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)

Aging with HIV

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Conflict of Interest

In relation to this presentation and manuscript:

- ❑ the Author has no conflict of interest in relation to this manuscript.
- ❑ the Author serves as medical consultant to: (insert company names)
- ❑ the Author is in the Advisory Board of: (insert company names)
- ❑ the Author received research support from: (insert company names)
- ❑ the Author received unrestricted research grants from: (insert company names)
- ❑ the Author received speaker's honoraria from: (insert company names)
- ❑ the Author received consulting honoraria from: (insert company names)

HIV and Aging

- Gabriele Arendt
- Dept. Of Neurology, University of Duesseldorf, Medical Faculty

- EAN, Oslo, 2019

"Disclosures"

Honoraria from:
- Abbvie
- BMS
- Gilead Sciences
- Jansen-CILAG Germany
- MSD

IITs sponsoring by:
- Jansen-CILAG Germany
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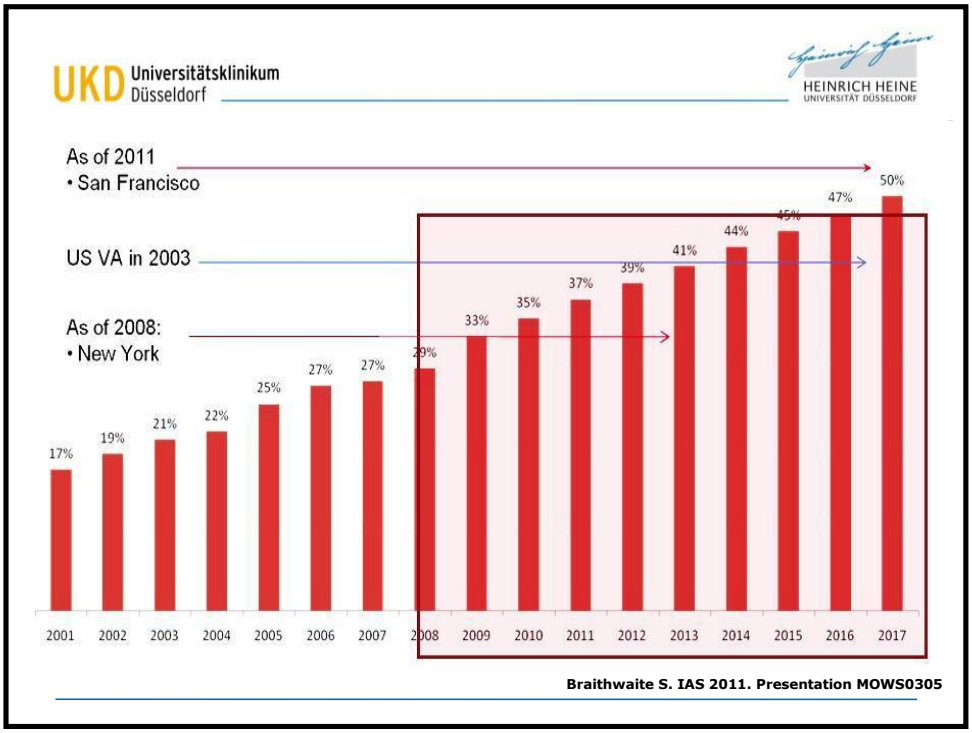

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cART 2019

NRTIs *(Nukleosid-/Nukleotid-Reverse-Transkriptase-Inhibitors)*

- Lamivudin (3TC)
- AZT + 3TC
- Abacavir (ABC)
- 3TC + ABC
- Tenofovir (TDF)
- Zidovudin (AZT)
- Emtricitabin (FTC)
- FTC + TDF
- Tenofoviralafenamidfumarat= TAF/FTC
- Doravirin

Multiple Combinations

AZT + 3TC + ABC

- TDF + FTC + EFV
- TDF + FTC + Rilpivirin
- TDF + FTC + Elvitegravir + Cobicistat
- ABC+3TC+Dolutegravir
- Tenofoviralafenamidfumarat/TAF + FTC +Elvitegravir + Cobicistat

Tenofoviralafenamidfumarat=TAF/ FTC/Rilpivirin

Tenofoviralafenamidfumarat = TAF/FTC /Darunavir/c

Dolutegravir = DTG/Rilpivirin = RPV

TDF+FTC+Doravirin

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

Nevirapin (NVP)/Viramune

Efavirenz (EFV)

Etravirin (ETR)

Rilpivirin (RPV)

Fusion Inhibitors

- Enfurvirtide T20

Integrase-Inhibitors

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Bictegravir (BCG)

PIs *(Protease-Inhibitors)*

- Saquinavir (SQV)
- Ritonavir(RTV)
- Fosamprenavir (FPV)
- Lopinavir/Ritonavir
- Atazanavir (ATV)
- Tipranavir (TPV)
- Darunavir (DRV)

CCR5-Antagonists

- Maraviroc (MVC)

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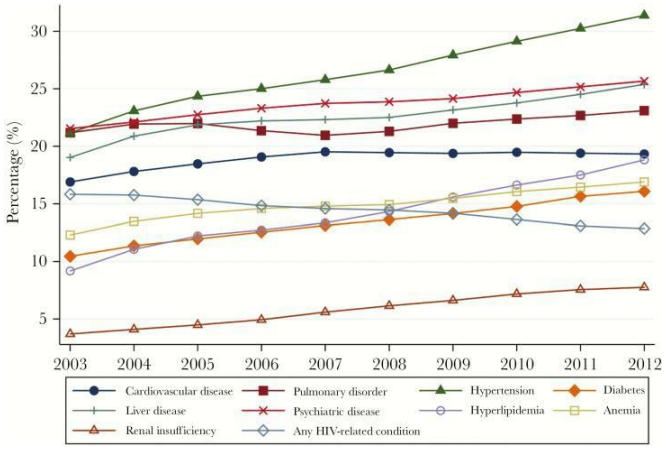
Three groups of HIV-positive patients with different risks for pathological aging

1. ***HIV-positive patients*** under stable antiretroviral combination therapy (cART) with permanently suppressed viral load in blood ***without age- and/or HIV-associated comorbidities/cofactors***
2. As above, but ***with HIV- and/or age-associated comorbidities/cofactors***
3. HIV-positive patients with ***instable course of the infection***

Age dependant comorbidities/cofactors

- cardio-vascular disease
- pulmonary disease
- liver disease
- renal insufficiency
- psychiatric disease
- arterial hypertension
- diabetes
- hypercholesterinemia/hyperlipidemia
- anemia
- nicotine
- alcohol
- overweight

Top 10 most common comorbid conditions among HIV Medicaid enrollees, 2003–2012 (n = 5 848 394 person-quarters)



Cole MB, Galárraga O, Rahman M, Wilson IB.: Trends in Comorbid Conditions Among Medicaid Enrollees With HIV. Open Forum Infect Dis. 2019 Mar 10;6(4)

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HIV-dependant comorbidities

- HIV-associated neurological disorders (HAND)
- psychiatric disease
- hepatitis-virus-C-coinfection
- neurosyphilis

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Three „Stages" of Aging

- physiological aging
- frailty
- dementia

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Signs of physiological aging:

- declining physical and mental fitness
- slowing of motor and cognitive processes

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Frailty assessment in older adults with HIV

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Frailty Measurement:	Frailty Phenotype	Frailty Index	VACS Index
Components:	5 Criteria: 1. Shrinking (Weight loss) 2. Exhaustion (self-report CES-D) 3. Weakness (grip strength) 4. Slowness (gait speed) 5. **Low activity** (Minnesota Leisure Time Scale)	Include at least 30 Items: -can be signs, symptoms, disabilities, diseases -items included must increase with age -different domains (e.g. cognition, function)	Items: 1. Age 2. CD4 count 3. HIV viral load 4. **Hemoglobin (anemia)** 5. FIB-4 **(liver tests, platelets)** 6. eGFR (renal function) 7. **Hepatitis C Co-infection**
	Many HIV studies have included a modified version, relying all on self-report measures	Example items included in HIV Frailty index: Lipoatrophy, **Hepatitis C co-infection**, polypharmacy, **low physical activity**, abnormal lab values (CRP, lipids, **liver tests, anemia, platelets**)	
Scoring/Criteria:	3/5 criteria=frail 1 or 2/5 criteria= pre-frail	Binary yes/no to each item and then generate total frailty index score	Each item assigned points based on cut points (more points for higher abnormalities); generate total score; race in online calculator used for estimation of eGFR
Brief Summary Comments:	Model used in majority of studies in HIV; shown to predict mortality and AIDS progression	Examined in only 1 study; shown to predict mortality and incident multimorbidity	Index originally designed to predict mortality; associated with frailty phenotype, markers of frailty including biomarkers, and fragility fractures

Note. Bolded items are common items across assessments; VACS= Veterans Aging Cohort Study

Greene M, Justice AC, Covinsky KE. Assessment of geriatric syndromes and physical function in people living with HIV. Virulence. ;8(5):586–598. doi:10.1080/21505594.2016.1245269

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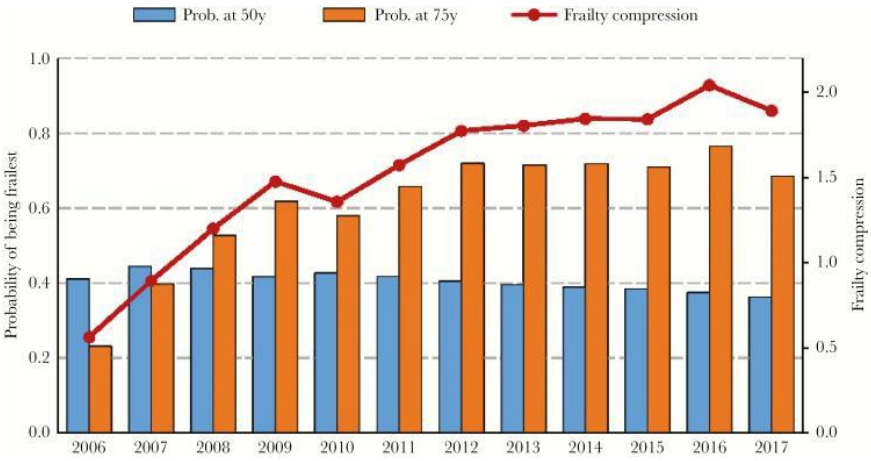
Frailty prevalence at the ages of 50 and 75 years and frailty compression ratio per calendar year



Guaraldi G, De Francesco D, Milic J, et al. The Interplay Between Age and Frailty in People Living With HIV: Results From an 11-Year Follow-up Observational Study. Open Forum Infect Dis. 2019;6(5):ofz199. Published 2019 May 17. doi:10.1093/ofid/ofz199

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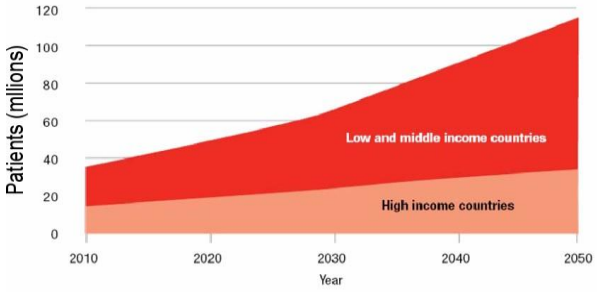
Dementia prevalence



World Alzheimer Report 2010, http://www.alz.co.uk/research/files/WorldAlzheimerReport2010.pdf

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Signs of HIV-associated dementia (HAD)

Motor signs:	- **psychomotor slowing** - **bradykinesia** - **postural instability** - **gait disturbances** - **rigidity** - **hypomimia** - **hypophonia** - **saccadic slowing**
Cognitive deficits:	- **bradyphrenia** - **memory deficits** - **apathy**
Emotional deficits:	- **depression** - **psychosis**

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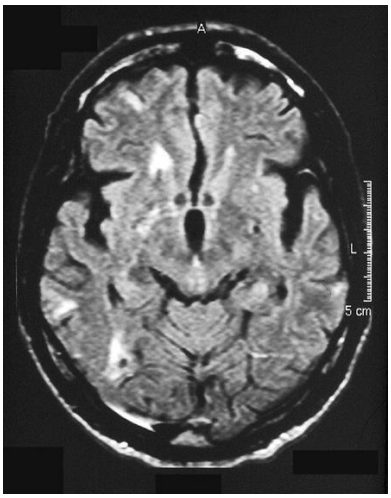
cMRI Flair-weighted image



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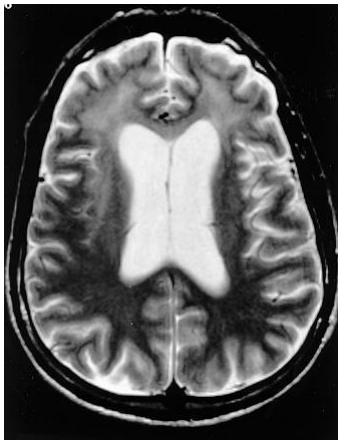
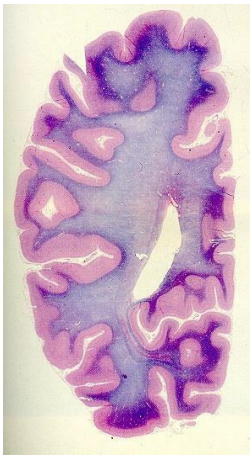
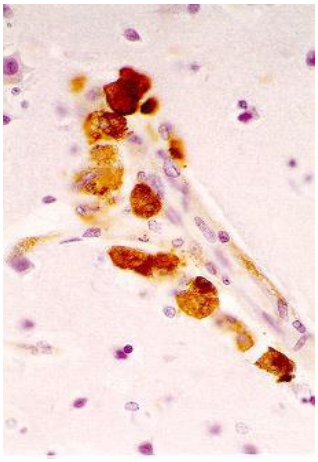
HIV-Associated Dementia







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Alzheimer´s Disease

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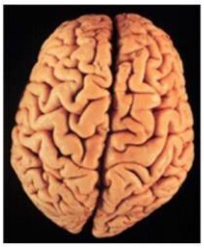
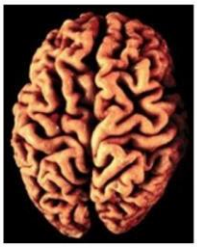
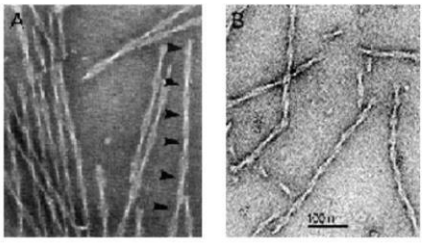


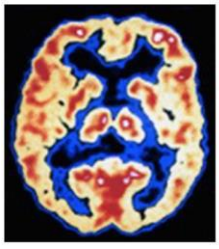
normal



M.Alzheimer



Electron micrographs of paired helical filaments



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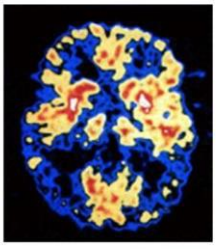
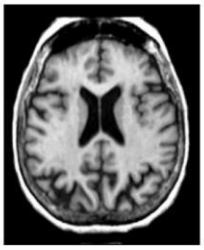


M. Alzheimer



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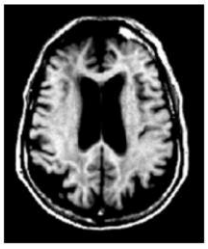

M. Alzheimer

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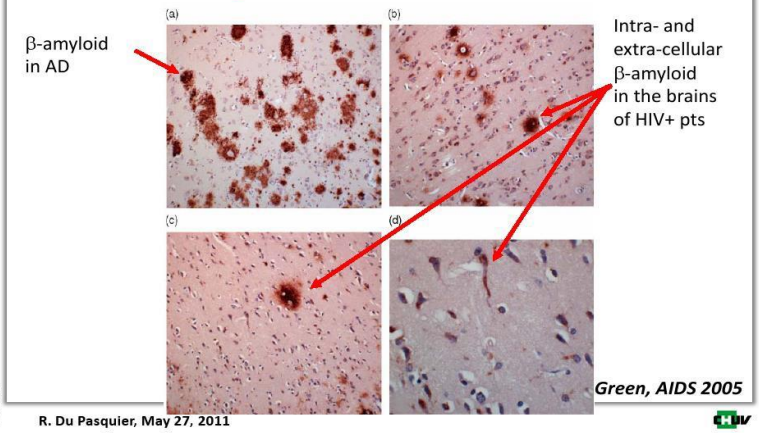
↑ β-amyloid in the brains of older HIV+ patients on HAART



Green, AIDS 2005

R. Du Pasquier, May 27, 2011

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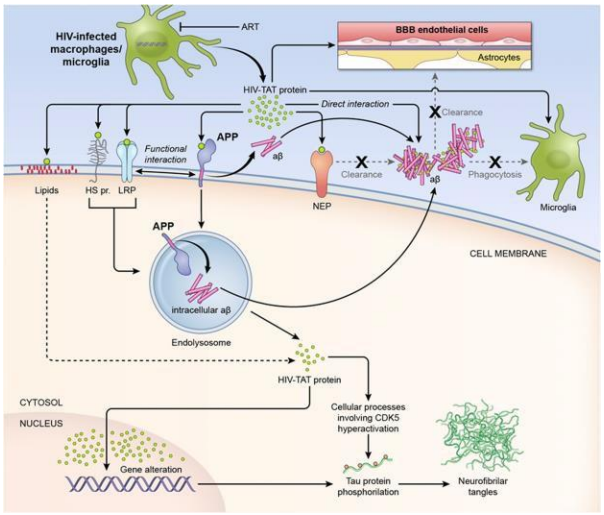
Model of the interaction of Tat with Aβ and Tau



Hategan, A., Masliah, E. & Nath, A. J. Neurovirol. (2019). https://doi.org/10.1007/s13365-019-00736-z

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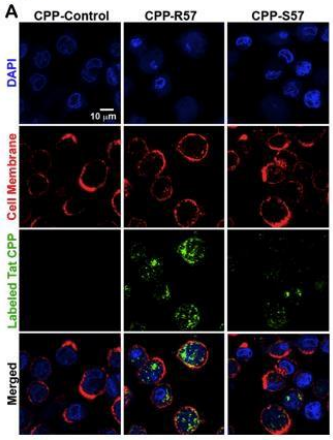
Figure 2



Confocal microscopy reveals differential cellular uptake of Tat-CPP-R57 and Tat-CPP-S57. Incubation of fluorescently labeled Tat-CPP peptides with PMA-differentiated THP-1 cells indicates a greater internalization of CPP-R57 over CPP-S57. (**A**) Confocal fluorescence microscopy images of cells stained for cell nuclei (DAPI, purple), cell membrane (WGA-633, red) or of cells exposed to 1 µM of indicated peptide CPP-control, CPP-R57 or CPP-S57 (green) are shown. Images were captured at 63X magnification. (**B**) The total intensity corresponding to the peptide (green signal) was quantified and presented as a sum of all the cells in 3 fields each for control, CPP-R57 and CPP-S57 and plotted. The control peptide uptake was set at 1 and the corresponding increases for the two experimental peptides as compared to control were plotted.

Arthur P. Ruiz, David O. Ajasin, Santhamani Ramasamy, Vera DesMarais, Eliseo A. Eugenin & Vinayaka R. A Naturally Occurring Polymorphism in the HIV-1 Tat Basic Domain Inhibits Uptake by Bystander Cells and Leads to Reduced Neuroinflammation Prasad Scientific Reportsvolume 9, Article number: 3308 (2019)

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Vascular Dementia (1)

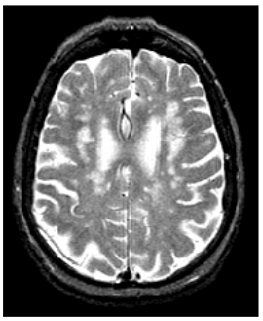
a) subcortical arteriosclerotic encephalopathy (SAE)
b) Multi-infarcti dementia
c) CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

Epidemiology:
- frontotemporal lobule degeneration
- highest incidence before the age of 65 yrs.
- third most form of dementia

Signs:
- hypomimia, mental alteration
- cognitive deficits
- dysbasia
- hemiparesis, pyramidal tract signs, aphasia, apraxia
- urine bladder incontinence

Vascular Dementia (2)

Neuropsychological test:
Mini-Mental-Test: 25-27/30



cMRI

Pathogenesis
Micro-/Macro-angiopathy following
longterm marked arterial hypertension
Diabetes
vasculitis

Therapy:
Risk factor management
ASS, Clopidogrel, oral anticoagulation

Biomarker for HIV related dementia Development(1)

Blod	CSF
Peripherale Monozyten-HIV DNA (Cysique et al., 2015; Valcour et al., 2013; de Oliveira et al., 2015)	Neurofilament Leichtketten (NFL) (Peluso et al., 2013; Abdulle et al., 2007)
CD16+ Monozyten (Kusao et al., 2012; Ndhlovu et al., 2014)	t-tau (Peterson et al., 2014)
sCD163 (Burdo et al., 2013)	sAPPβ (Peterson et al., 2014)
sCD14 (Lyons et al., 2011)	sCD14 (Kamat et al.. 2012)
CCR2 (Ndhlovu et al., 2015)	Humanes Prion Protein (PRP^c) (Megra et al., 2013)
Spezifische Plasma Mikro RNAs (Asahchop et al., 2016)	IL-8 (Yuan et al., 2013)
Neurofilament Leichtketten (NFL) (Gisslen et al., 2016)	Monocyte chemotatic protein-1 (MCP-1) (Yuan et al., 2013)
Osteopontin (Brown et al., 2011)	Induced protein-10 (IP-10) (Yuan et al., 2013)
IFNα-2b (Cassol et al., 2013)	Granulocyte colony-stimulating factor (G-CSF) (Yuan et al., 2013)
IL-6 (Cassol et al., 2013)	IFNα (Anderson et al., 2017)

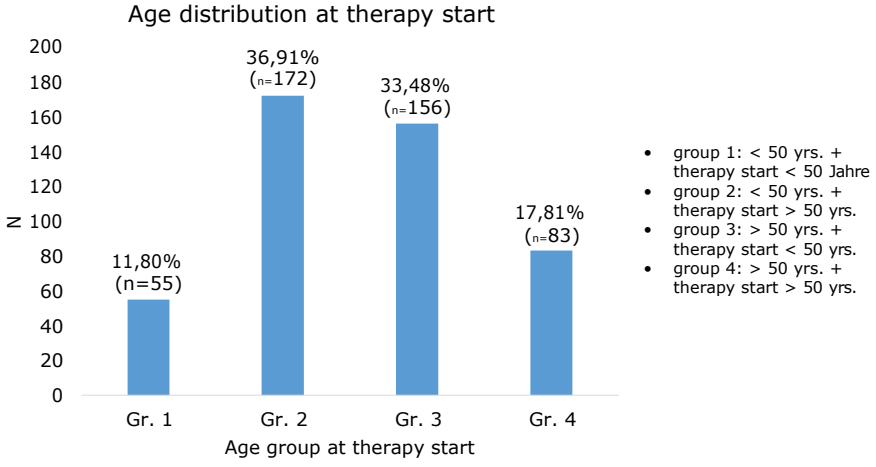
Rosenthal, J. & Tyor, W. J. Neurovirol. (2019). https://doi.org/10.1007/s13365-019-00735-0

Biomarker for HIV related dementia Development(2)

Blod	CSF
IL-2 (Cassol et al., 2013)	Neopterin (Hagenberg et al., 2010; Eden et al., 2016)
TNFα (Sevigny et al., 2004)	Osteopontin (Burdo et al., 2008)
Lipopolysaccharide (LPS) (Ancuta et al., 2008)	Glutamine (Dickens et al., 2015)
Neuron-derived exosomes (NDEs) (Pulliam et al., 2019)	Coeruloplasmin (Kallianpur et al., 2018)
	Haptoglobin (Kallianpur et al., 2018)
	Vascula endothelial growth factor (VEGF) (Kallianpur et al., 2018)
	Galectin-9 (Gal-9) (Premeaux et al., 2018)
	Induced protein-10 (IP-10) (Yuan et al., 2013)

Rosenthal, J. & Tyor, W. J. Neurovirol. (2019). https://doi.org/10.1007/s13365-019-00735-0

Patient cohort (n=2356)



- group 1: < 50 yrs. + therapy start < 50 Jahre
- group 2: < 50 yrs. + therapy start > 50 yrs.
- group 3: > 50 yrs. + therapy start < 50 yrs.
- group 4: > 50 yrs. + therapy start > 50 yrs.

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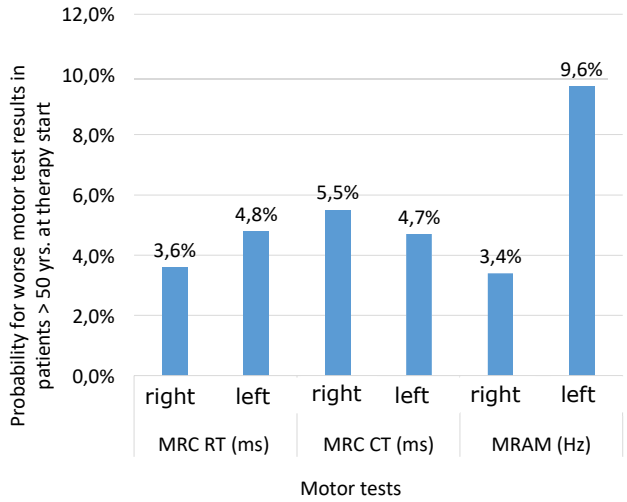
Patient Cohort – Motor Test results (1)



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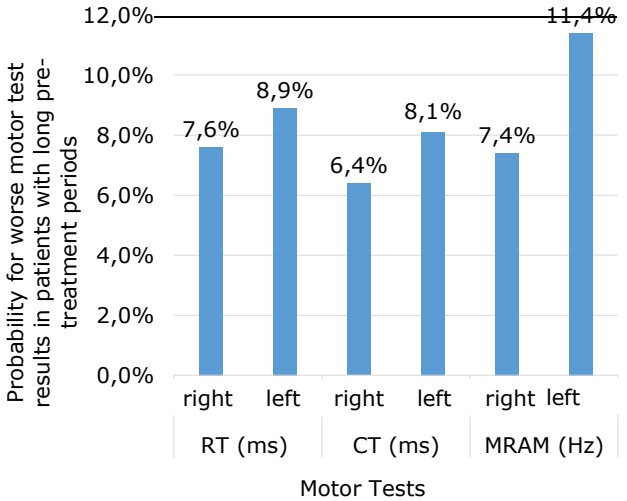
Patient Cohort – Motor Test results (2)



- ***Age*** is only a risk factor for dementia when underlying HIV-infection is ***a long-term untreated disease***!

Co-workers

- Eser Orhan, data management and biostatistics
- Florian Dimmers –data acquisition
- Katharina Doerner – data acquisition
- Nicole Mueller – data acquisition
- Jens Rathjen – data acquisition
- Milhiko Tominaga – data acquisition
- Janna Terplak – data acqusition

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www.neuro-hiv.de