HIV and ageing of the brain

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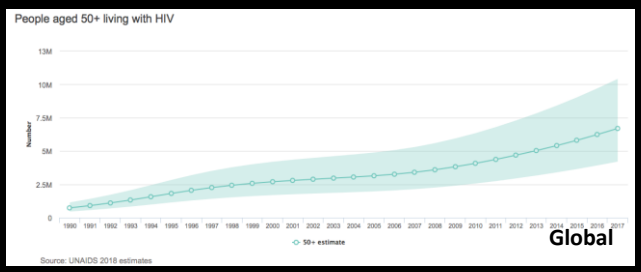
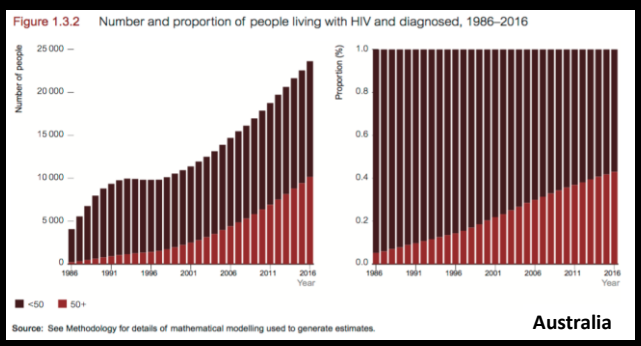
ASHM 2018
Comorbidities session

Ageing of the HIV epidemic

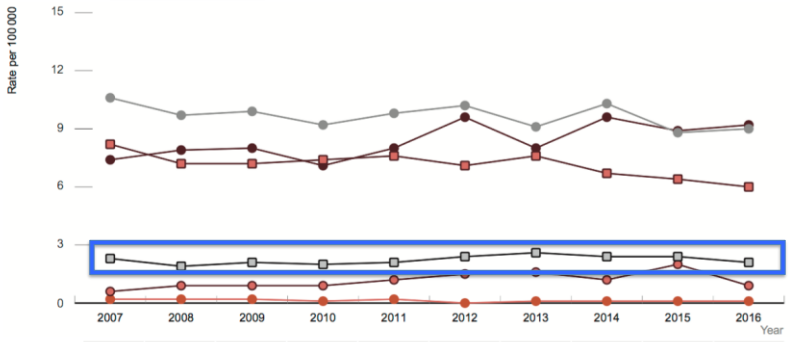
www.hips.org





Australian HIV epidemic by age group

Figure 1.1.4 HIV notification rate per 100 000 population, 2007–2016, by age group

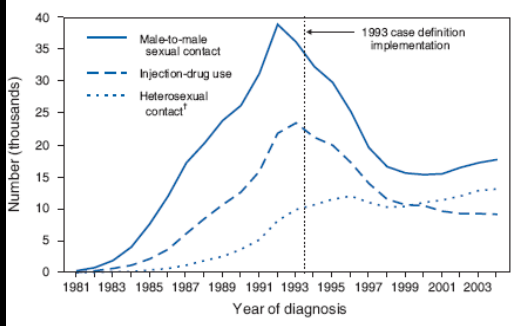


	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
0–14	0.2	0.2	0.2	0.1	0.2	0.0	0.1	0.1	0.1	0.1
15–19	0.6	0.9	0.9	0.9	1.2	1.5	1.6	1.2	2.0	0.9
20–29	7.4	7.9	8.0	7.1	8.0	9.6	8.0	9.6	8.9	9.2
30–39	10.6	9.7	9.9	9.2	9.8	10.2	9.1	10.3	8.8	9.0
40–49	8.2	7.2	7.2	7.4	7.6	7.1	7.6	6.7	6.4	6.0
50+	2.3	1.9	2.1	2.0	2.1	2.4	2.6	2.4	2.4	2.1

Source: State and territory health authorities; see Methodology for detail.

<u>Currently</u> Well Treated HIV Infection
=
<u>Chronic</u> HIV infection
=
Ageing ~ long HIV duration
=
Soon to be the majority of PLHIV worldwide

FIGURE 1. Number of acquired immunodeficiency syndrome (AIDS) cases, by major transmission category and year of diagnosis — United States, 1981–2004*



* Data adjusted for reporting delays. Cases without an assigned transmission category were redistributed on the basis of historical trends in risk factors.
† Defined as sexual contact with a person at high risk for or infected with HIV.

Dementia risk factors or comorbidities ?

- Ageing, mid-life cardiovascular diseases (T2 Diabetes, high cholesterol, high blood pressure) heart disease, stroke), mid-life obesity, ApoE 4, Family history, Head injury, loss of sex hormones after mid-life, immune and regeneration senescence, immune dysregulation, female gender, depression, automimmune diseases, lifestyle factors (smoking, alcohol, drugs?, lack of exercise, unhealthy diet), ethnicity, chronic stress, social isolation…

A risk factor is anything that increases a person's risk of developing a condition. For dementia there are a mixture of factors – some that can be avoided and others that are impossible to control.

https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_risk_factors_for_dementia.pdf

Alzheimer's Society
United Against Dementia

?

Other conditions

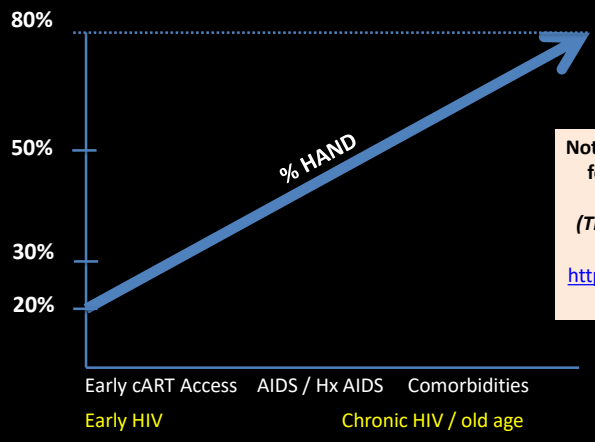
Other medical conditions that can increase a person's chances of developing dementia include Parkinson's disease, multiple sclerosis and HIV. Down's syndrome and other learning disabilities also increase a person's risk of dementia. See factsheets 442, Rarer causes of dementia, and 430, Learning disabilities and dementia.

HIV-associated Neurocognitive Disorders (HAND)

	Acquired Impairment in ≥2 Cognitive Abilities	Interferes with Daily Functioning	
Asymptomatic Neurocognitive Impairment (ANI)	YES	NO	Mild HAND
Mild Neurocognitive Disorder (MND)	YES	MILD	Mild HAND
HIV-Associated Dementia (HAD)	MARKED	MARKED	Dementia

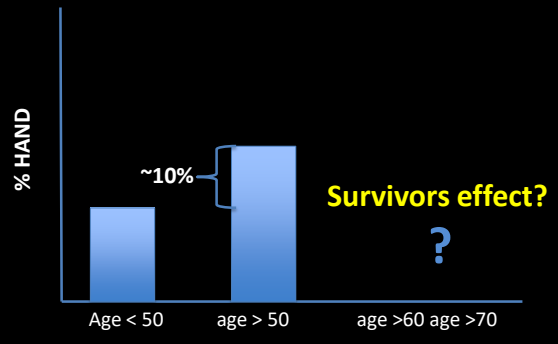
Antinori et al., Neurology 2007

HAND prevalence in different population worldwide depends on *cART* access and timing, rate of AIDS & immune compromise, comorbidities



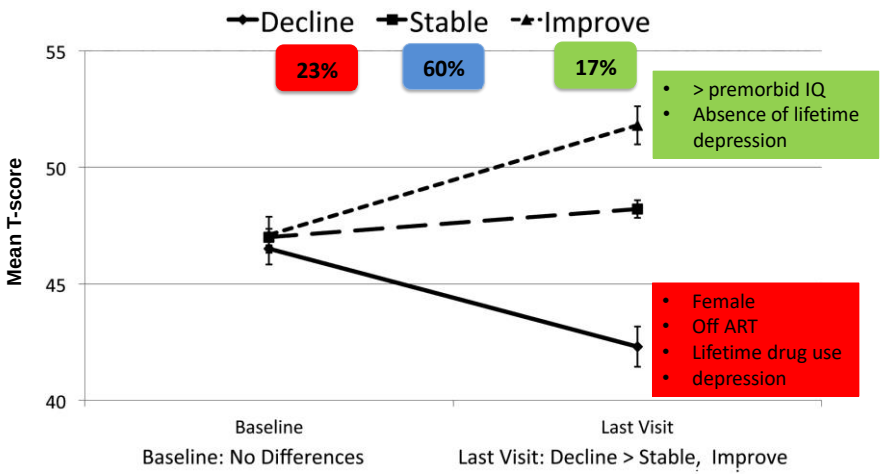
Not all HIV+ people have same risk for HAND: ~50% will probably never have HAND
(This figure does not account for pediatric HIV or old age)
https://www.ncbi.nlm.nih.gov/pubmed/29198283

Mild HAND is about 10% more common once age 50+



1st generation of aging PLHIV

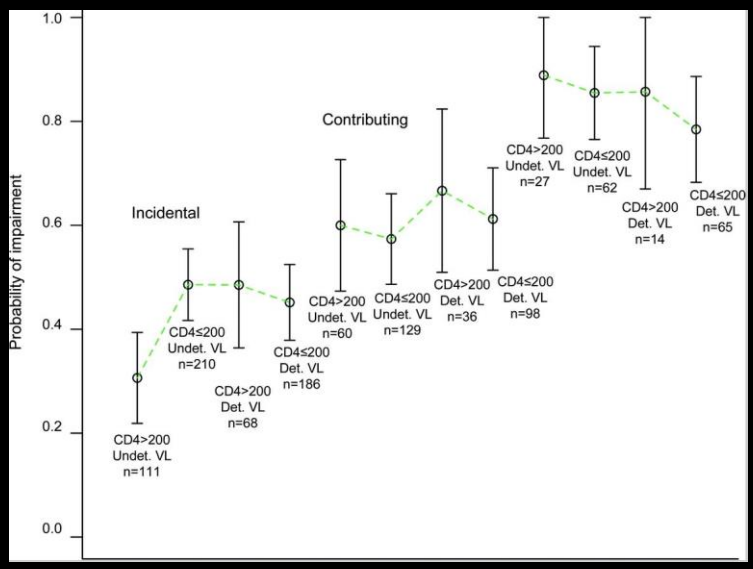
HAND has a relapsing and remitting profile



Study duration: 16-72 (mean, 35) months

US data **Robert K. Heaton et al. Clin Infect Dis. 2015**

HAND USA figures (all ages)



HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy
CHARTER Study (Heaton et al., 2010 Neurology)

HAND International figures (all ages)

Table 4. HAND prevalence in other international settings using the same neuropsychological test battery.

Region	N	Age (Mean, SD)	Education (Mean, SD)	% Male	NCI Prevalence
US	947	40.5 (9.4)	12.9 (2.5)	69%	36%
Anhui	199	40.3 (6.2)	5.9 (2.1)	63%	35%
Yunnan	403	35.8 (5.8)	9.8 (2.4)	66%	39%
India (Pune)	246	32.1 (8.0)	10.3 (3.5)	57%	45%
India (Chennai)	69	37.4 (8.1)	10.2 (2.9)	68%	33%
Zambia	366	37.4 (12.7)	11.0 (2.5)	48%	35%

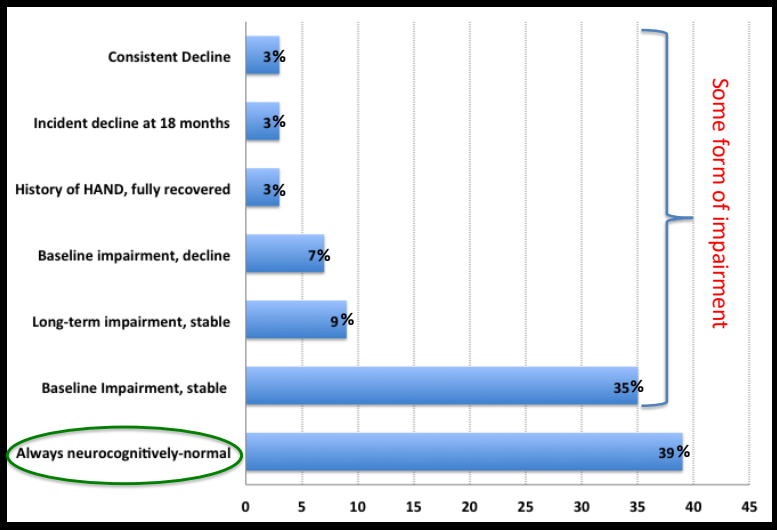
International figures

Aged 50+ HAND prevalence

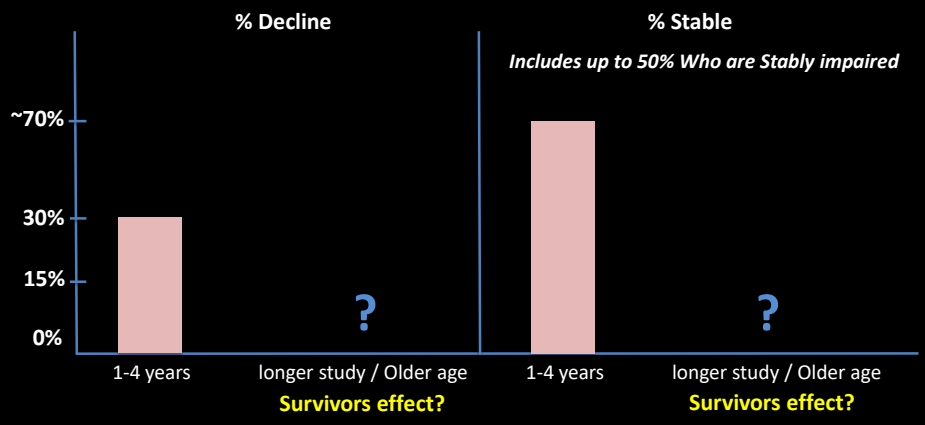
~ 10% higher

HIV Neurobehavioral Research Program data provided in Knut et al. JAIDS *In press*

Neurocognitive trajectories

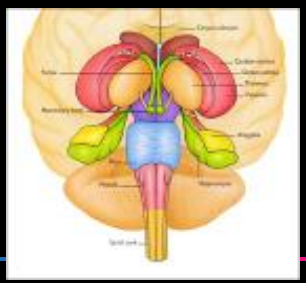


Cognitive change in chronic HIV: International Figures



27 Volumetric MRI studies 2006-2018

- Entirely virally suppressed cohort=5
- Appropriate HIV- control group=13
- Heterogeneity in segmentation softwares and analytic platforms
- Report of HAND prevalence not systematic
- Inclusion of key biomarkers relevant to chronic HIV infection inconsistent



Subcortical atrophy is more prominent
Cortical differences depends on methods

HIV *age interaction effect was inconsistently observed

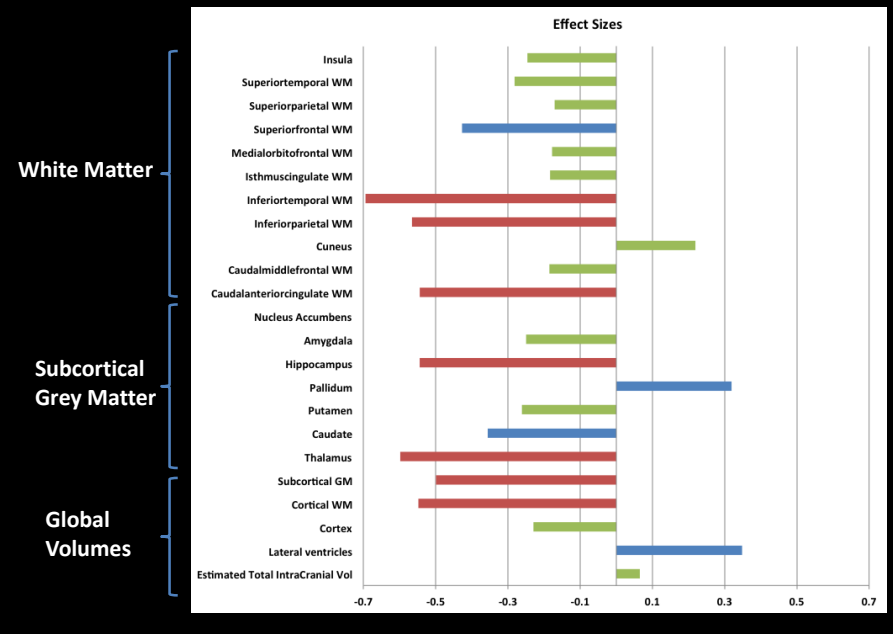
Longitudinal studies are just emerging

Most robust risk factors for atrophy: Age, HAND severity, Low nadir CD4, HIV duration, longer ART exposure

Emerging/less robust risk factors for atrophy: Detectable/Residual CSF HIV RNA; Higher cholesterol, Diabetes; plasma HIV DNA; smoking; early life trauma, old age, accelerated aging, accentuated aging

No gender difference (1 study)

Magnitude of the atrophy



Mild neurocognitive impairment 'atrophic signature'

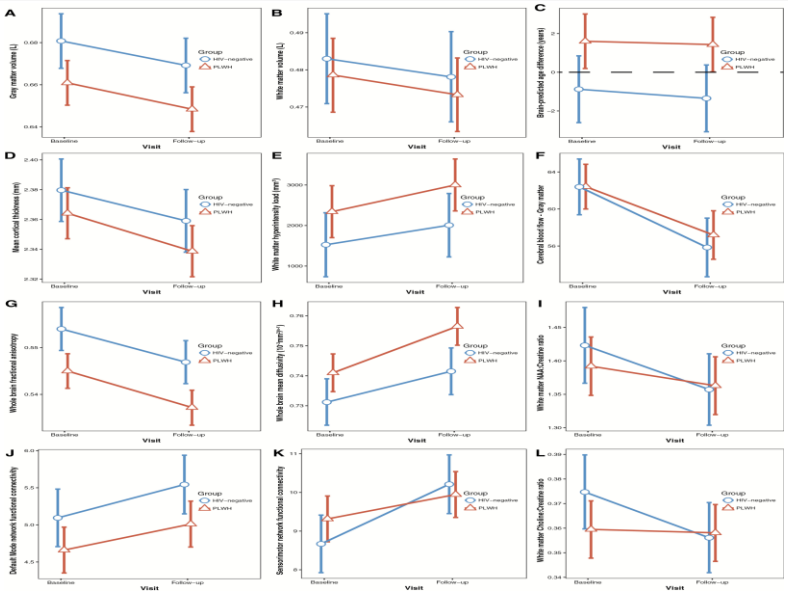
Compared to NP-normal

ANI

Reduced medial-orbitofrontal WM (p=.04, β=-.31).

MND

Enlarged lateral ventricles (p=.02, β=.34)
Reduced caudal-middle-frontal WM (p=.04, β=-.32)
Reduced caudal-anterior-cingulate WM (p=.006, β=-.42)
Reduced inferior-parietal WM (p=.04, β=-.33)



From: **No Evidence for Accelerated Aging-Related Brain Pathology in Treated Human Immunodeficiency Virus: Longitudinal Neuroimaging Results From the Comorbidity in Relation to AIDS (COBRA) Project**

Clin Infect Dis. 2018;66(12):1899-1909. doi:10.1093/cid/cix1124

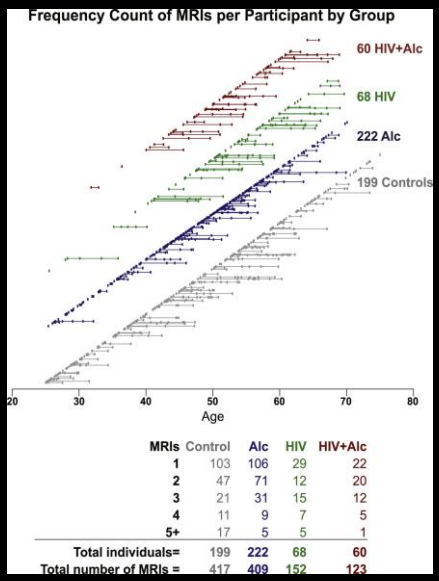
Accelerated and Premature Aging

Characterizing Regional Cortical Volume Loss in Human Immunodeficiency Virus Infection: Contributions From Alcohol, Substance Use, and Hepatitis C Coinfection

Adolf Pfefferbaum, Natalie M. Zahr, Stephanie A. Sassoon, Dongjin Kwon, Kilian M. Pohl, Edith V. Sullivan

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging

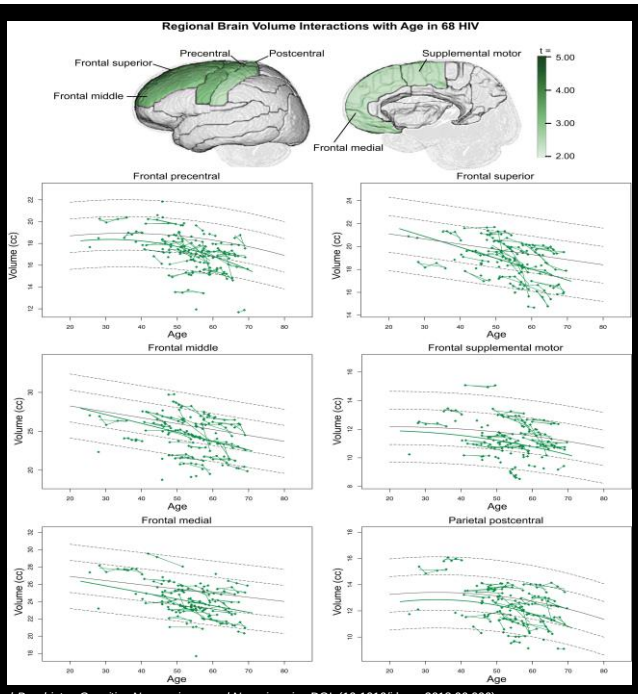
DOI: 10.1016/j.bpsc.2018.06.006



MRIs	Control	Alc	HIV	HIV+Alc
1	103	106	29	22
2	47	71	12	20
3	21	31	15	12
4	11	9	7	5
5+	17	5	5	1
Total individuals=	199	222	68	60
Total number of MRIs =	417	409	152	123

14 years!

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging DOI: (10.1016/j.bpsc.2018.06.006)



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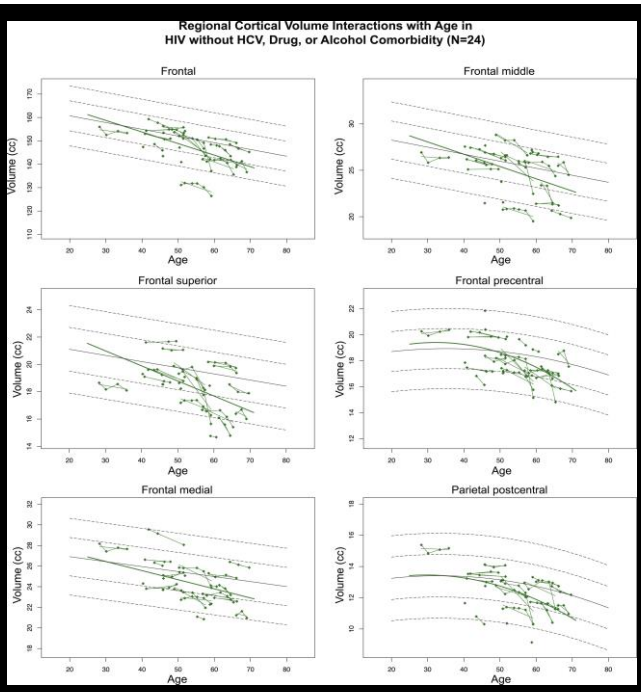
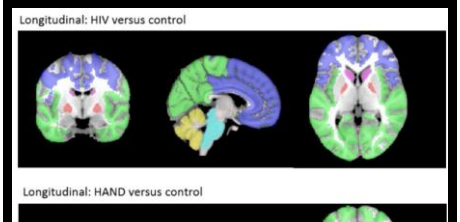


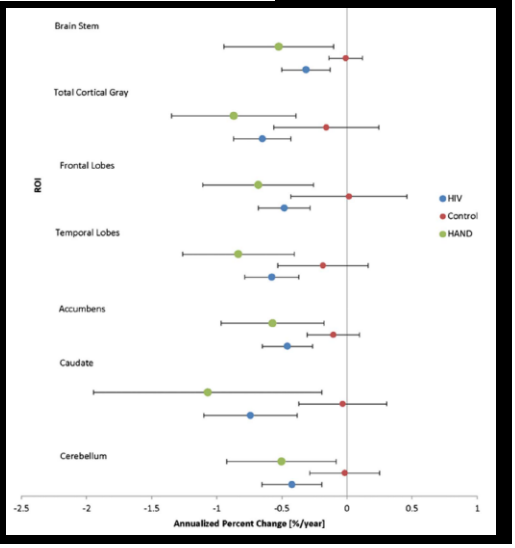
Biological Psychiatry: Cognitive Neuroscience and Neuroimaging DOI: (10.1016/j.bpsc.2018.06.006)

Progressive Brain Atrophy Despite Persistent Viral Suppression in HIV Patients Older Than 60 Years

Katherine M. Clifford, BA,† Vishal Samboju, MS,* Yann Cobigo, PhD,* Benedetta Milanini, PhD,* Gabriel A. Marx, BA,* Joanna M. Hellmuth, MD, MHS,* Howard J. Rosen, MD,* Joel H. Kramer, PsyD,* Isabel E. Allen, PhD,‡ and Victor G. Valcour, MD, PhD*§*

J Acquir Immune Defic Syndr • Volume 76, Number 3, November 1, 2017





Diffusion Tensor Imaging: HIV * aging: Results

1st Author date	FA	MD	Comments
Chang 2008	HIV effect (parietal WM)	HIV effect (frontal WM) HIV *age effect (CC genu)	Trends for HIV*age effect in putamen but meaning of MD is different in non-WM
Nir 2014	HIV effect (+CC, across the WM)	HIV effect (across the WM) Also for AD and RD	No HIV*age effect WM changes correlated with age Lower cognition correlated with WM changes Older participants but restricted range
Seider 2016	Age effect HIV*age effect	-	No HIV effect on FA HCV effect on FA
Khun 2018	Predicted brain age gap (BAG) from DTI metrics		

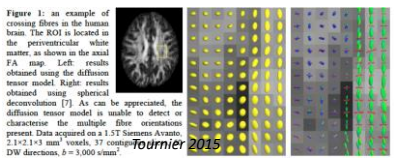
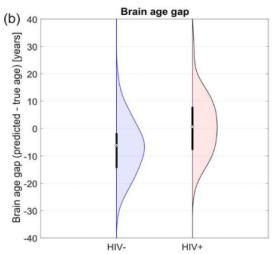


Figure 1: an example of crossing fibres in the human brain. The ROI is located in the periventricular white matter, as shown in the axial FA map. Left: results obtained using the diffusion tensor model. Right: results obtained using spherical deconvolution [7]. As can be appreciated, the diffusion tensor model is unable to detect or characterise the multiple fibre orientations present. Data acquired on a 1.5T Siemens Avanto. 2.1×2.1×3 mm³ voxels, 37 contiguous DW directions, $b = 3{,}000$ s/mm².

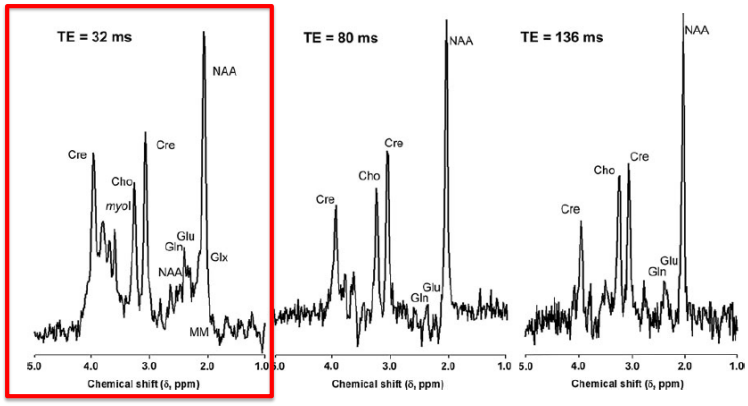
Tournier 2015



^{1}H MRS: methodological overview

Scanners	Scanner	SV	Long/Short TE	PRESS	Absolute/relative
	76% 1.5T 18% 3T 6% 4T	100%	94% short TE	85%	45% relative to Cr 15% relative to H_2O 40% absolute

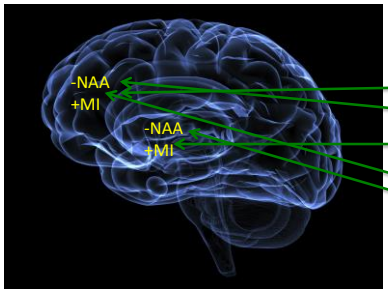
1 study used MSRI



Rae CD. A guide to the metabolic pathways and function of metabolites observed in human brain 1H magnetic resonance spectra. Neurochem Res 2014;39:1-36.

MRS & persistent HIV-injury on cART: HIV effects

Most common findings

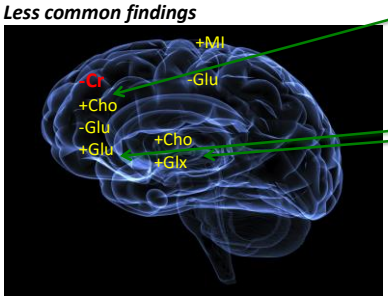


Low nadir

Detectable plasma VL

HIV duration

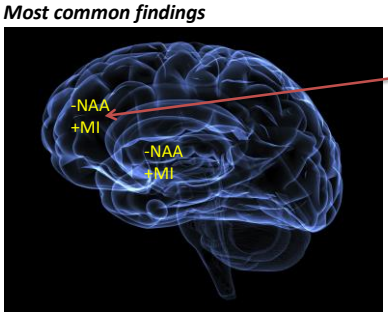
Less common findings



Detectable plasma VL;
Low nadir

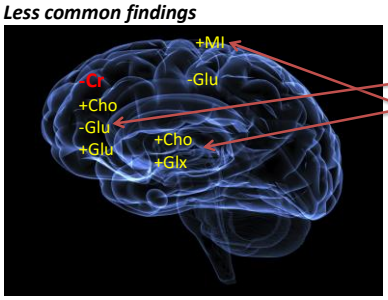
MRS & Persistent HIV-injury on cART: aging, CVD

Most common findings



HIV * Aging

Less common findings

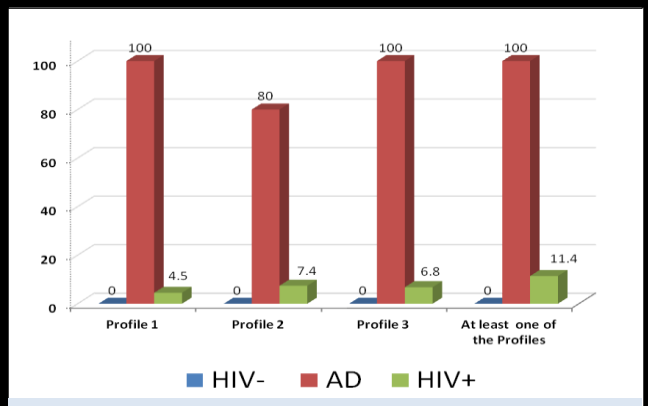


Neuro-asymptomatic

Aging

Pathological aging; CVD

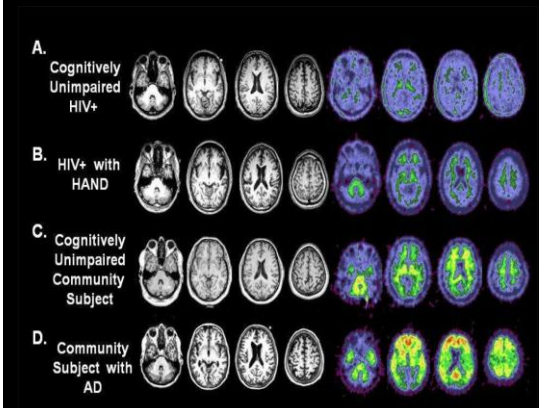
Some are vulnerable for neurodegeneration



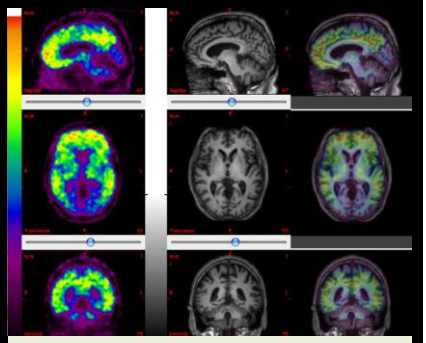
- No elderly controls had a CSF-AD profile
- All AD patients had a at least one CSF-AD profile.

- Of the HIV+ individuals, 11.4% (5/44) had a CSF-AD profile
  - 4.5% had profile 1, 7.1% had profile 2 and 6.8% had profile 3
  - 1 case met the AD-CSF profile on all 3 cut-offs.
  - Age adjusted p-tau cut-offs yielded same results

HAND and AD in HIV+ people aged 40-60 remains rare



* Arch Neurol. 2012 Jan;69(1):72-7

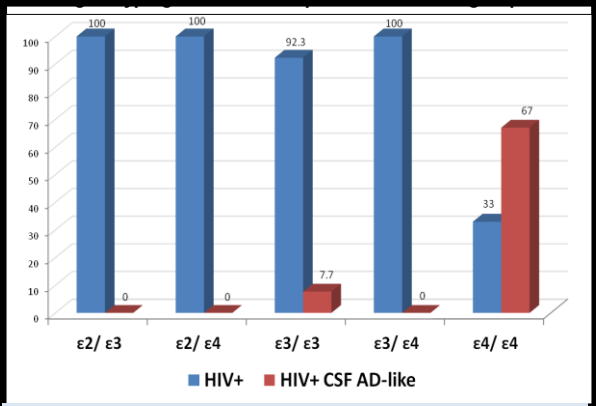


Cysique et al. PIB PET pilot in HAND

- 1/10 cases. Was virally suppressed, 26 years with HIV
- Significant PiB retention = 2.14; (age 66)
- Mainly in fronto-temporal areas
- PiB mean in 100 local elderly controls =1.45; median=1.25;
- PiB in local AD median = 2.25 with marked involvement of striatum and cortex

Studies in age 60+ are needed while taking into account cardiovascular risk factors

Attention to study which do not account for known dementia genetic risk



- CSF-AD like profile was predicted by having:
  - APOE genotype ε4/ε4 (p<.02)
  - lower current neurocognitive performance (p<.01)
  - Past HIV-associated dementia (p<.01)
  - lower nadir CD4 and longer HIV duration (but those results were at trend levels)

• Non-pharmacological Interventions
• Risk Reduction strategies for HAND & dementia

Non Pharmacological Interventions are being tested with encouraging results, but need large RCTs

- **Cognitive training, Psychosocial management, Exercise training**
- **Multimodal interventions** (Physical & mental activity, nutrition, sleep, social engagement, emotional health, substance use) https://www.ncbi.nlm.nih.gov/pubmed/28669770

Healthy Ageing recommendations

- Peer support, reduction of stigma, reduction of social isolation
- Being proactive about Mental health
- Keep cognitively and physically active & reduce cardiovascular diseases risk factors
- Healthy lifestyle strategies and maintained a positive outlook living with HIV

Are older PLHIV health care needs met?

- AIDS Survivor Syndrome
- Care accessibility
- Training of professionals to reduce stigma
- Plan for multi-morbidity assessment in geriatric PLHIV
- Longitudinal studies on cognitive and mental health are needed
- Risk of dementia starts to increase in the general population at age 60+
- We need to know what is the risk of dementia in PLHIV aged 60+

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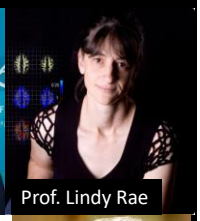
Prof. Bruce Brew


Prof. Lindy Rae


Prof. Paul Maruff


Prof. Robert Heaton


Prof. Edwina Wright


Prof. Sean Rourke