Influence of Hepatits Virus B and C as Co-Factors for Neurocognitive Disease in HIV-Infected Patients

- **7th International Symposium on Neuropsychiatry and HIV, Barcelona, June, 2014**
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Introduction (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*

Introduction (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 B (1)

- HBV provokes virus-related cirrhosis and in parallel primarily neurocognitive dysfunction (minimal hepatic encephalopathy = MHE),but no overt hepatic encephalopathy.
- MHE is present in 30-84% of cirrhotic patients who show normal neurological and mental status on standard clinical examinations, but exhibit deficits when tested neuropsychologically and impairment in daily functioning (*Groeneweg et al., Hepatology, 1998*).

Hepatitis Virus B (2)

- Minimal hepatic encephalopathy (MHE) typically affects psychomotor and executive function while other cognitive abilities are relatively preserved *(Amodio et al., J Hepatol, 2008).*
- Cirrhotic patients with MHE more frequently develop episodes of overt encephalopathy then those without *(Hartmann et al., Am J Gastroenterol, 2000)*.

Hepatitis Virus B (3)

- The mechanisms underlying MHE are still unclear, but there is an implicit role of the prefrontal cortex and its connections with the basal ganglia-thalamic circuits.
- Abnormal iron and manganese metabolism is discussed as a cause for MHE.

Hepatitis Virus B (4)

- Neuropsychological tests (psychometric hepatic encephalopathy score= PHES) usually applied to MHE patients are:
  - **Number Connection Test-A (NCT-A)** – measures cognitive/motor abilities, time needed to connect numbers from 1 to 25, time > 2 SD from that of controls is considered to be abnormal
  - **Letter Digit Substitution Test (LDST)** – measures executive functions, replacement of randomized letters with the appropriate digit indicated by a key, the score is the number of correct substitutions made in 60 s
  - **Rey-Osterrieth Complex Figure Test (RCFT)** – measures non-verbal memory, immediate (3 min.)and delayed (30 min.) recall
  - **Mini-Mental State Examination (MMSE)** – meausures overall cognitive stauts, 19 scored items, scores ranging from 0-30, <26 considered abnormal, duration: 10 min
  - **Critical Flicker frequency (CFF)** (Kircheis et al., *Gastroenterology*, 2014)

Hepatitis Virus B (5)

- Resting state functional MRI: amplitude of low-frequency fluctuation = ALFF)
- (Lu et al., *Metab Brain Dis* 2013, 28(3): 485-492):

- Abnormal neuronal activity in:
- ***Visual association*** areas
- ***Motor related*** areas

Hepatitis Virus C (1)

- 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 (2)

- 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 (3)

- 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 (4)

- 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 (5)

- 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 (6)

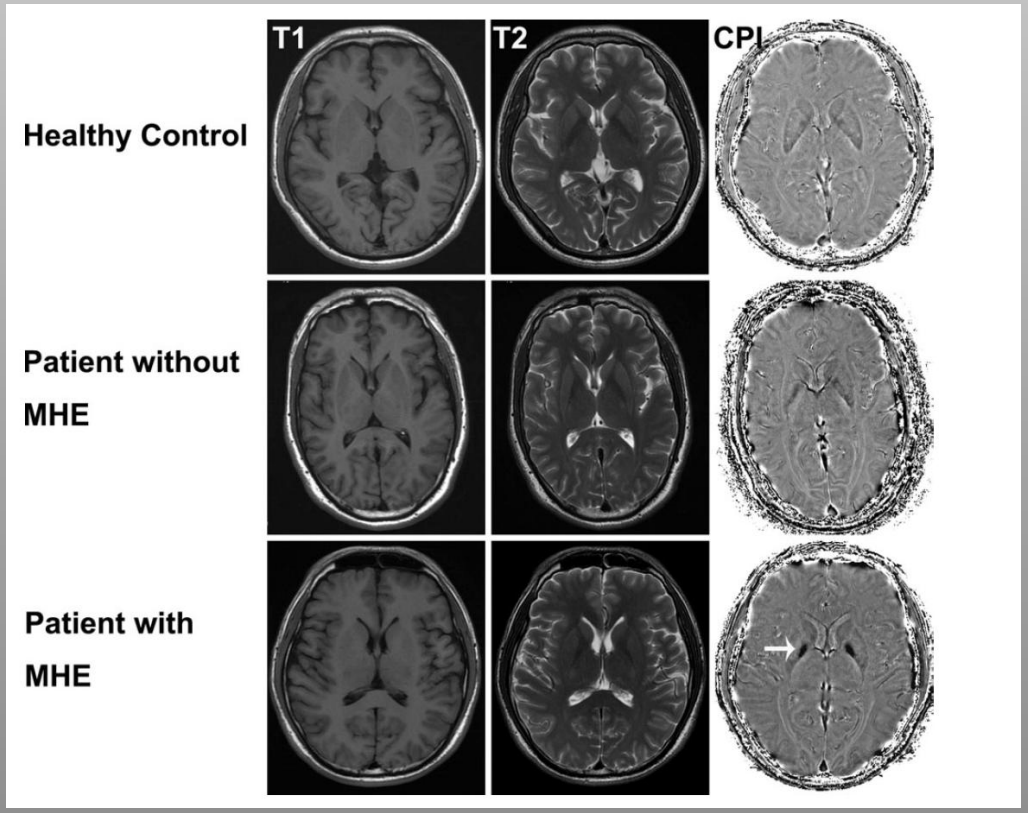
- Clifford et al., *Neurology*, 2009: Clinically significant neurocognitive dysfunction and peripheral neuropathy were ***not*** exacerbated by active hepatits C virus infection in the setting of optimally treated HIV infection.
- Letendre et al., *AIDS*, 2005: HIV, HCV and methamphetamine independently injure the CNS. HCV may injure the brain by viral or immune-mediated mechanisms.

Hepatitis Virus C (7)

- 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 et al., *J Hepatol*, 2012

Hepatitis Virus C (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 (9)

Table 1
Demographic and Clinical Characteristics and Cognitive Performances of Study Participants

	Patients with MHE (n=28)	Patients without MHE (n=12)	Controls (n=22)
Age (years)	49.57±7.83	46.45±6.86	46.45±6.86
Sex male%	92.86(26/28)	91.67(11/12)	90.91(20/22)
Education (years)	10.46±3.17	11.08±3.09	10.45±3.16
LDST	21.68±6.84[b,d]	37.42±5.37	40.14±3.85
NCT-A	53.86±10.73[b,d]	27.67±6.08	26.73±4.12
MMSE	28.39±1.23	29.08±0.67	28.95±1.05
RCFT-copy	32.77±5.45	34.79±1.16	34.31±3.03
RCFT-immediate recall	18.75±8.34[a,c]	23.71±4.94	24.41±4.98
RCFT-delayed recall	17.68±7.92[a,c]	23.04±5.08	23.12±7.52

*Data were expressed in mean ± SD.
[a] $P < 0.05$ compared to controls.
[b] $P < 0.001$ compared to controls.
[c] $P < 0.05$ compared to patients without MHE.
[d] $P < 0.001$ compared to patients without MHE.
LDST = Letter Digit Substitution Test; MMSE = Mini Mental State Examination; NCT-A = Number Connection Test A; RCFT = Rey-Osterrieth Complex Figure Test.

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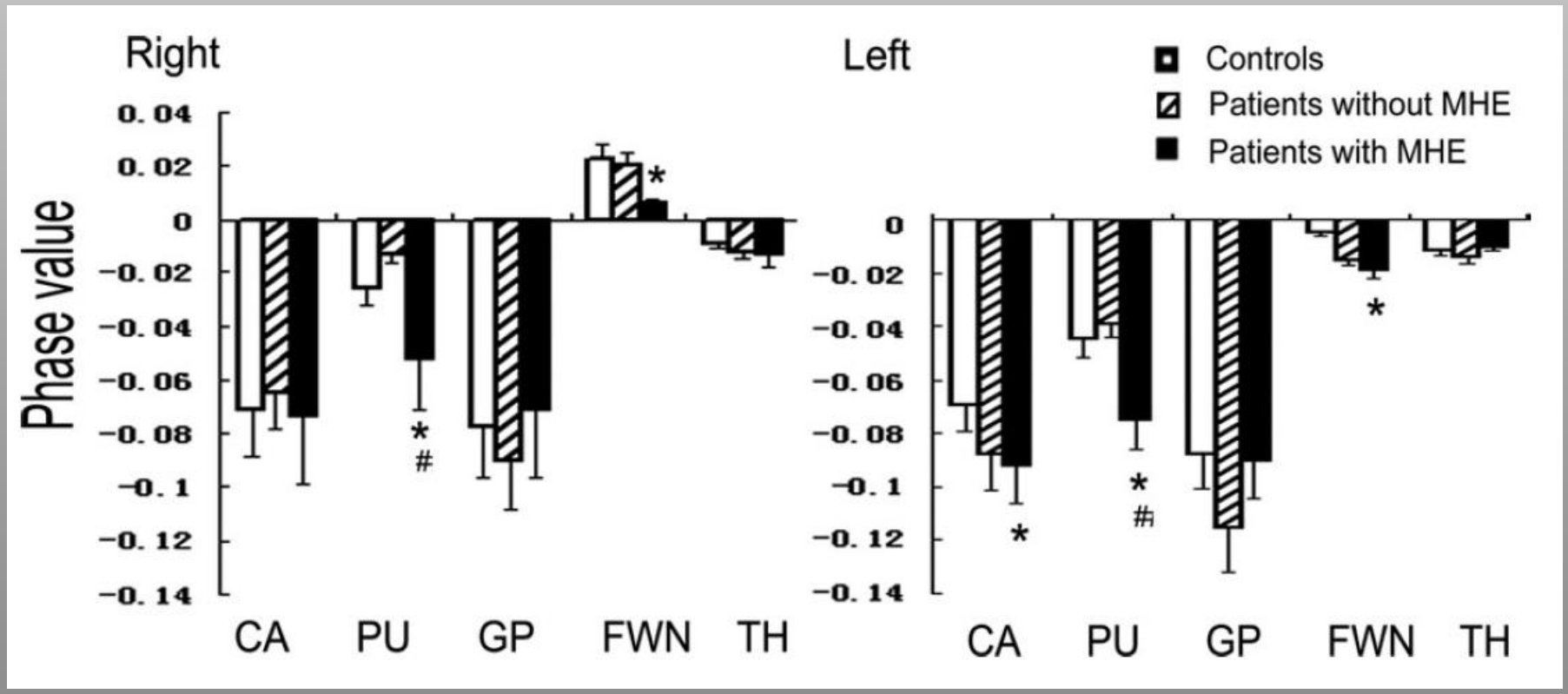
Hepatitis Virus C (10)



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Hepatitis Virus C (11)

Table 2
Spearman Correlation Between Age, Phase Values of the Frontal–Basal Ganglia–Thalamocortical Circuits, and Cognitive Performance in MHE Patients

		LDST		NCT-A		RCFT Immediate recall		RCFT Delayed recall	
		r	*P*	r	*P*	r	*P*	r	*P*
Age (years)		−0.491	0.008[a]	0.427	0.023[a]	−0.454	0.015[a]	−0.502	0.006[a]
Education (year)		0.328	0.088	−0.269	0.166	0.371	0.052	0.536	0.003[a]
TH	Right	0.190	0.332	−0.078	0.695	0.024	0.904	−0.056	0.776
	Left	0.064	0.746	0.077	0.696	0.028	0.887	0.008	0.967
CA	Right	0.345	0.073	−0.500	0.007[a]	0.220	0.261	0.074	0.708
	Left	0.129	0.514	−0.304	0.116	0.173	0.378	0.005	0.980
PU	Right	0.579	0.001[a]	−0.559	0.002[a]	0.687	0.000[b]	0.632	0.000[b]
	Left	0.658	0.000[b]	−0.655	0.000[b]	0.662	0.000[b]	0.627	0.000[b]
GP	Right	−0.033	0.869	−0.043	0.826	0.199	0.310	0.064	0.746
	Left	0.031	0.877	−0.097	0.624	−0.124	0.530	−0.238	0.222
FWM	Right	0.429	0.023[a]	−0.345	0.072	0.279	0.150	0.290	0.134
	Left	0.259	0.183	−0.231	0.236	0.289	0.136	0.172	0.382

CA = caudate; FWM = frontal white matter; GP = globus pallidus; LDST, Letter Digit Substitution Test; MHE, minimal hepatic encephalopathy; NCT, Number Connection Test A; PU = putamen; TH = thalamus.
[a] $P < 0.05$.
[b] $P < 0.001$.

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Hepatitis Virus C (12)

Table 3
Multiple Linear Regression Analysis Between Each Cognitive Performance and Age, Education, and Phase Values of Frontal–Basal Ganglia–Thalamocortical Circuits in MHE Patients

Independent determinant		LDST β	NCT-A β	RCFT immediate recall β	RCFT delayed recall β
Age		-[a]	-[a]	-[a]	-[a]
Education		-[a]	-[a]	-[a]	0.401[a]
TH	Right	-[a]	-[a]	-[a]	-[a]
	Left	-[a]	-[a]	-[a]	-[a]
CA	Right	-[a]	-[a]	-[a]	-[a]
	Left	-[a]	-[a]	-[a]	-[a]
PU	Right	-[a]	-[a]	0.687[c]	0.529[a]
	Left	0.637[c]	-0.638[c]	-[a]	-[a]
GP	Right	-[a]	-[a]	-[a]	-[a]
	Left	-[a]	-[a]	-[a]	-[a]
FWM	Right	0.394[a]	-0.311[a]	-[a]	-[a]
	Left	-[a]	-[a]	-[a]	-[a]

CA = caudate; FWM = frontal white matter; GP = globus pallidus; LDST, Letter Digit Substitution Test; MHE, minimal hepatic encephalopathy; NCT, Number Connection Test A; PU = putamen; TH = thalamus.
[a]Independent was excluded in this analysis.
[a]$P < 0.05$.
[c]$P < 0.001$.

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Hepatitis Virus C (7)

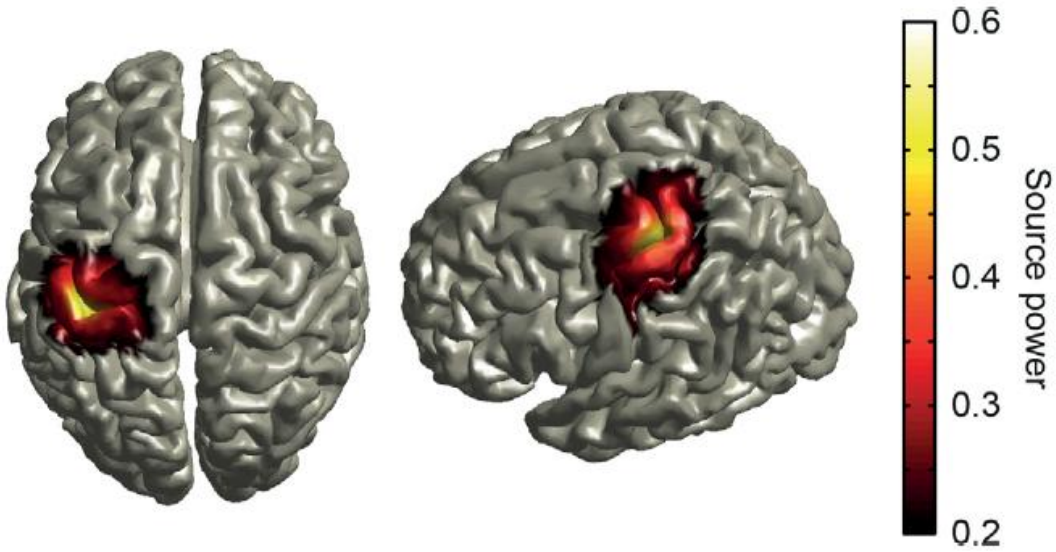

Fig. 1. Localization of evoked responses for virtual sensor analysis. Locations for the virtual sensor analysis were obtained from analysis of evoked responses to median nerve stimuli and were consistent with the primary somatosensory cortex contralateral to the stimulated hand. For visualization, individual maps of stimulus-evoked power increases were normalized by setting their maximum value to 1 and averaged across all subjects. This resulted in an average power increase with dimension-less values (color-coded). Values below 0.2 are masked. For each subject, the point of the individual maximum of the power increase was used as virtual sensor location. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Hepatic encephalopathy is associated with slowed and delayed stimulus-associated somatosensory alpha activity
May E. et al., Clinical Neurophysiology, 2014

Hepatitis Virus C (7)

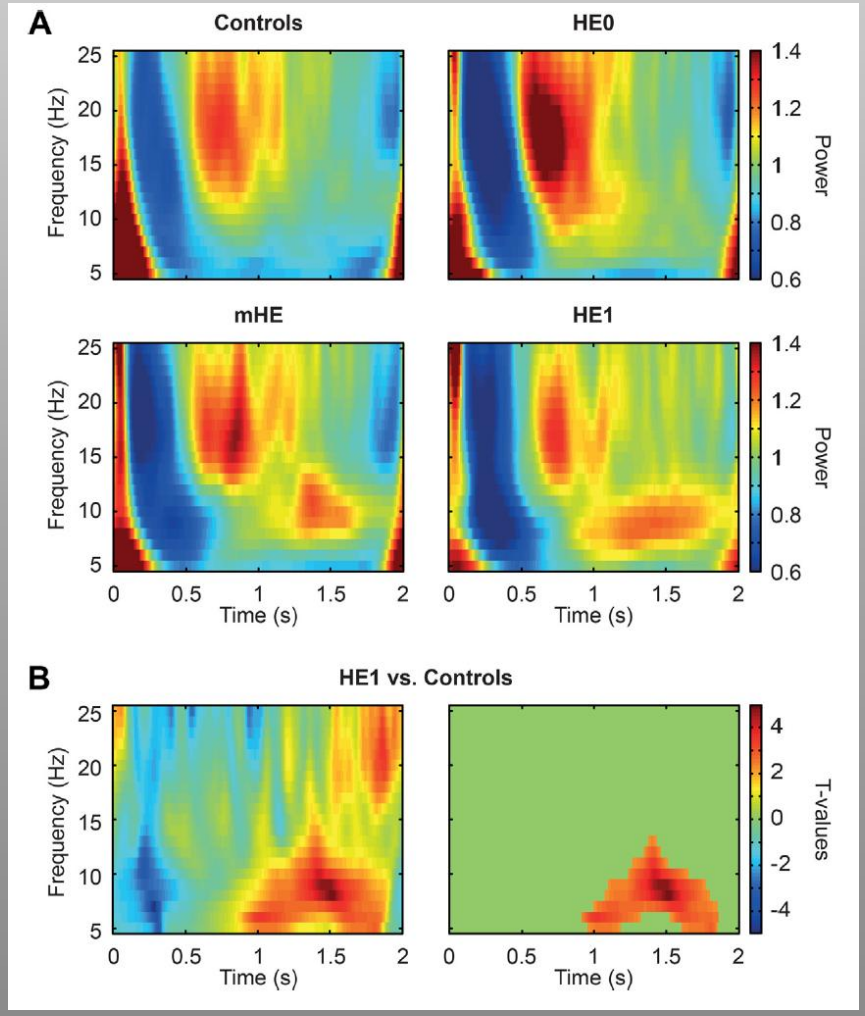

Fig. 2. Time–frequency representations and statistical results. (A) Virtual sensor time–frequency representations (TFRs) averaged across subjects in the four different subject groups (controls, HE0, mHE, HE1). Time point 0 represents the onset of the median nerve stimulus. The subsequent stimulus was administered at 2 s. Color-coded are power values expressed relative to the average power across the complete time interval (0 to 2 s). A value of 1 corresponds to the average power, while values higher than 1 indicate power above and values smaller than 1 power below average. (B) Statistical comparison of TFRs between the groups of HE1 patients and healthy control subjects. Color-coded are t-values quantifying the contrast between the two groups. Positive values indicate higher, negative values lower power for HE1 patients. In the left panel, t-values are shown for all time–frequency points. In the right panel, non-significant time–frequency points are masked. Statistical analysis revealed a significant cluster ($p < 0.01$) of increased alpha power in HE1 patients compared to healthy controls. This cluster extends from 5 to 15 Hz and between 0.9 and 1.9 s, indicating an increased and/or delayed alpha rebound in HE1 patients. HE0 = cirrhotic patients showing no signs of hepatic encephalopathy, mHE = minimal hepatic encephalopathy, HE1 = hepatic encephalopathy grade 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Hepatitis Virus C (7)

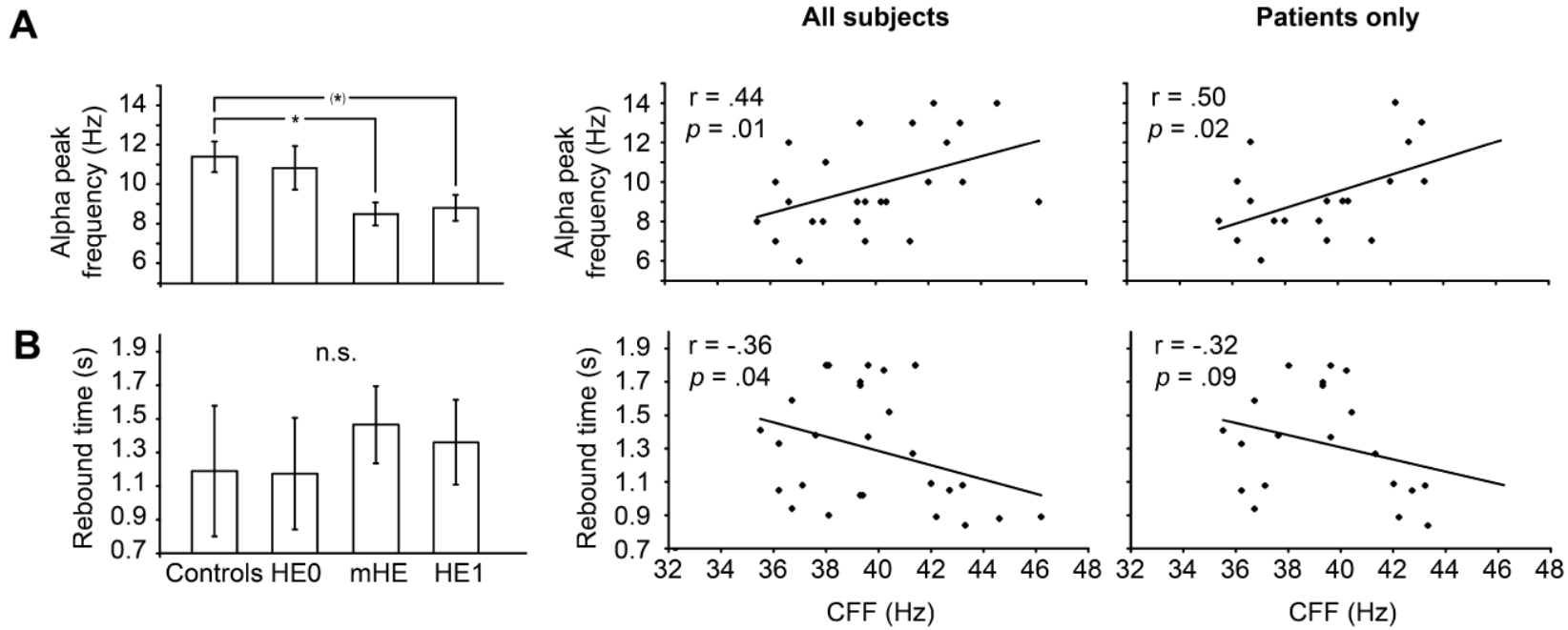

Fig. 3. Analysis of alpha peak frequencies and time of alpha rebound. (A) Left panel: Mean values of alpha peak frequencies for all four subject groups (controls, HE0, mHE, HE1). Error bars indicate the standard error of measurement. Analysis of variance and subsequent post hoc tests were performed to investigate group differences in alpha peak frequencies. Comparisons showing differences between groups are marked ($^{(*)}p < 0.1$, $^{*}p < 0.05$). Compared to healthy controls, statistics revealed lower alpha peak frequencies in mHE patients. Middle and right panel: correlation of the critical flicker frequency (CFF) with the alpha peak frequency for all subjects (middle panel) and patients only (right panel). Correlation coefficients and corresponding *p*-values are given within the figure. All correlation coefficients were corrected for effects of age. Correlations revealed that a lower CFF is associated with a lower alpha peak frequency. (B) Same as (A) but for the time of maximal alpha rebound, i.e. the time point of maximum alpha power between 0.7 and 1.8 s (n.s. = not significant). While no significant group differences were observed, an inverse correlation between the CFF and the time of alpha rebound for all subjects was revealed. Thus, a lower CFF was associated with a later alpha rebound. HE0 = cirrhotic patients showing no signs of hepatic encephalopathy, mHE = minimal hepatic encephalopathy, HE1 = hepatic encephalopathy grade 1.

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HIV neurobehavioural disturbances

HIV Associated Neurocognitive Disorders (HAND)

Primary HAND
- Asymptomatic neurocognitive impairment
- Mild neurocognitive disorder
- HIV-associated dementia

Secondary HAND
- Infection
- Neoplasia
- Cerebrovascular
- Nutritional
- Treatment related

Emotional & behavioral impact

New Onset
- Depression
- Anxiety
- Adjustment disorders
- HIV mania
- HIV psychosis

Pre-exist / recurrent / comorbid
- Mood disorders
- Substance use disorders
- Other mental disorders

Modified according to Igor Grant, San Diego

Short-Neuro-AIDS-Screening (SNAS) (1)

Key Questions 1

- Do you realise since more than 3 months concentration deficits in work or activities of daily living?

- Do you feel depressed since more than 3 months without any changes in your life or other obvious reasons?

- Do you feel tired during the day, although sleeping well at night?

- Do you have difficulties in sleeping for more than 3 months?

Short-Neuro-AIDS-Screening (SNAS) (2)

Key Questions 2

- Did friends or relatives tell you that you might have changed?

- Did you stay away from work during the last twelve months although there was no physical illness?

SNAS-Positivity

- In case one key question 1 is answered „yes“, patients get one probability score point and a „zero“, if the answer to every question is „no“.
- In case one key question 2 is answered „yes“, relatives, partners or friends are interviewed for confirmation; in case they confirm, patients get one probability score point and a „zero“,if the answer to the questions is „no“ or if relatives, partners or friends do not confirm.

Establish a Probability

5 domains:

1. Self-reported deficits and/or SNAS-positivity
2. Duration of HIV-1-positivity
3. Age
4. CD4+-cell count
5. Viral load in plasma

Probability Score (1)

Self-reported Deficits:

Yes → 1 score point

No → 0 score points

Age:

1-25 years	→ 1 score point
25 - 50 years	→ 2 score points
>50 years	→ 3 score points

Duration of HIV-positivity:

0 - 1 year	→ 1 Score point
1 - 5 years	→ 2 score points
> 5 years	→ 3 score points

Probability Score (2)

CD4+-cell nadir (/microl):

> 500	→ 1 score point
150 – 499	→ 2 score points
< 150	→ 3 score points

alternatively:

Direct CD4+-cell count (/microl):

> 500	→ 1 score point
250 - 499	→ 2 score points
< 0 - 250	→ 3 score points

Viral load (copies/ml):

BLD	→ 0 score points
2 - 10.000	→ 1 score point
10.000 to 50.000	→ 2 score points
50.000 und mehr	→ 3 score points

Probability Score (3)

A total score of 7 or more is highly predictive for HIV-associated brain disease. The patient should be diagnosed (either with a short screening {HIV-therapist} - or with a full neuropsycholgical test battery {neurologist/neuropsychologist}).

Nomenclature of HIV associated neurocognitive disorders (HAND)

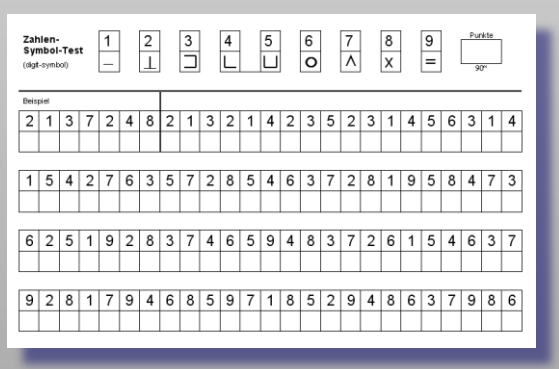
	Pre-existing Cause	Delirium Absent	Acquired Impairment in ≥ 2 Cognitive Abilities	Interferes with Daily Functioning
Asymptomatic Neurocognitive Impairment (ANI)	No	Yes	Yes	No
Mild Neurocognitive Disorder (MNCD)	No	Yes	Yes	Mild
HIV-Associated Dementia (HAD)	No	Yes	Marked	Marked

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

Short Diagnosing HAND (Short Neuropsych-Test Battery)

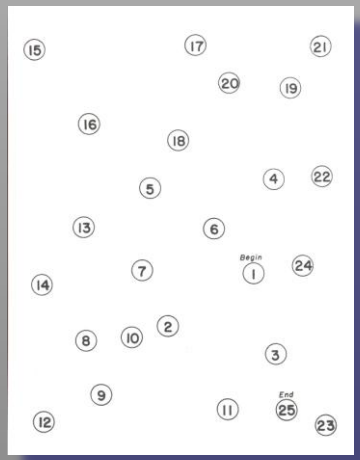
Neuropsychological tests for HAD and its precursor stages (ANI, MNCD)

Digit symbol test



Grooved pegboard

Trail-making test 1+2



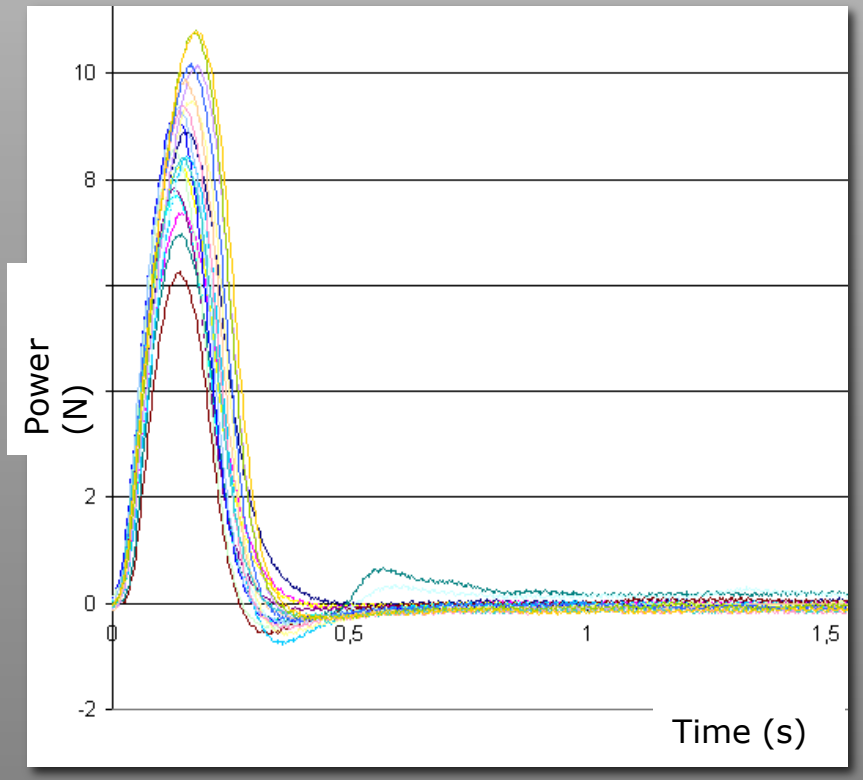
Motor Test Battery, Arendt et al., 1990

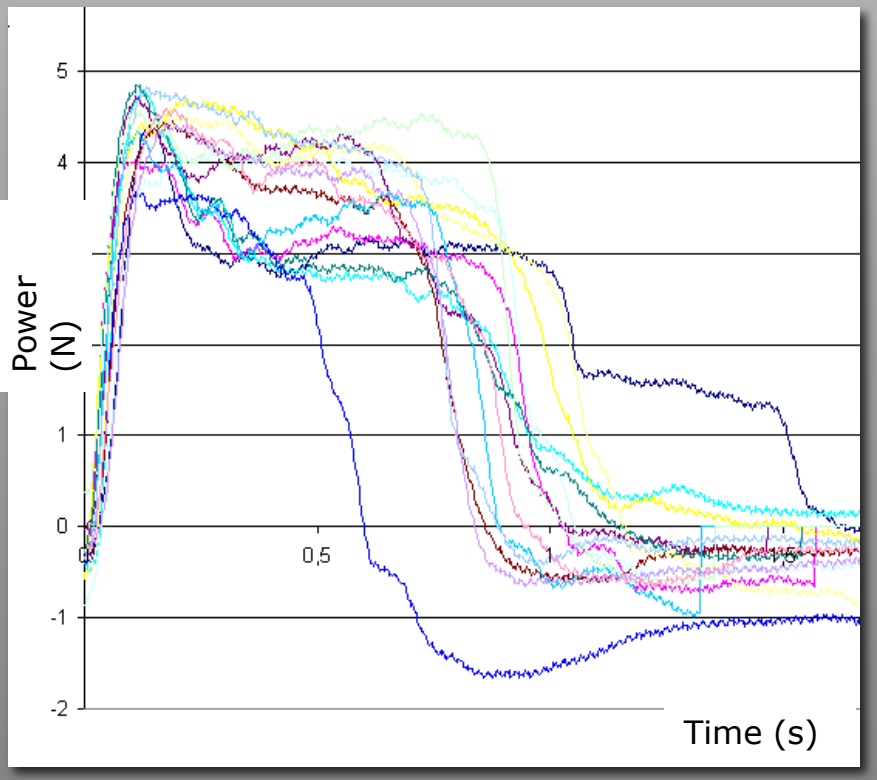
ANI = Asymptomatic Neurocognitive Disorder
MCND = Mild Neurocognitive Disorder
HAD = HIV-Associated Dementia

Fine Motor Testing

Most Rapid Index Finger Extensions (MRC):

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





Stroop Color Test

Neuropsychological Domains

Verbal

•Letter Fluency (F-A-S)

Motor

• Grooved Pegboard

•Motor Test Battery (Arendt et al., 1990)

Abstraction/Executive Functioning

• WCST-64

• Trails B

Processing Speed

• WAIS-3 Symbol Search

• WAIS-3 Digit Symbol

• Trails A

Attention/Working Memory

• WAIS-3 Letter Number Sequencing

• Paced Auditory Serial Addition Test

Learning

•Hopkins Verbal Learning Test (HVLT-R)

• Brief Visuospatial Memory Test (BVMT-R)

Delayed Recall

• HVLT-R Delayed Recall

• BVMT-R Delayed Recall

Methods (1)

- 247 HVB- und 40 HVC-co-infected HIV-positive patients were matched with HIV-mono-infected individuals with respect to age, CD4+-cell count and plasma viral load.

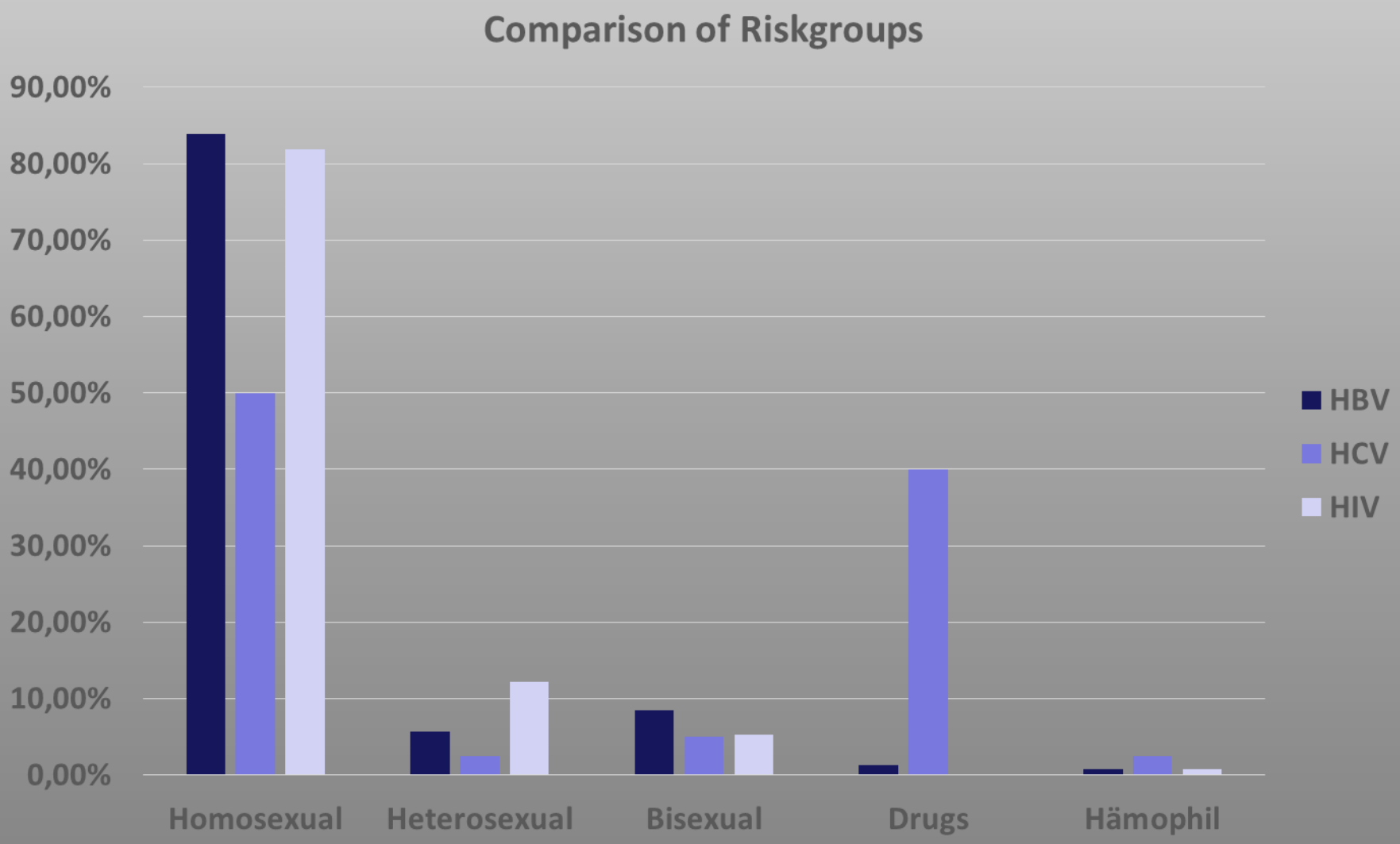
- Groups were compared regarding motor (RT + CT) and neuropsychological (GPT und verbal fluency) test results.

Methods (2)

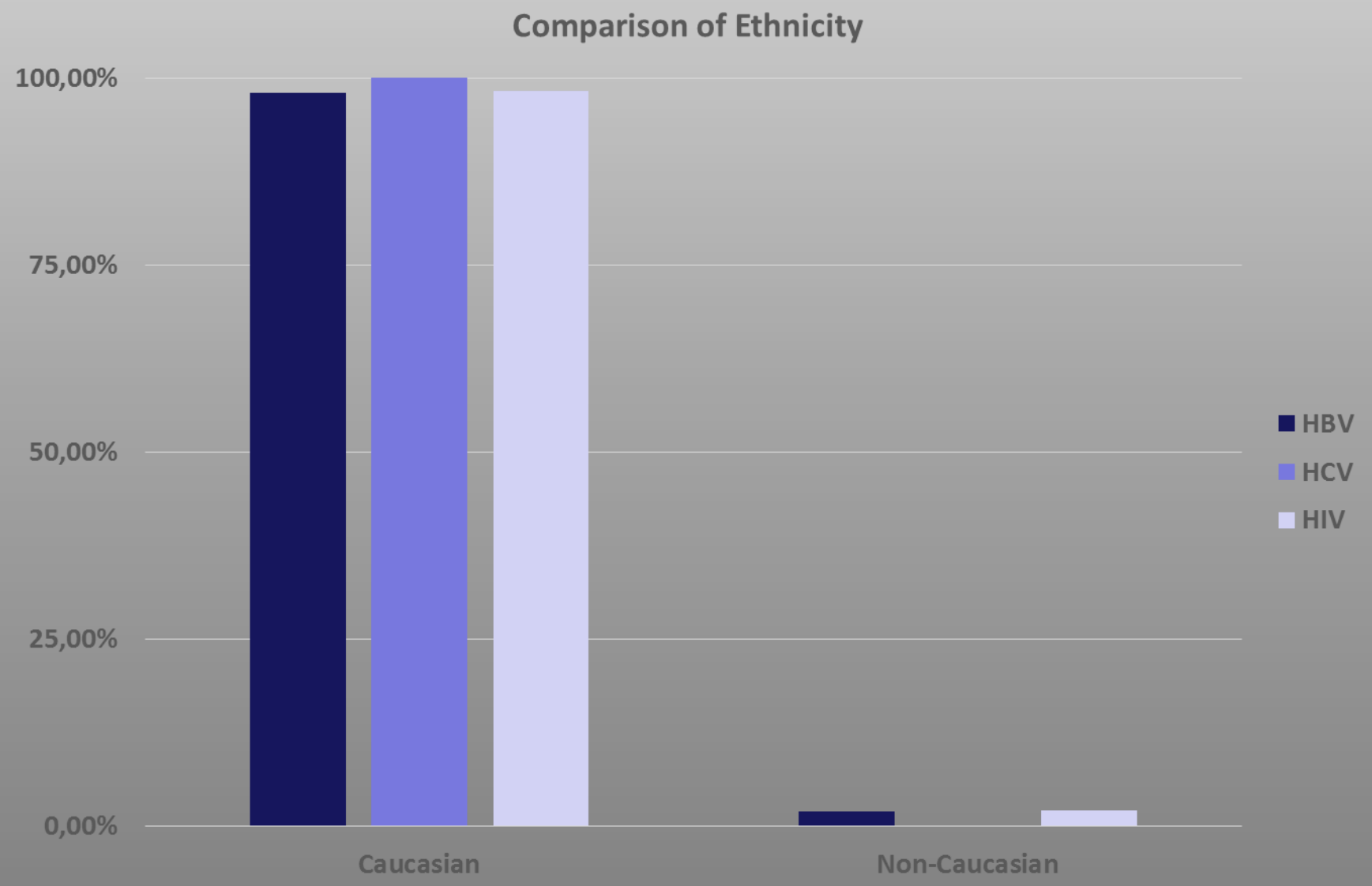
	HBV	HCV	HIV
GOT [U/l]	30,08±9,05	28,87±5,56	32,38±11,025
GPT [U/l]	30,00±9,42	18,22±5,31	27,82±8,47
Urea [mgl/dl]	32,88±8,51	27,88±8,62	33,01±10,57
Age [yrs.]	49,36±8,44	46,65±6,97	48,91±8,35
CD4+/µl	577,14±240,73	645,98±367,11	581,83±222,78
HI-Viral load [c/ml]	2285,00±15949,92	120,60±347,912	4938,49±31207,298
N	247	40	287

Normal values	
GOT	< 35 U/l
GPT	< 45 U/l
Urea	18-55 mg/dl

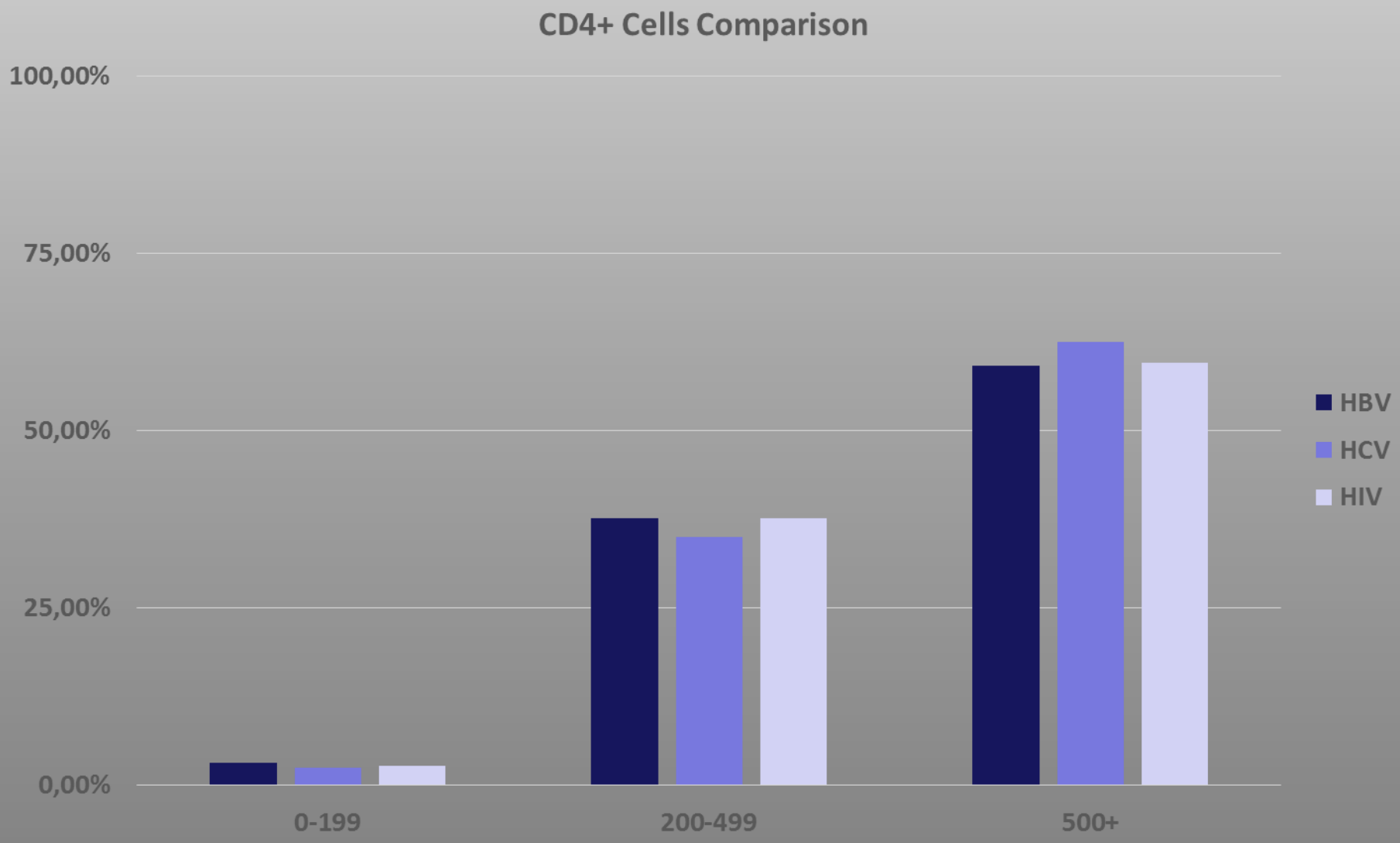
Methods (3)


Comparison of Riskgroups
90,00%
80,00%
70,00%
60,00%
50,00%
40,00%
30,00%
20,00%
10,00%
0,00%
Homosexual
Heterosexual
Bisexual
Drugs
Hämophil
HBV
HCV
HIV

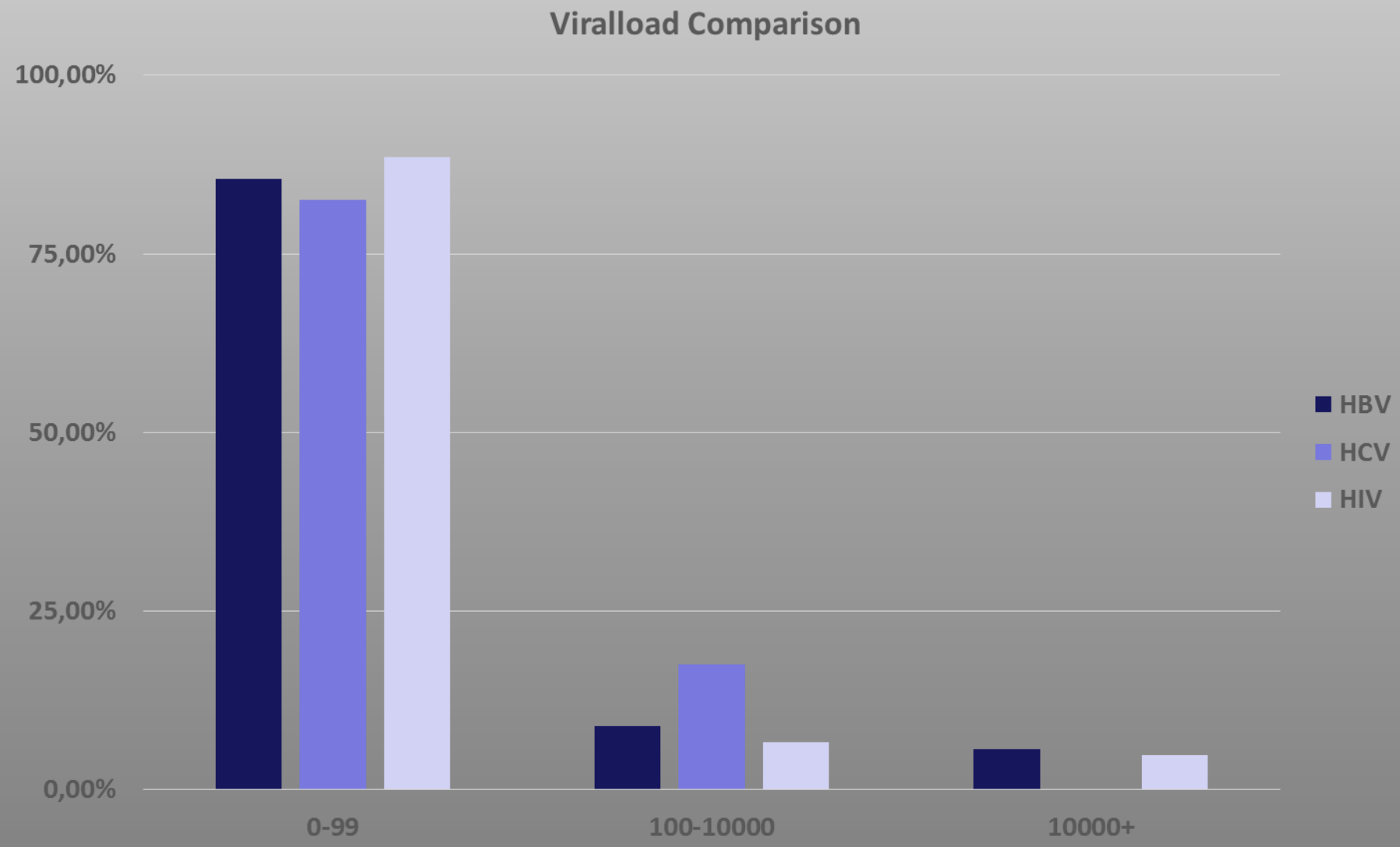
Methods (4)


Comparison of Ethnicity
100,00%
75,00%
50,00%
25,00%
0,00%
Caucasian
Non-Caucasian
HBV
HCV
HIV

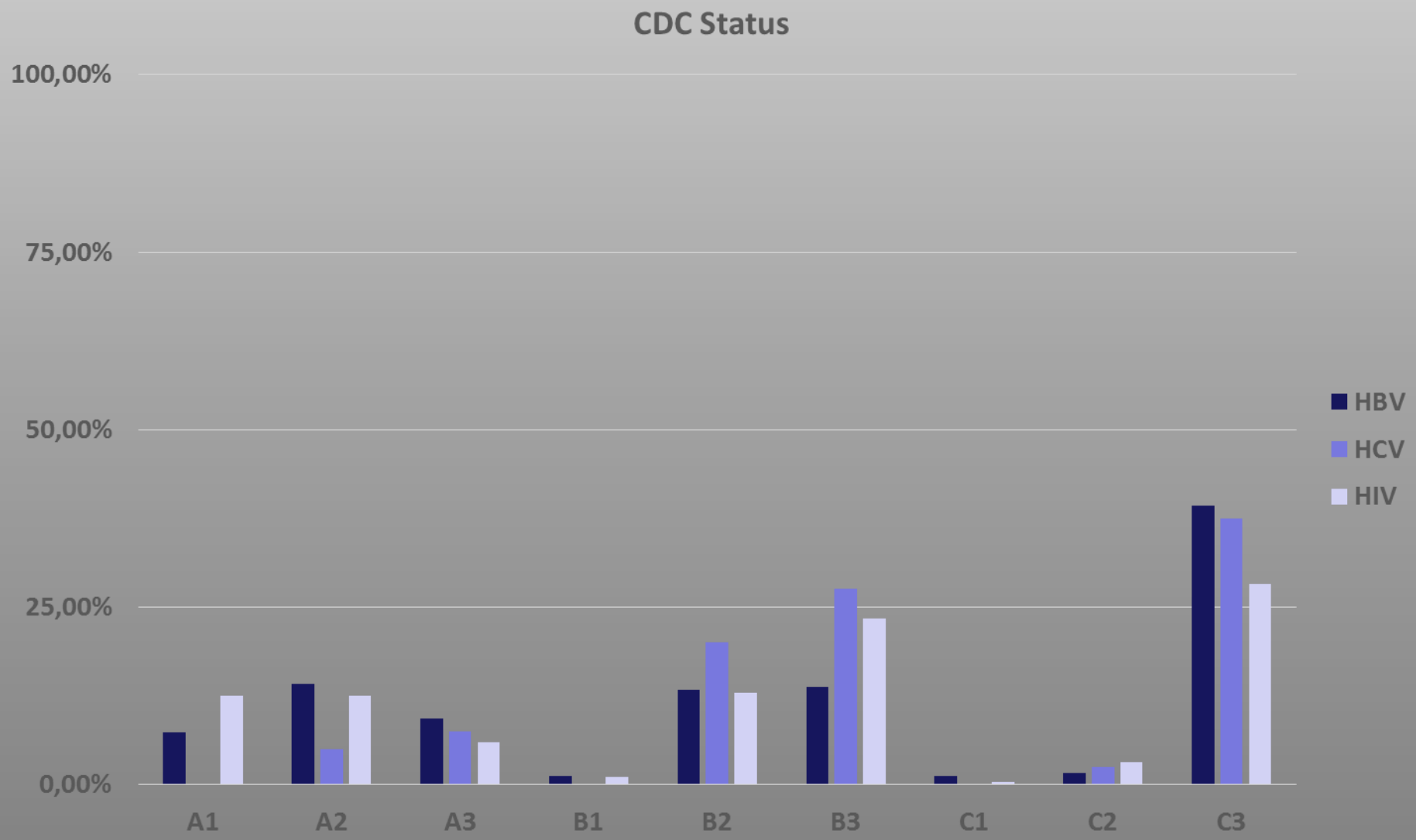
Methods (5)


CD4+ Cells Comparison
100,00%
75,00%
50,00%
25,00%
0,00%
0-199
200-499
500+
HBV
HCV
HIV

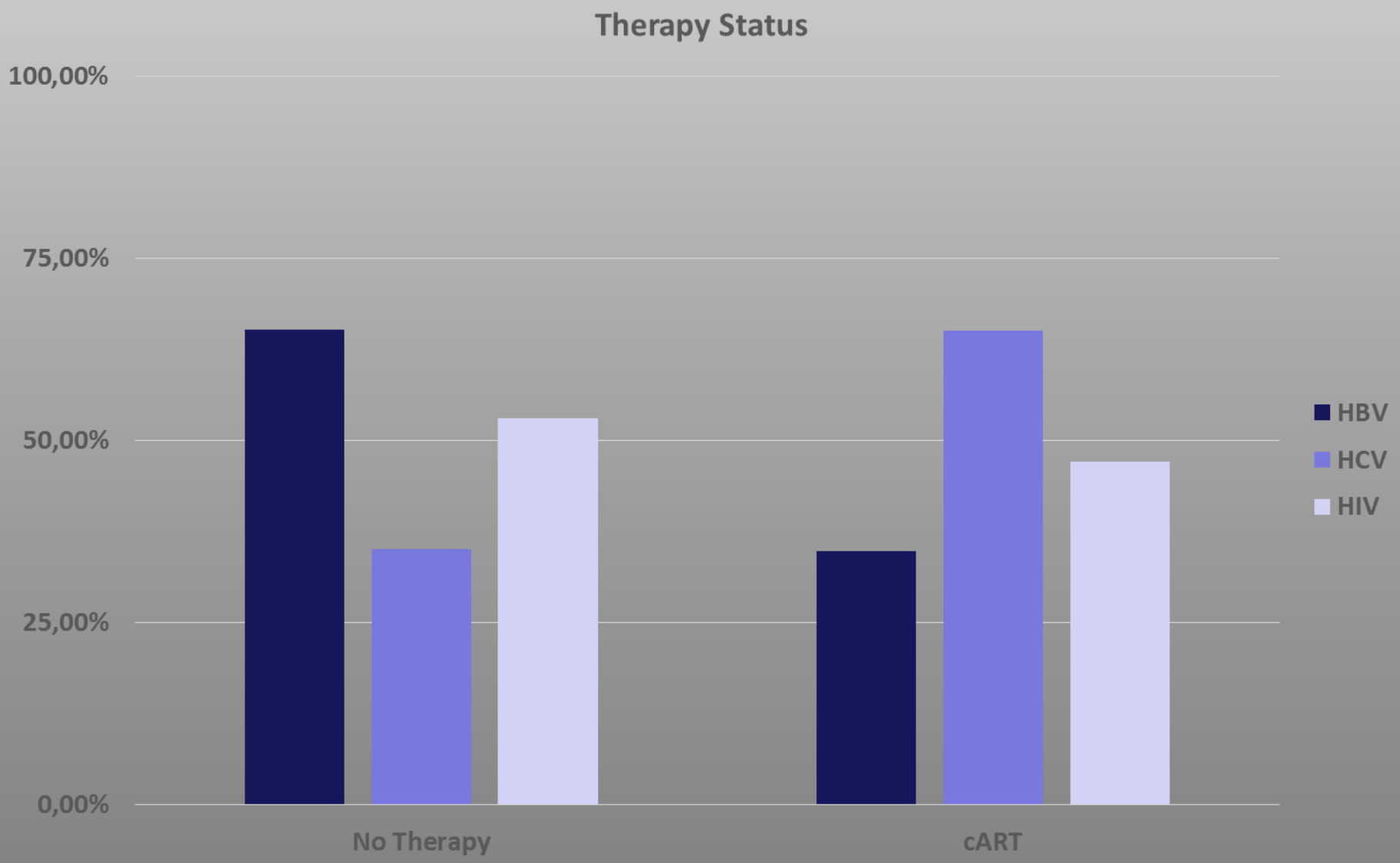
Methods (6)


Viralload Comparison
100,00%
75,00%
50,00%
25,00%
0,00%
0-99
100-10000
10000+
HBV
HCV
HIV

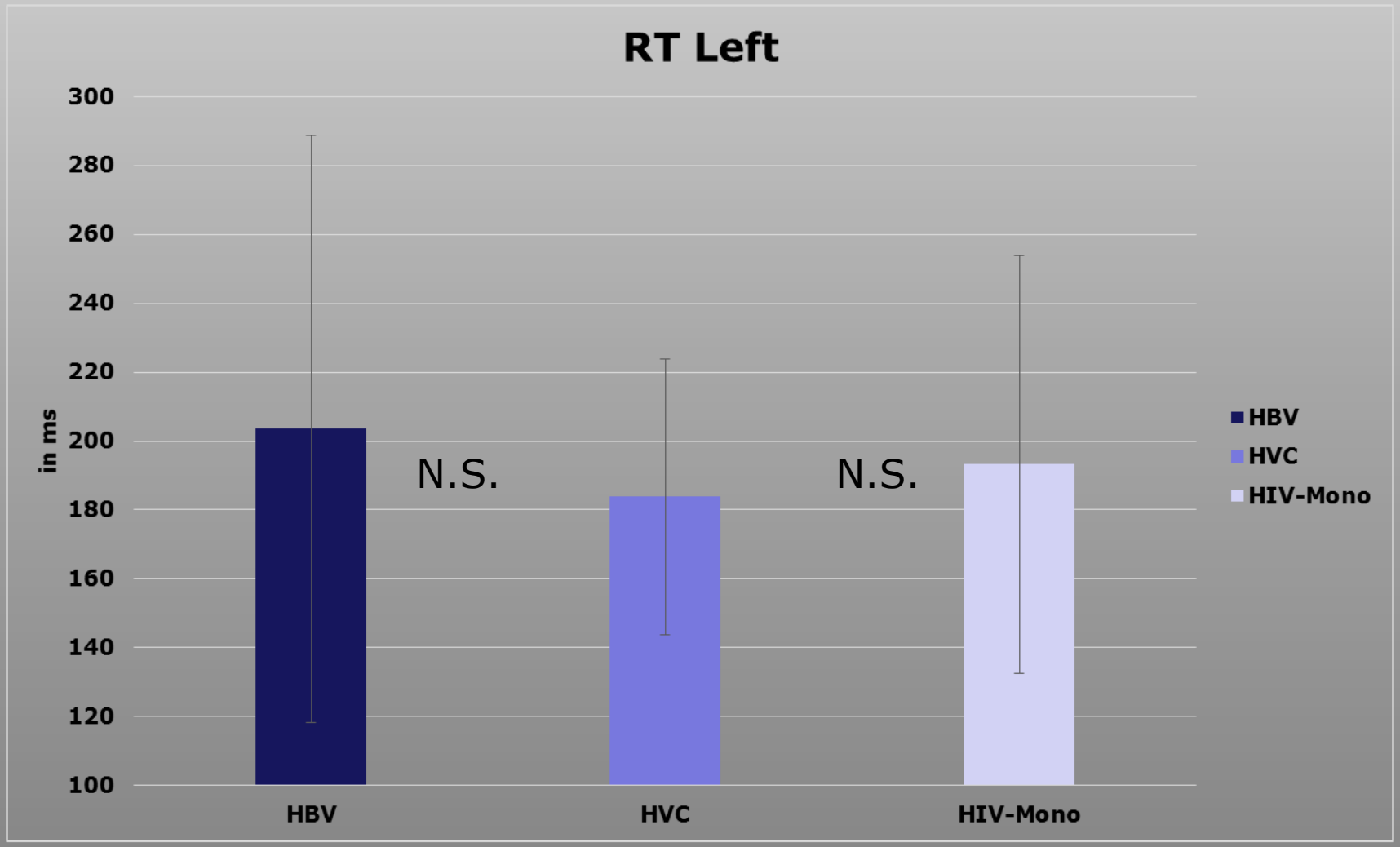
Methods (7)


CDC Status
100,00%
75,00%
50,00%
25,00%
0,00%
A1
A2
A3
B1
B2
B3
C1
C2
C3
HBV
HCV
HIV

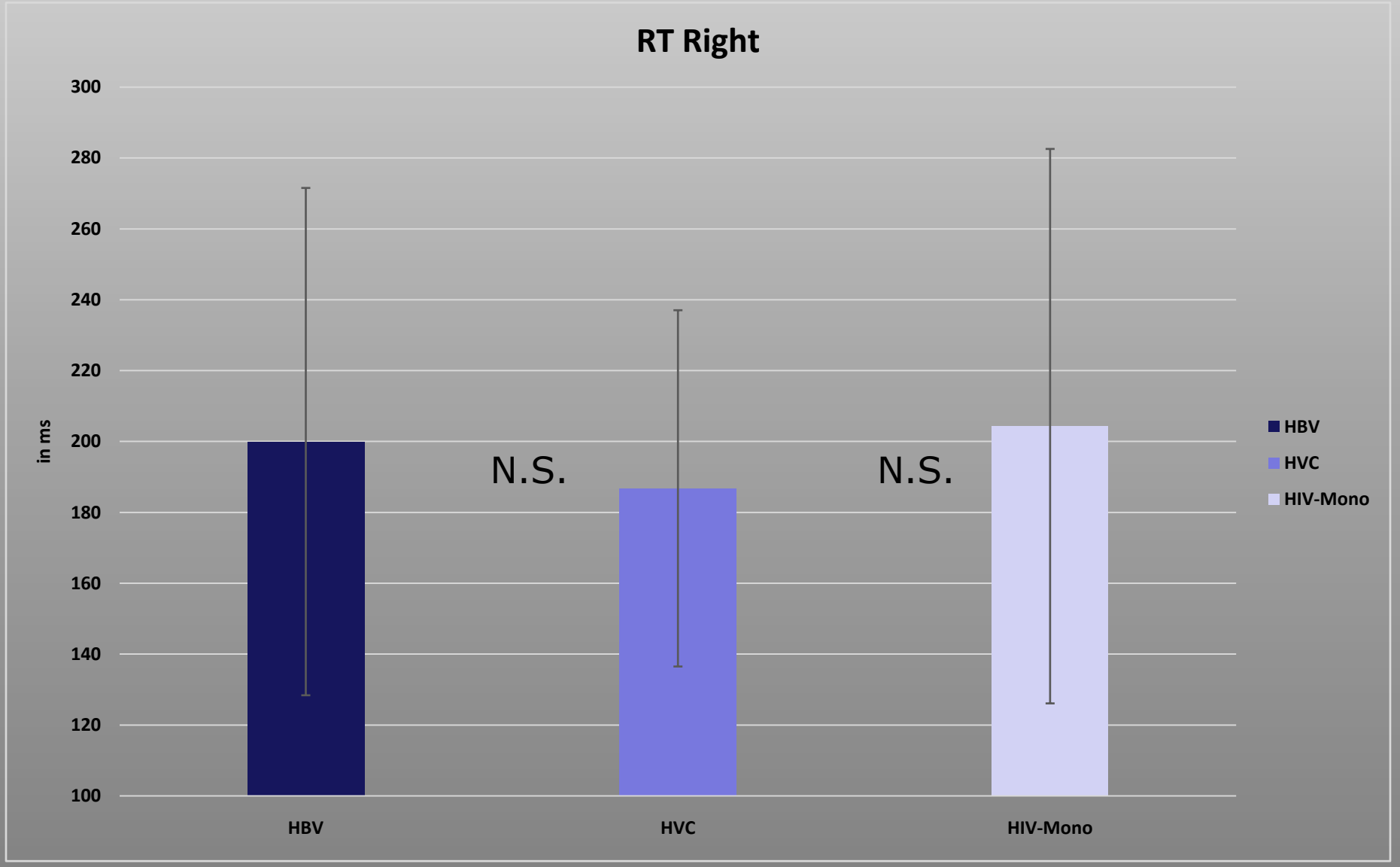
Methods (8)


Therapy Status
100,00%
75,00%
50,00%
25,00%
0,00%
No Therapy
cART
HBV
HCV
HIV

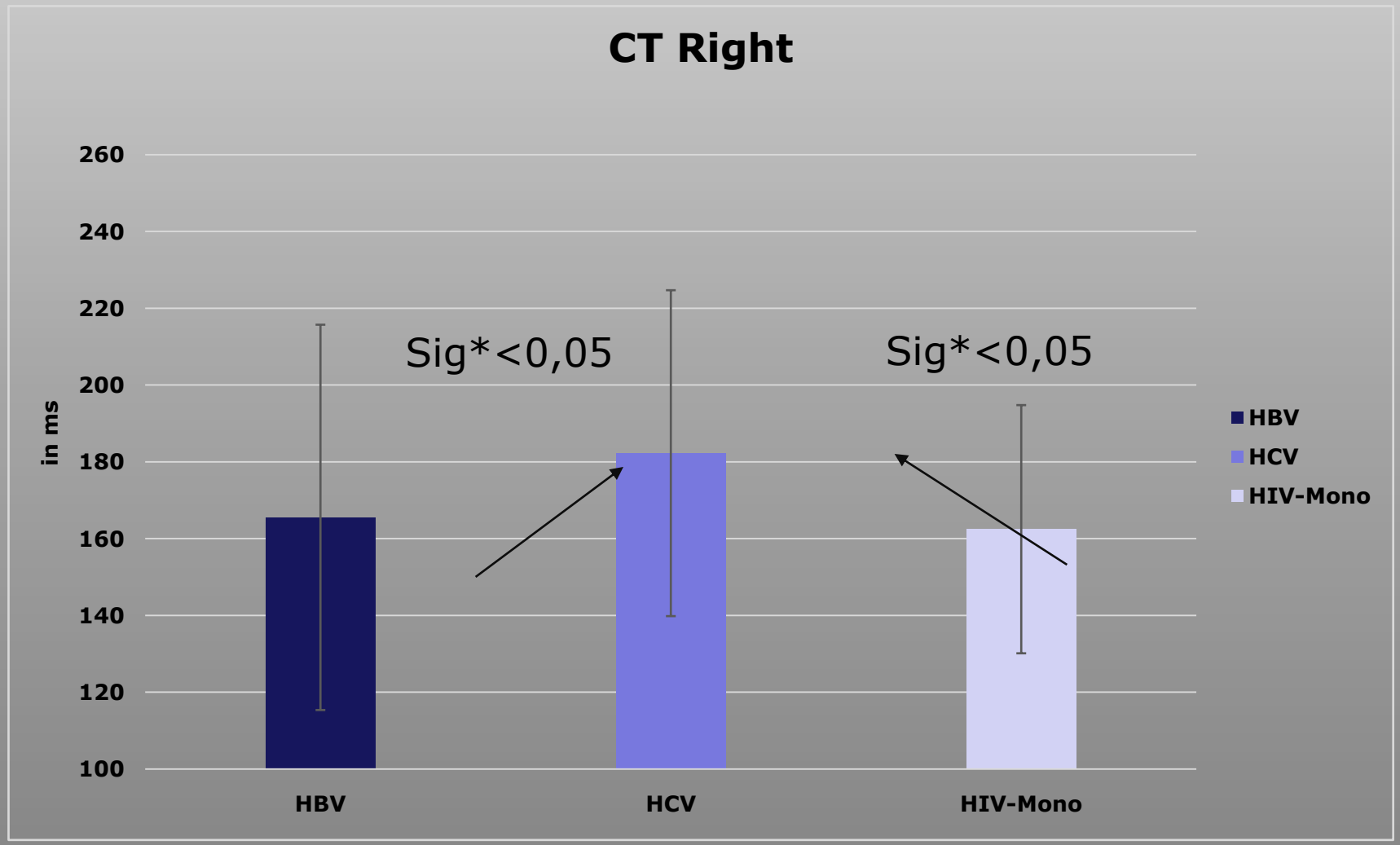
Results (1)


RT Left
300
280
260
240
220
200
180
160
140
120
100
in ms
N.S.
N.S.
HBV
HVC
HIV-Mono
HBV
HVC
HIV-Mono

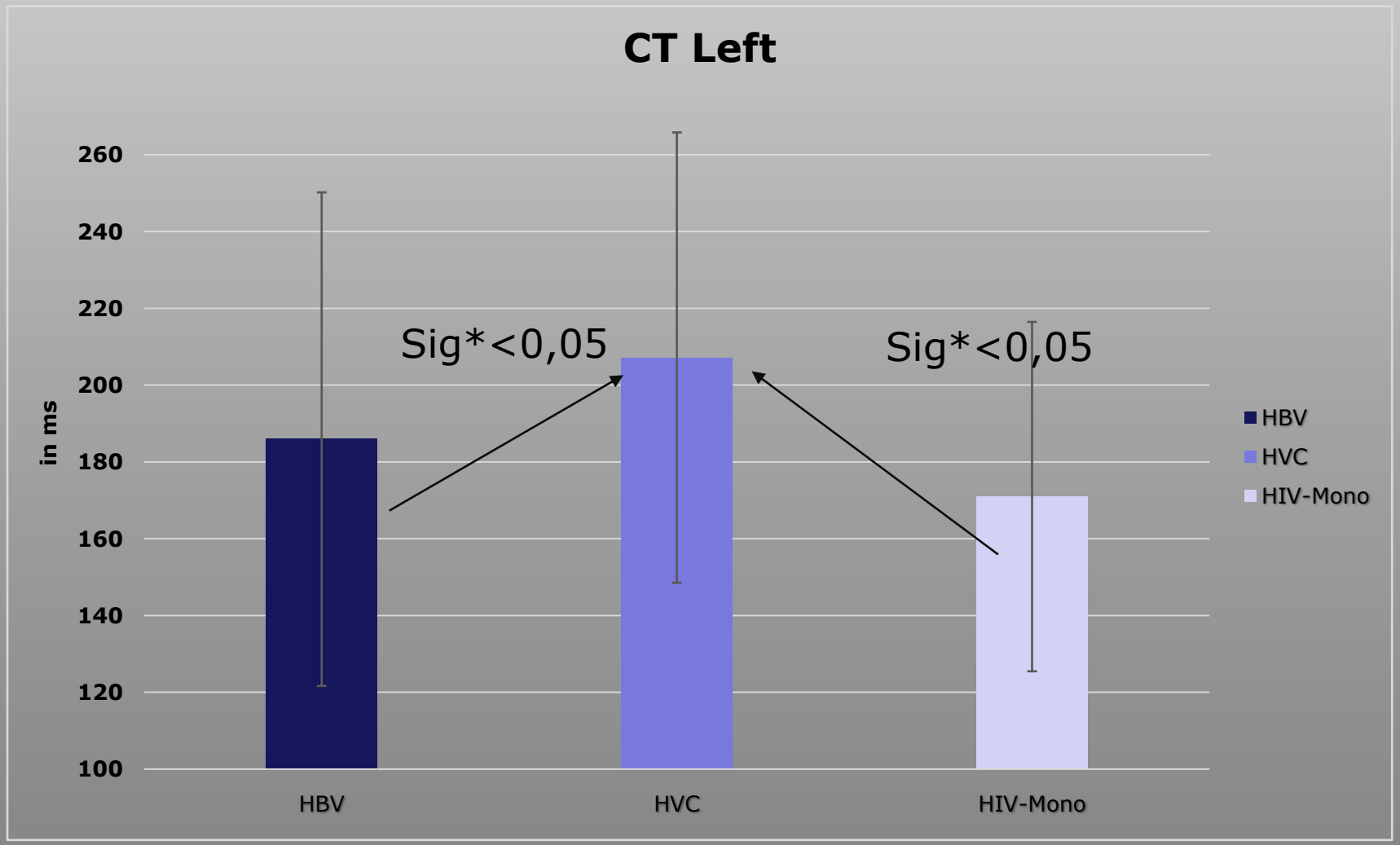
Results (2)


RT Right
300
280
260
240
220
200
180
160
140
120
100
in ms
N.S.
N.S.
HBV
HVC
HIV-Mono
HBV
HVC
HIV-Mono

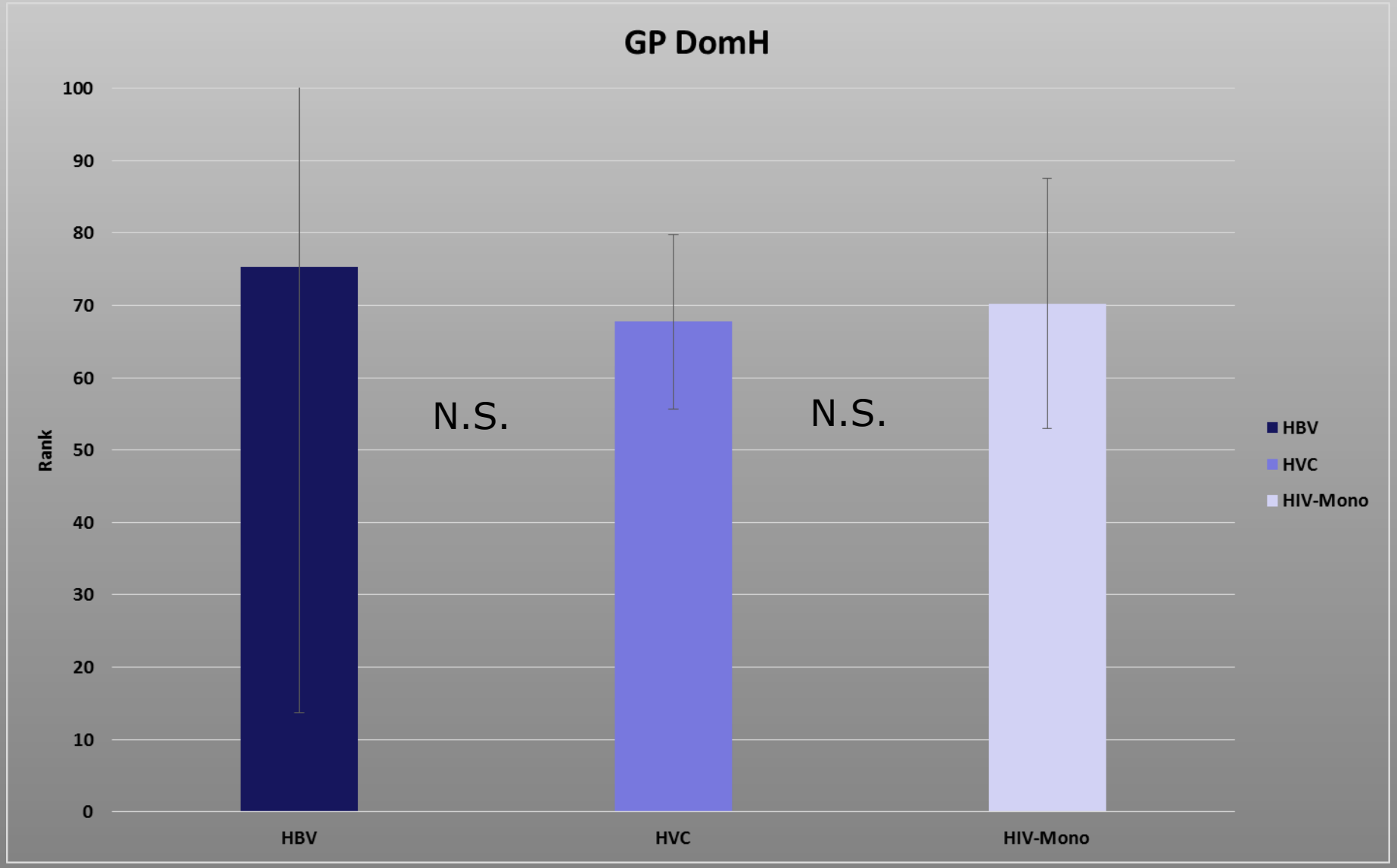
Results (3)


CT Right
260
240
220
200
180
160
140
120
100
in ms
Sig*<0,05
Sig*<0,05
HBV
HCV
HIV-Mono
HBV
HCV
HIV-Mono

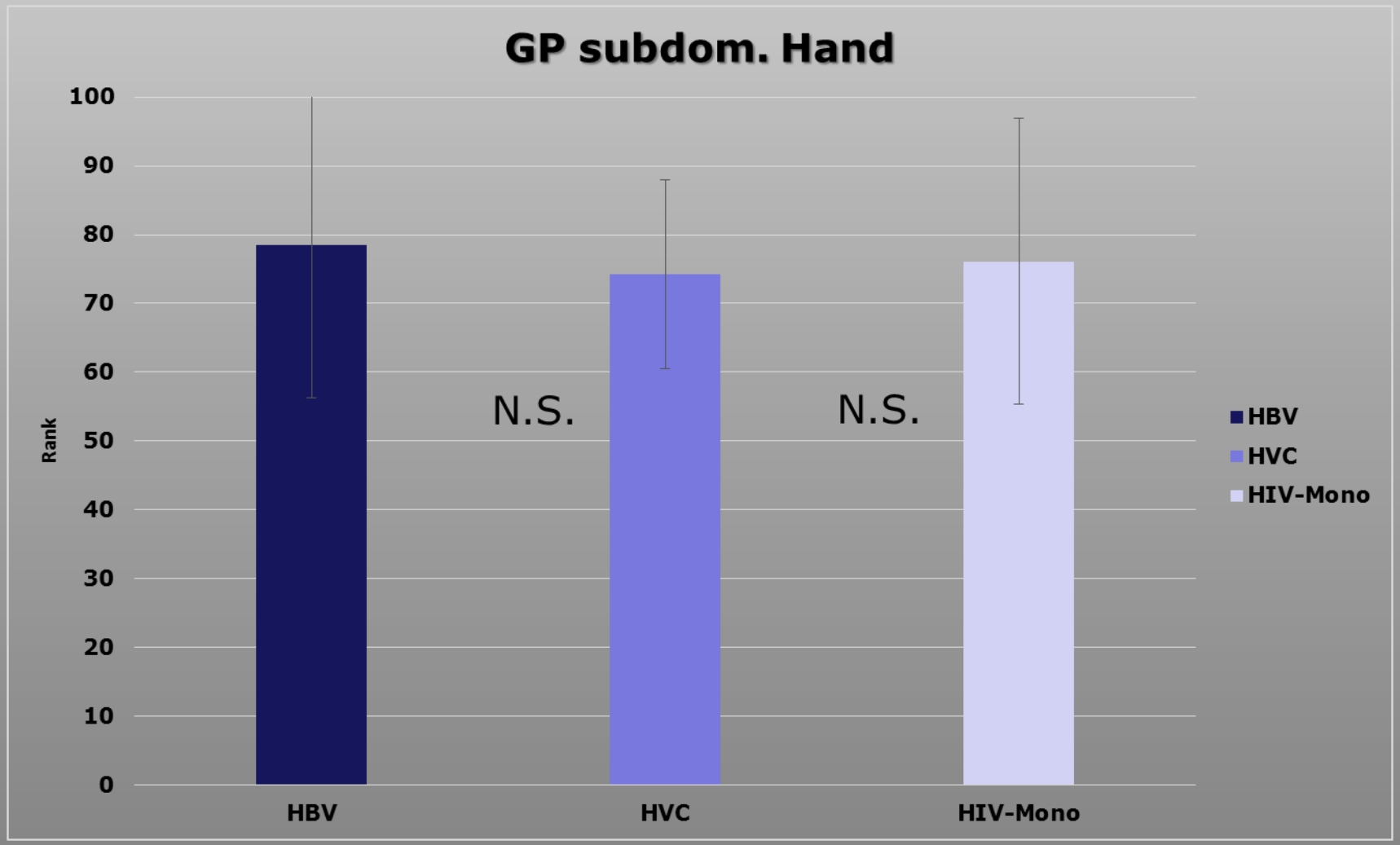
Results (4)


CT Left
260
240
220
200
180
160
140
120
100
in ms
Sig*<0,05
Sig*<0,05
HBV
HVC
HIV-Mono
HBV
HVC
HIV-Mono

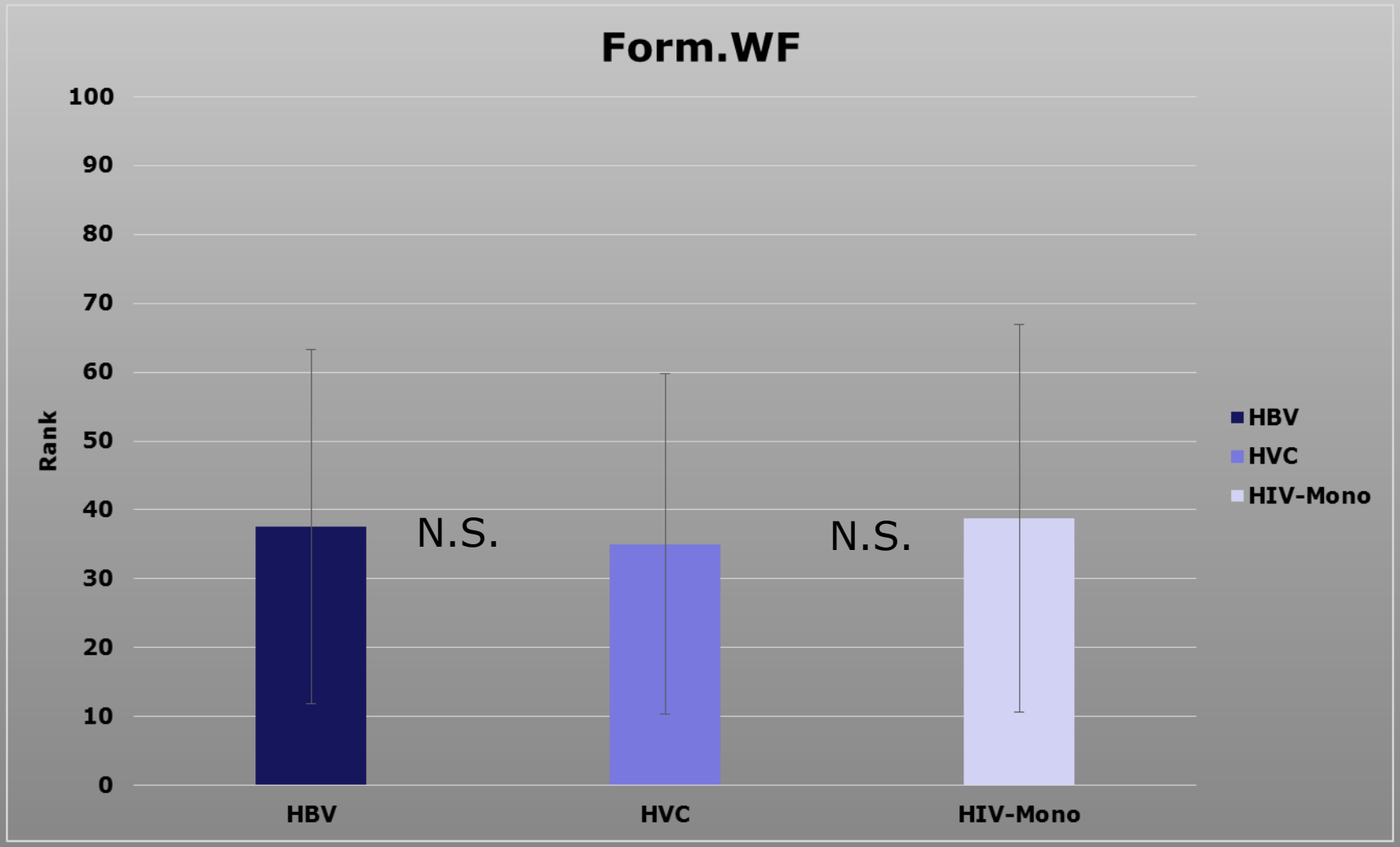
Results (5)


GP DomH
Rank
100
90
80
70
60
50
40
30
20
10
0
N.S.
N.S.
HBV
HVC
HIV-Mono
HBV
HVC
HIV-Mono

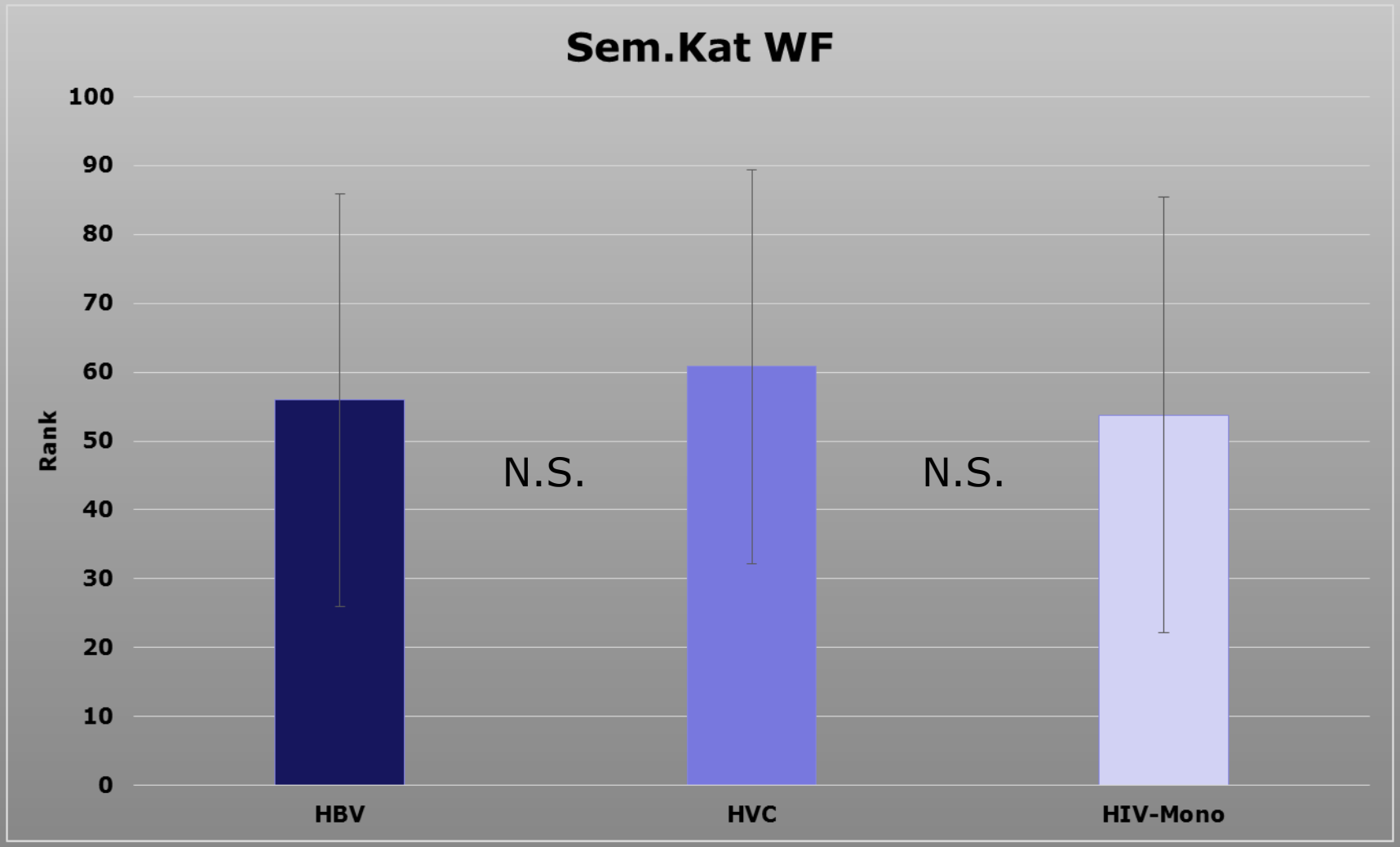
Results (6)


GP subdom. Hand
Rank
100
90
80
70
60
50
40
30
20
10
0
N.S.
N.S.
HBV
HVC
HIV-Mono
HBV
HVC
HIV-Mono

Results (7)


Form.WF
Rank
100
90
80
70
60
50
40
30
20
10
0
N.S.
N.S.
HBV
HVC
HIV-Mono
HBV
HVC
HIV-Mono

Results (8)


Sem.Kat WF
Rank
100
90
80
70
60
50
40
30
20
10
0
N.S.
N.S.
HBV
HVC
HIV-Mono

Conclusions

- Especially Hepatitis-Virus C provokes deterioration of motor performance in HIV-infected individuals.
- Whether there is a viral „trigger"- or „addition"- effect is unclear.
- The data show that motor deterioration in HCV/HIV co-infected patients is not caused by metabolic abnormalities.