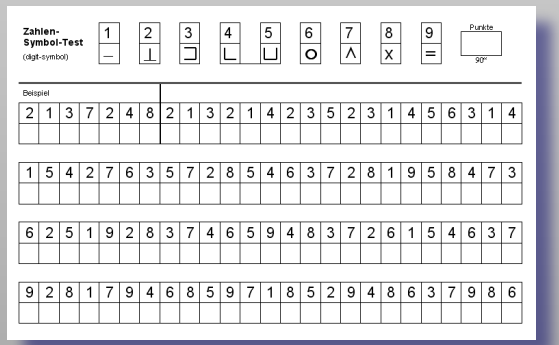
- **Classic eradication treatment in HCV-Co-Infection:**
- Interferon-Alpha + Ribavirine
- Boceprevir – NS3/4A-Protease-Inhibitor
- Telaprevir – NS3/4A Protease-Inhibitor
- **Modern eradication treatment:**
- Daclatasvir – HCV-NS5A-Inhibitor
- Dasabuvir – HCV-Polymerase-Inhibitor
- Ledipasvir – HCV NS5A-Inhibitor
- Simeprevir – HCV-Protease-Inhibitor
- Sofosbuvir – HCV-Polymerase

Hepatitis-Virus C-Co-Infection (15)

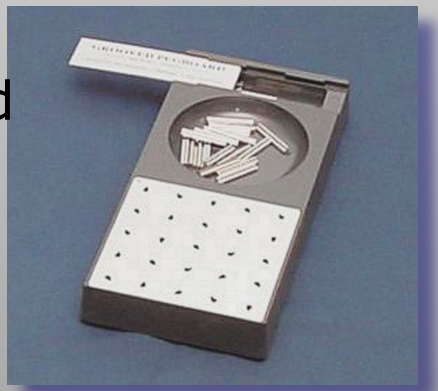
- Results of von Giesen et al., 2004, revealed that Hepatitis-Virus C provokes deterioration of motor performance, especially of reaction times, whereas another motor parameter, contraction time, is prolonged in HIV and HIV/ HCV co-infected individuals.
- Furthermore, the data showed that motor deterioration is not linked to metabolic abnormalities.

Neuropsychological tests for HAD and its precursor stages (ANI, MNCD)

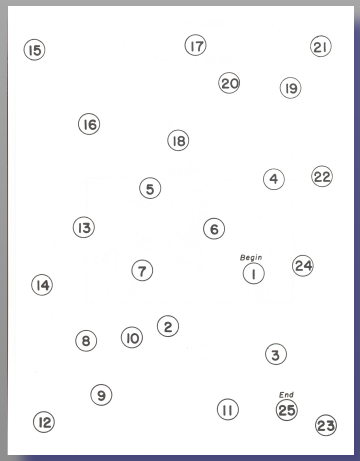
Digit symbol test



Grooved pegboard



Trail-making test 1+2



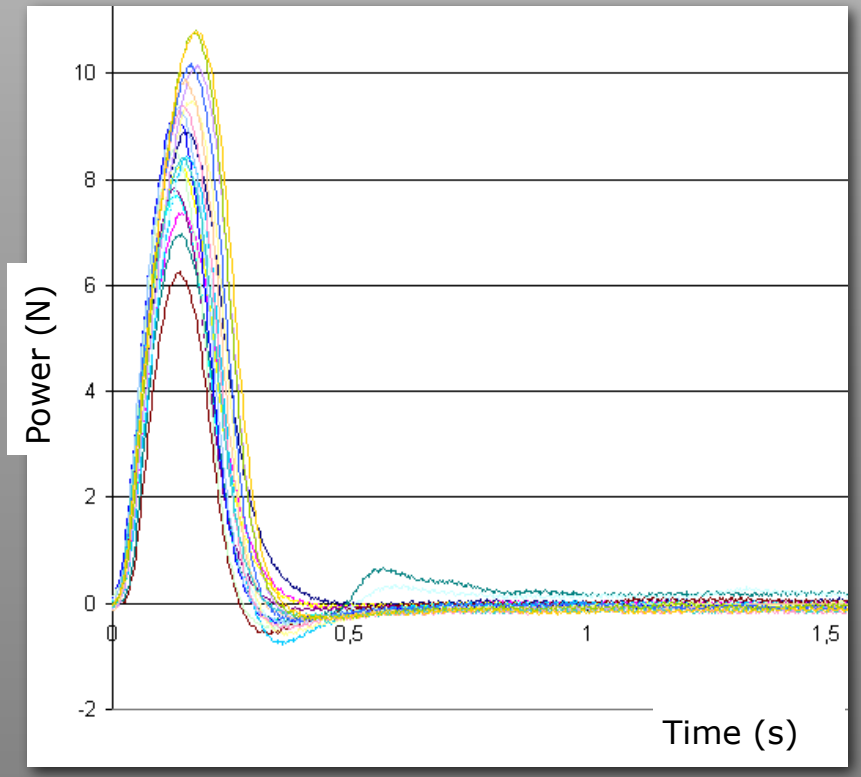
Motor Test Battery, Arendt et al., 1990

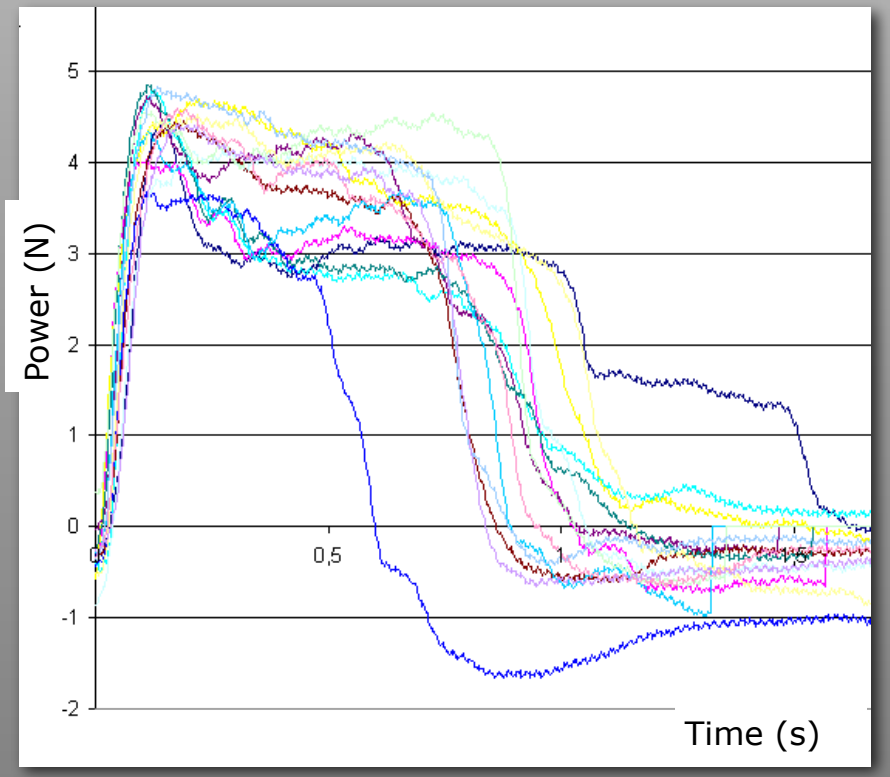
ANI = Asymptomatic Neurocognitive Disorder
MCND = Mild Neurocognitive Disorder
HAD = HIV-Associated Dementia

Fine Motor Testing

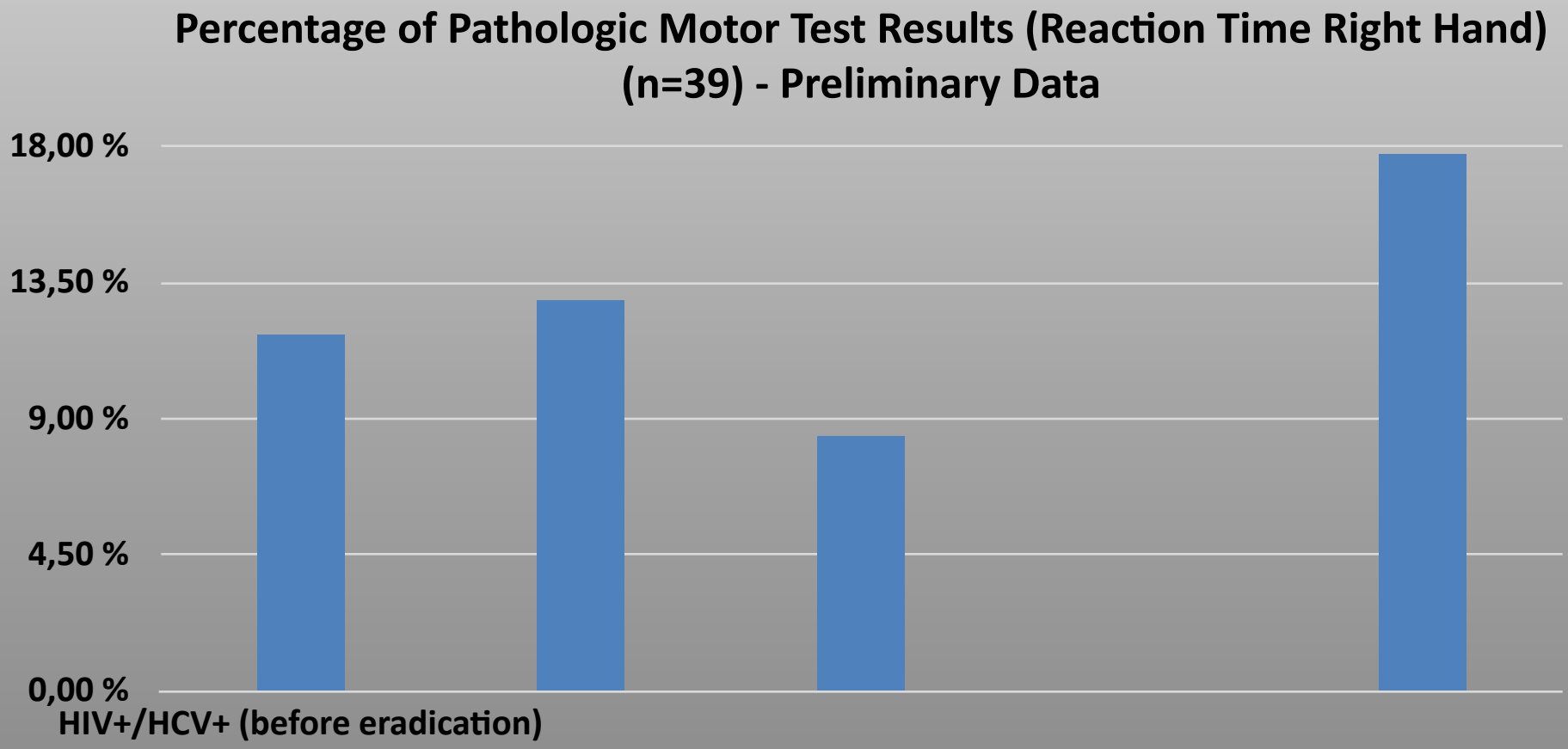
Most Rapid Index Finger Extensions (MRC):

- Reaction time (RT)
- Contraction time (CT)

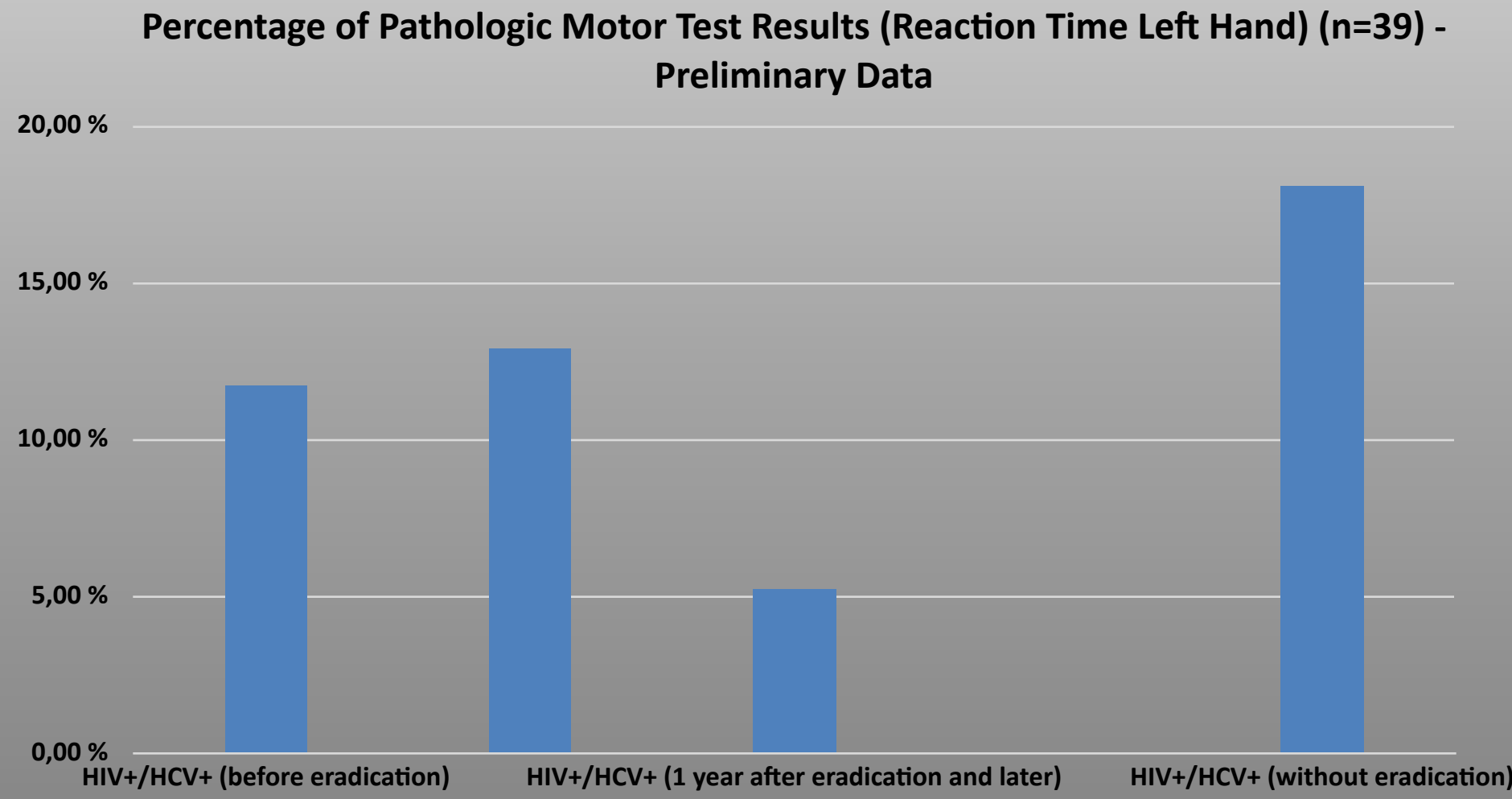




HCV Eradication Treatment and Cognition (16) – Preliminary Results from the Düsseldorf Cohort



HCV Eradication Treatment and Cognition (17) – Preliminary Results from the Düsseldorf Cohort



Neurosyphilis

Definite Neurosyphilis	Probable Neurosyphilis	Possible Neurosyphilis
positive Treponema-tests (TPPA und FTA-Abs) in blood and cerebrospinal fluid (CSF)	positive Treponema-Tests in blood and cerebrospinal fluid	positive Treponema-Tests in blood and cerebrospinal fluid
positive VDRL-Reaction in blood and cerebrospinal fluid	negative cerebrospinal fluid-VDRL-Reaction	negative cerebrospinal fluid-VDRL-Reaction
	lympho-monocytic CSF-pleocytosis and/or protein elevation	lympho-monocytic CSF-pleocytosis and/or protein elevation
	neurological complications pointing to Neurosyphilis as cranial nerve palsies, strokes or ophthalmological symptoms	no neurological or ophthalmological complications pointing to Neurosyphilis

Mdified after Marra C et al., 1992

Summary

- Differentialdiagnosis and modern treatment in HIV-positive patients must take into account multiple ***co-factors*** and ***co-morbidities*** and thus, will be challenging HIV specialists in the nearer future.