Hot Topics on CNS and HIV…From CROI

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Disclosures

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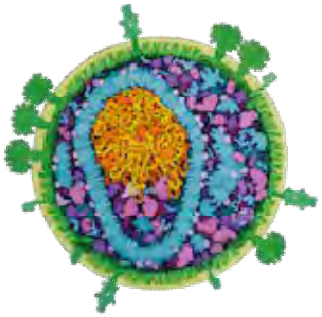

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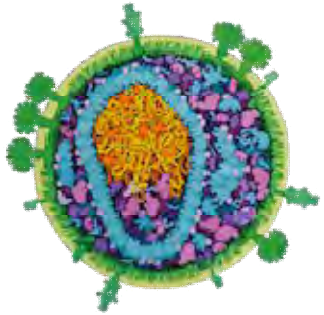
- **HAND Diagnosis-Related**
  - Novel Multivariate Method
  - Depression
- **Pathogenesis**
  - Host (Aging)
  - HIV
- **Treatment**

HAND Diagnosis



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Background

Cognitive impairment reportedly remains prevalent in the cART era.

How do we assess impairment?

- Neuropsychological tests
- Define a threshold

Novel multivariate method (NMM) using the Mahalanobis distance

- Analogous to a multivariate standard deviation

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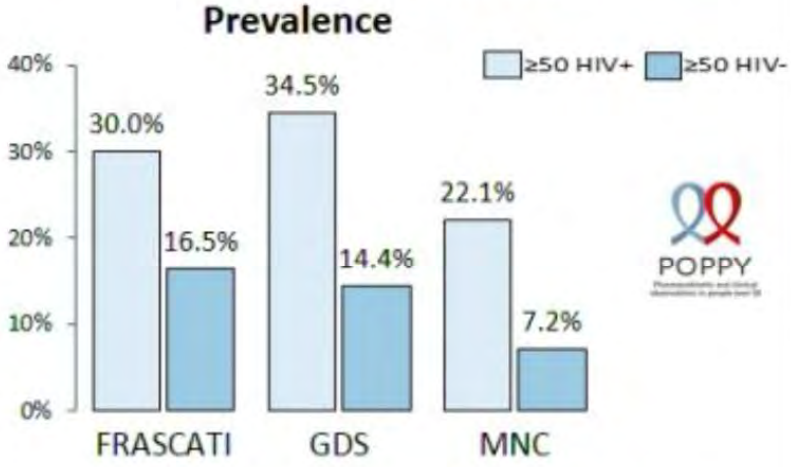
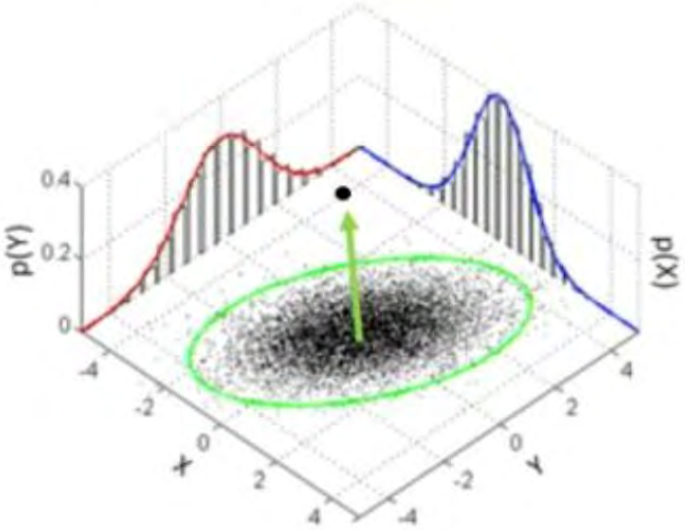


De Francesco *et al.* BMC Infect Dis. 2016 Oct 28;16(1):617.



Underwood et al, CROI 2018, Abstract 125

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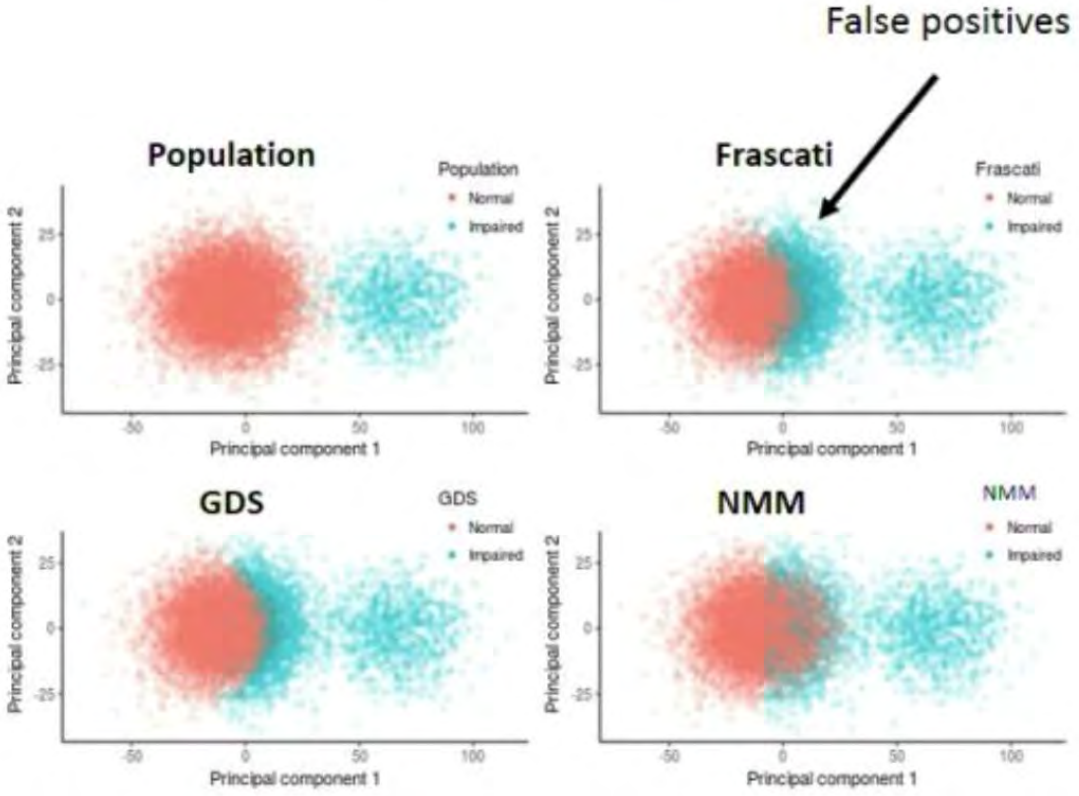
Background

The relationships with neuroimaging measures have been **inconsistent.**

The HAND (or 'Frascati') and global deficit score (GDS) have <80% specificity.

Novel multivariate method (NMM) allows specification of the expected false positive rate *a priori.*

Specificity = 1 – false positive rate



Underwood *et al, HIV medicine* (2017) [Abstract]

Methods – cognitive function

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139 PLWH - all plasma HIV RNA <50 copies/mL
- all had MRI

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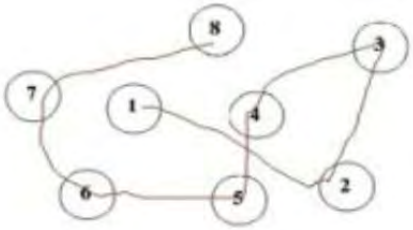
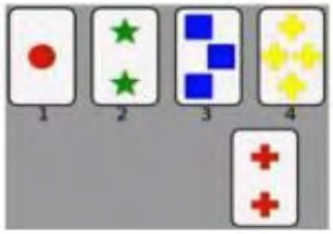
Neuropsychological test battery
(testing attention, executive function, language, learning, memory, motor function and processing speed)





Raw scores converted to demographically adjusted cognitive domain T-scores

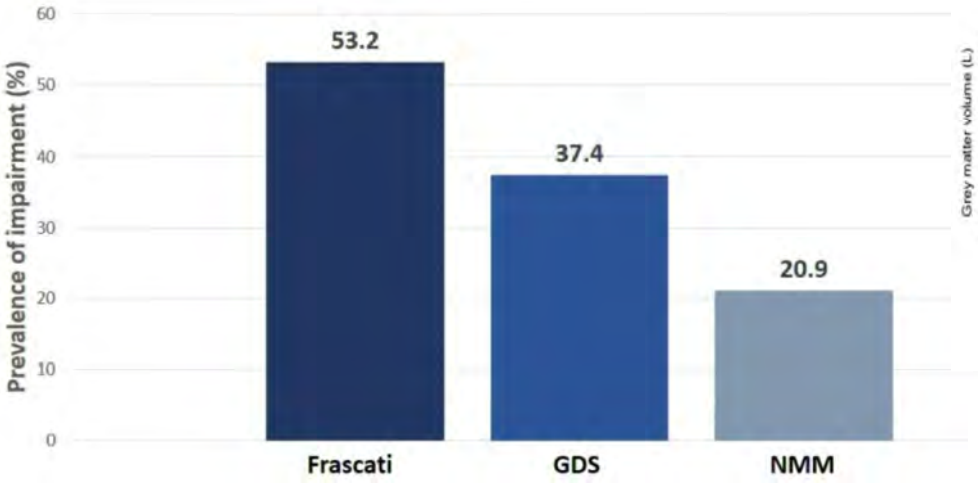
Cognitive impairment defined using Frascati[1], GDS[2] criteria and a novel multivariate method (NMM) with 85% *a priori* specificity

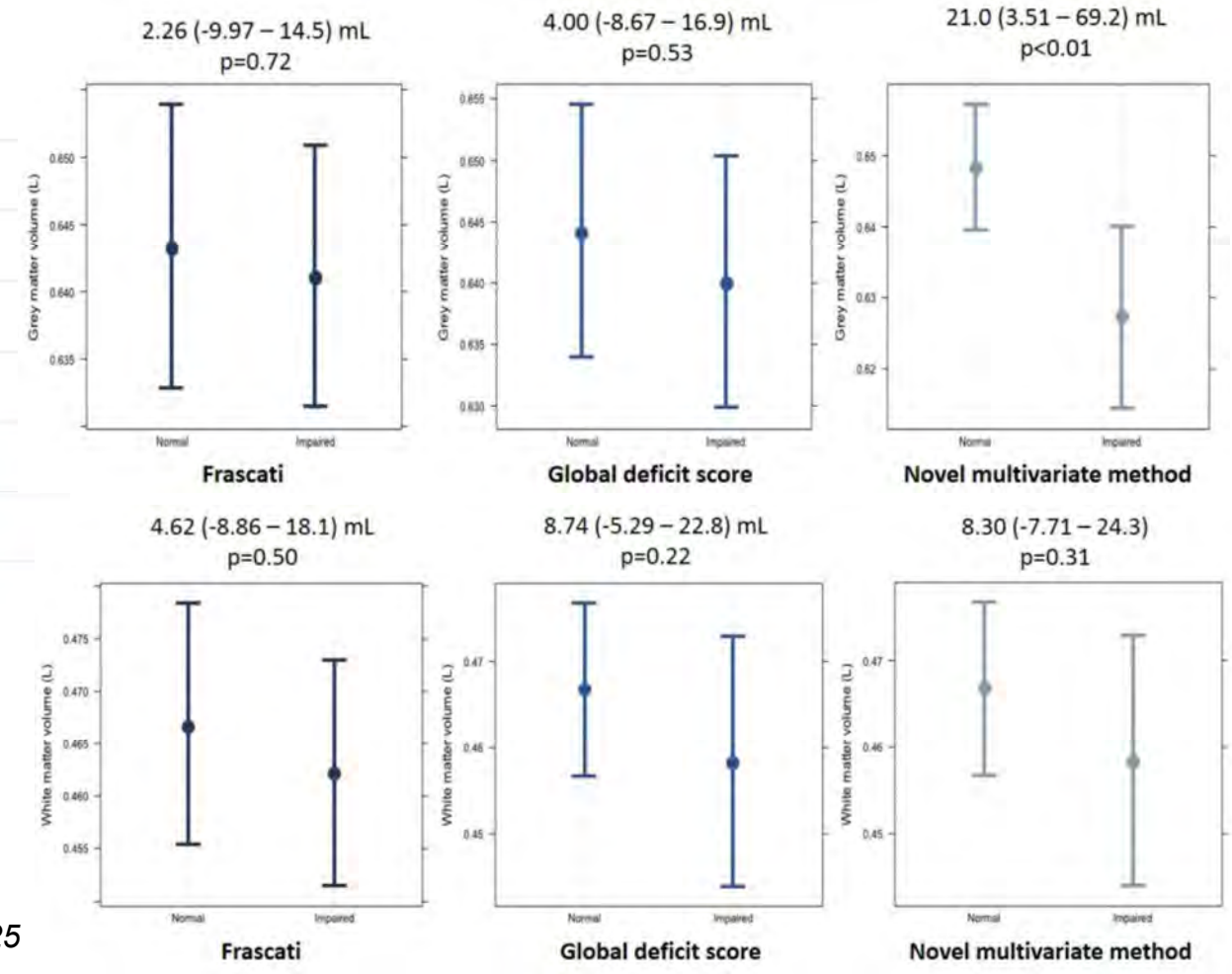
$$critical\ value = -\sqrt{\frac{(n-1)^2}{n} \cdot \beta_{\alpha;\frac{p}{2},\frac{(n-p-1)}{2}}}$$

Where:
n = the number of subjects
p = the number of domains/tests
β = the critical value from the β distribution with parameters $\frac{p}{2}$ and $\frac{(n-p-1)}{2}$ with α=0.05 (i.e. corresponding to the bottom 5th percentile of a normative population)

[1]Antinori A *et al, Neurology* (2007); [2]Carey CL *et al, J Clin Exp Neuropsyc* (2004); [3]Underwood *et al, HIV medicine* (2017) [Abstract]
http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/Posters/commended-poster-presentations/P83.pdf

More Conservative Classification Approach That Correlates Better with Structural Imaging





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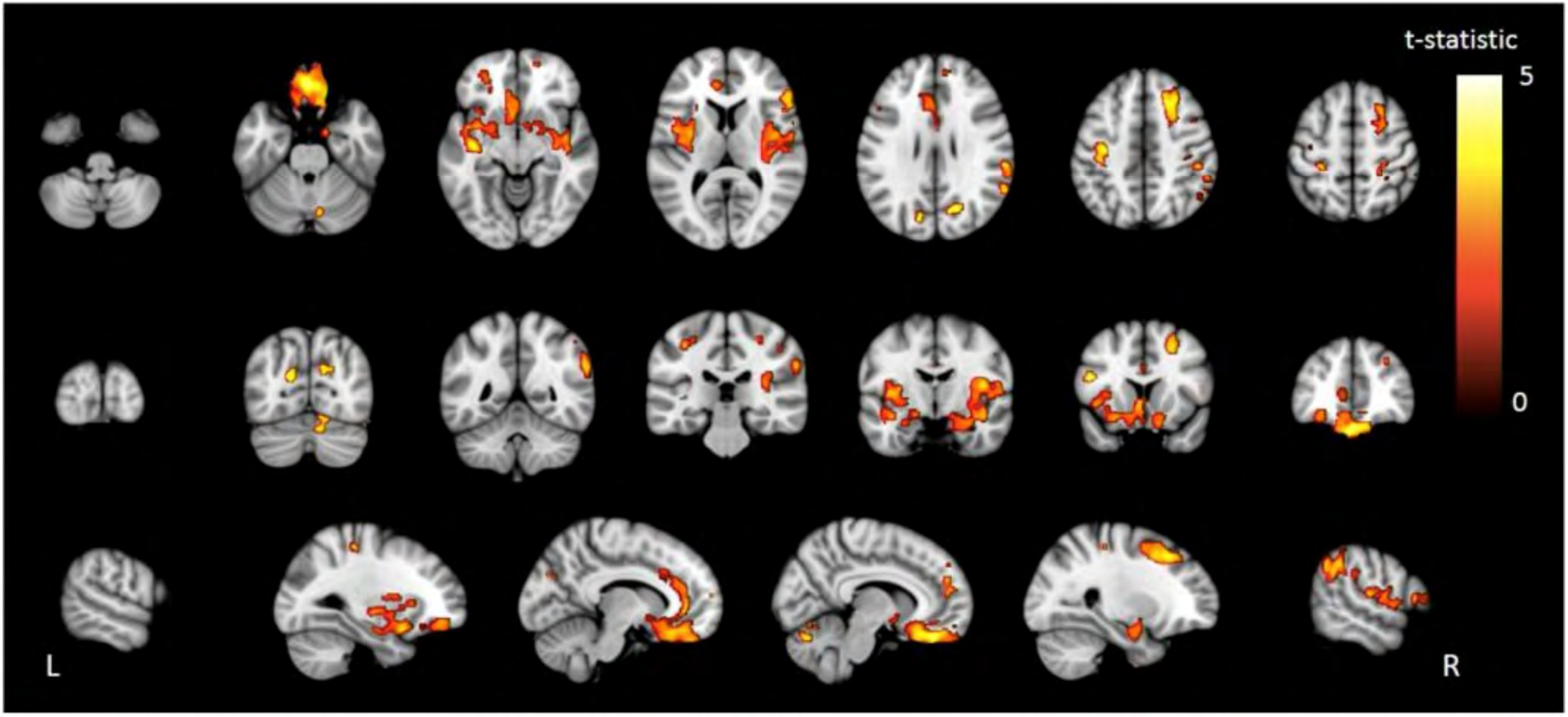
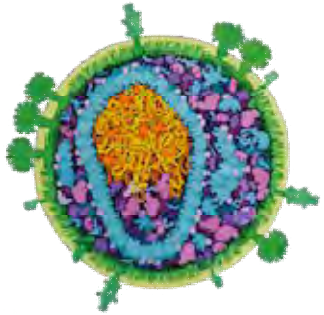
Underwood et al, CROI 2018, Abstract 125

NMM – grey matter voxelwise analysis



Grey matter voxel based morphometry group comparison. Areas with significantly ($p < 0.05$) lower grey matter volume in those with NMM impairment vs. no impairment coloured by the t-statistic - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume, scanner and comorbidity status. Statistical image overlaid on MNI 152 T1

Depression



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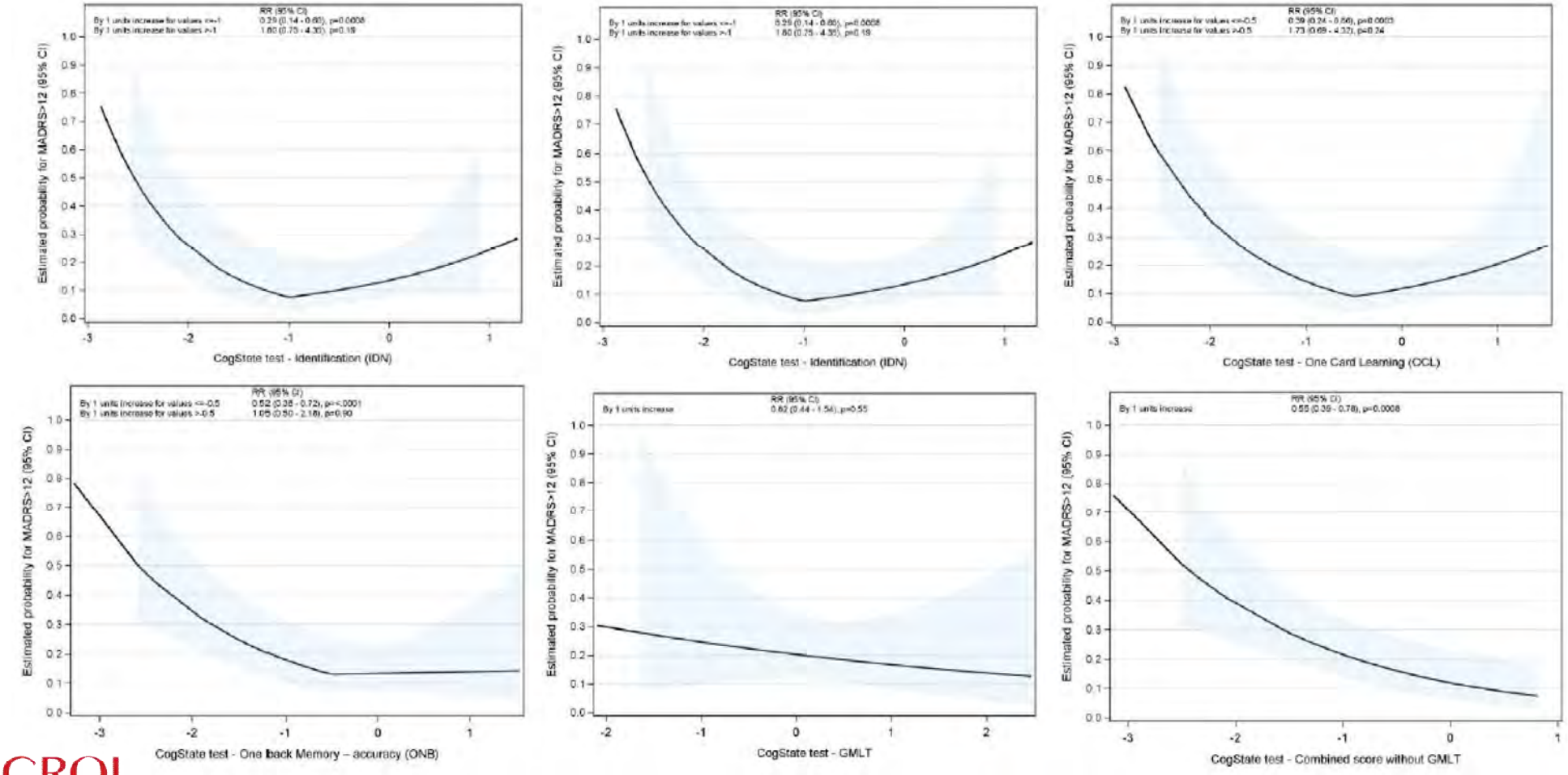
Depression Is Associated with NCI



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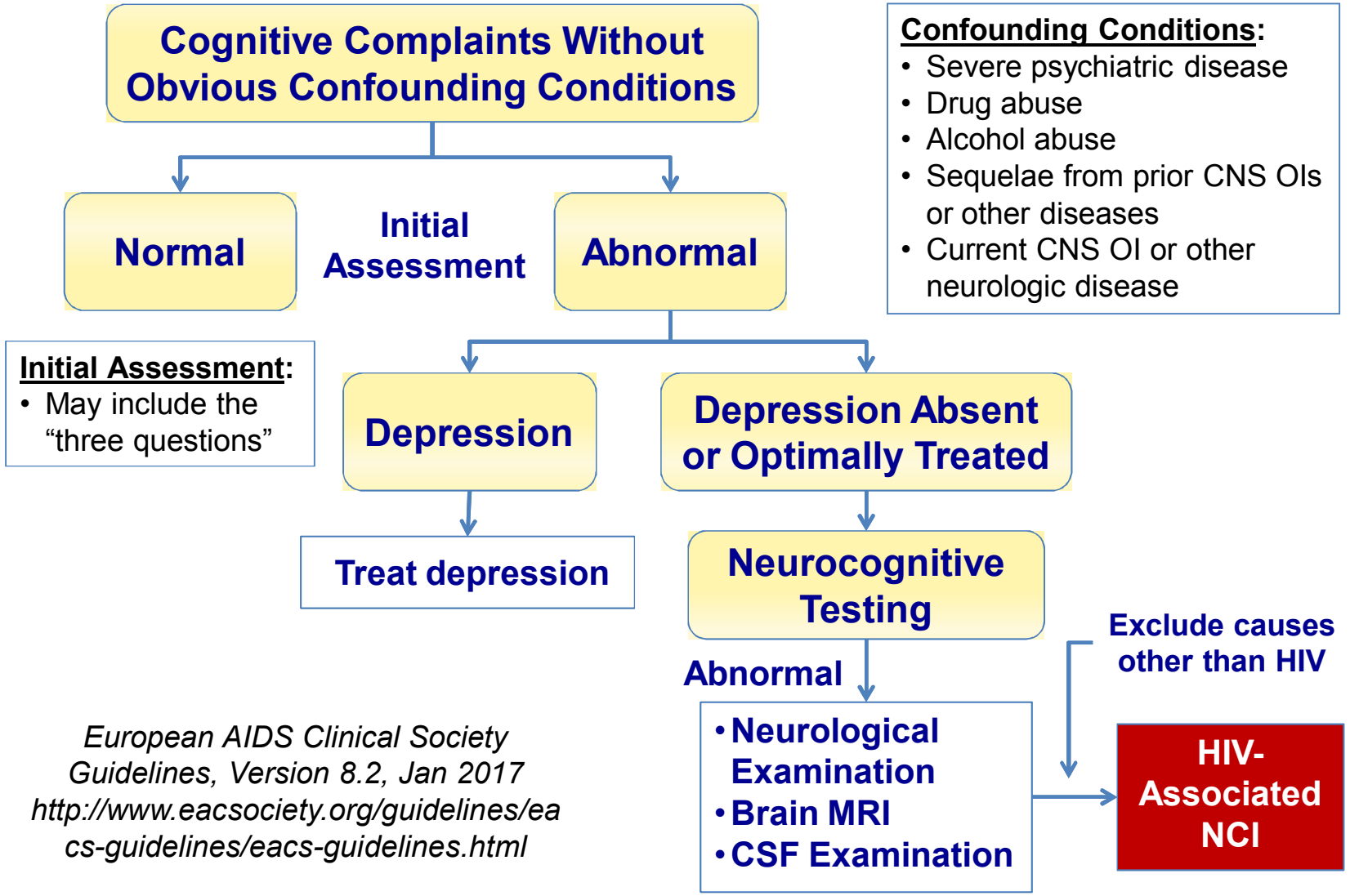
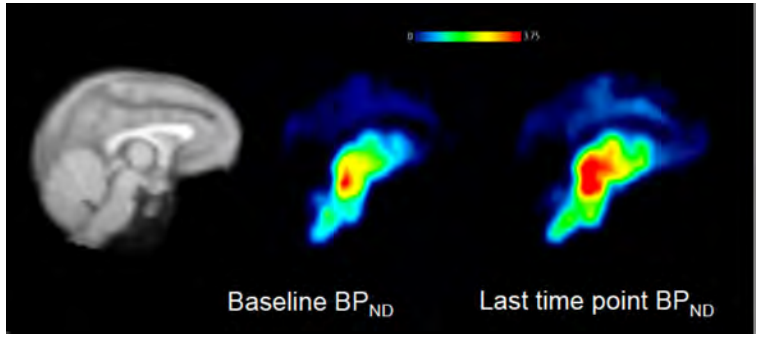
Mellgren et al, CROI 2018, Abstract 422

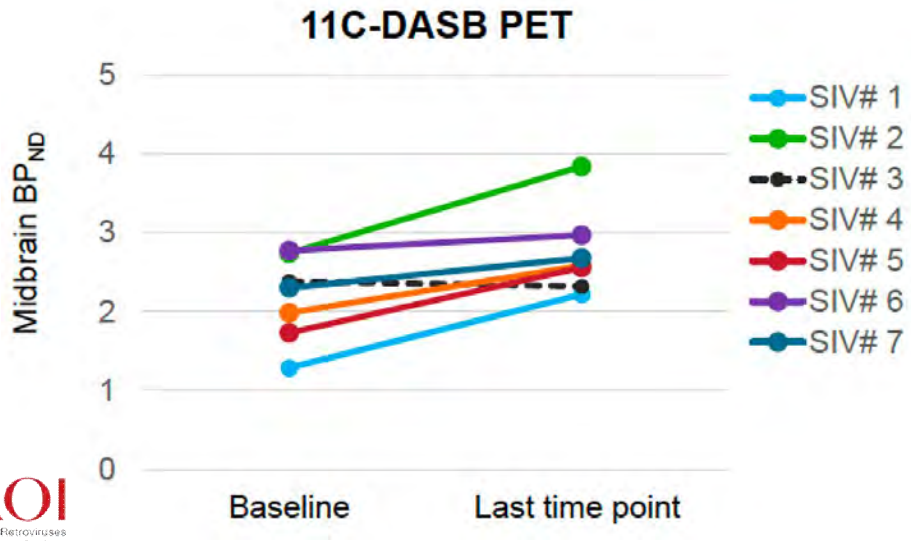
EACS Guidelines 2017

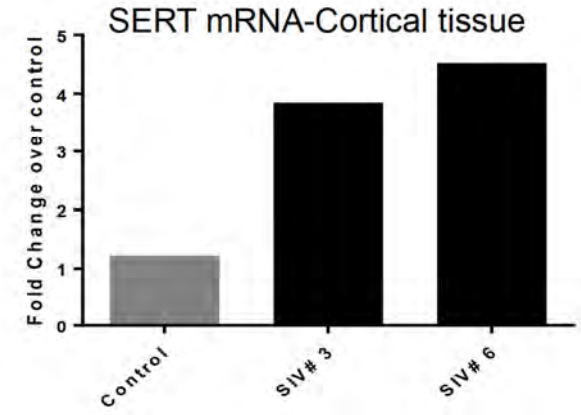


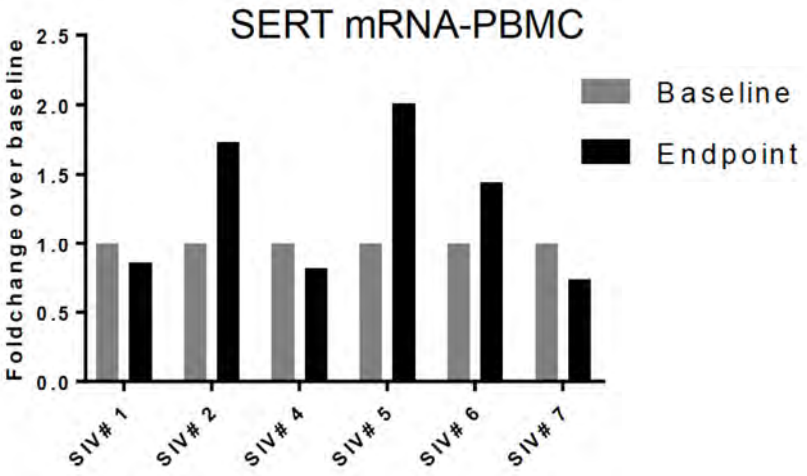
European AIDS Clinical Society Guidelines, Version 8.2, Jan 2017
http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

Serotonin Transporter Expression Increases with Duration of SIV Infection



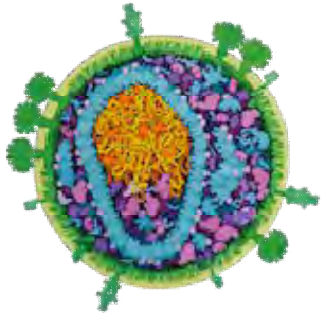






Shah et al, CROI 2018, Abstract 426

Pathogenesis- Aging



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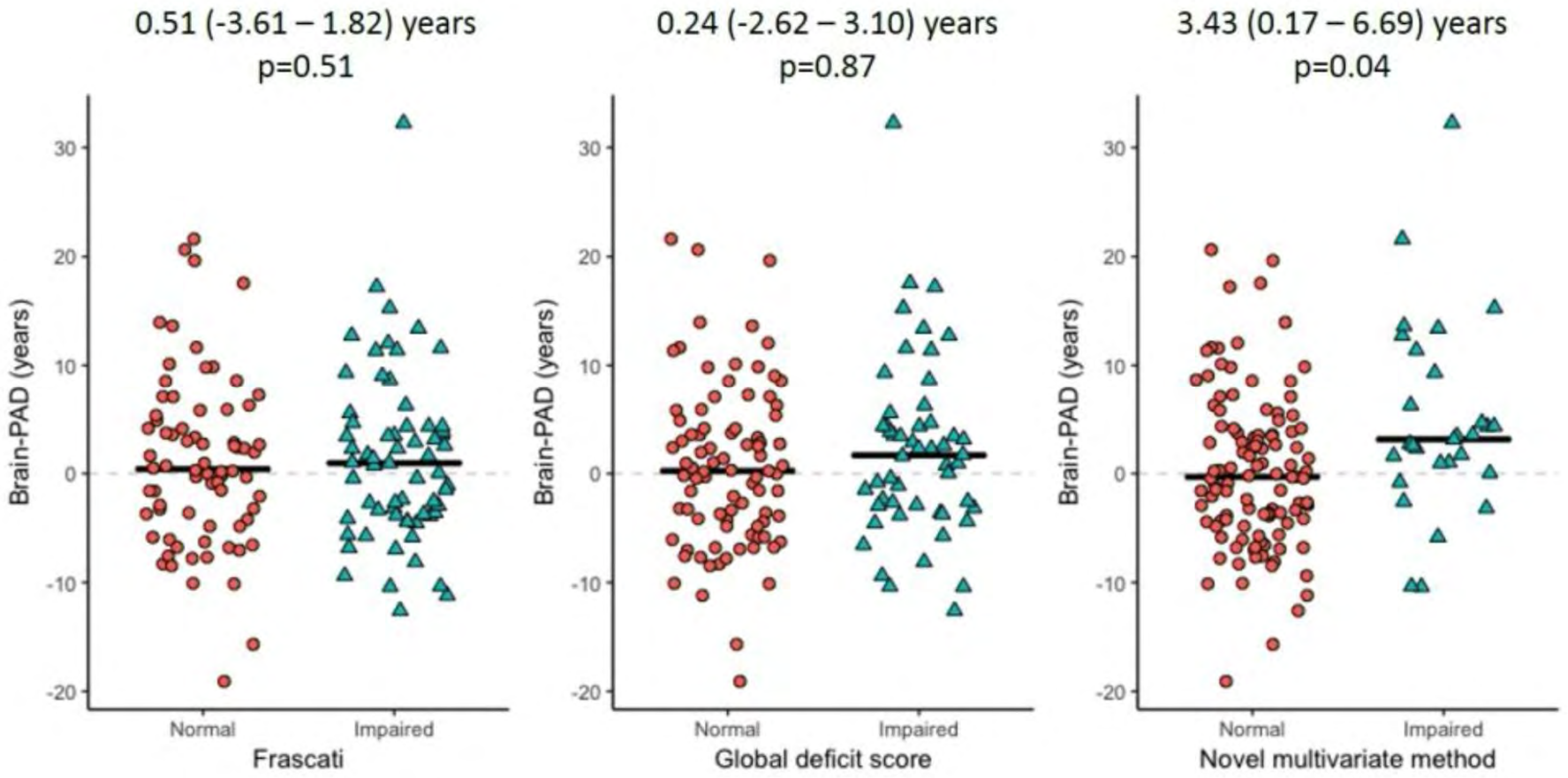
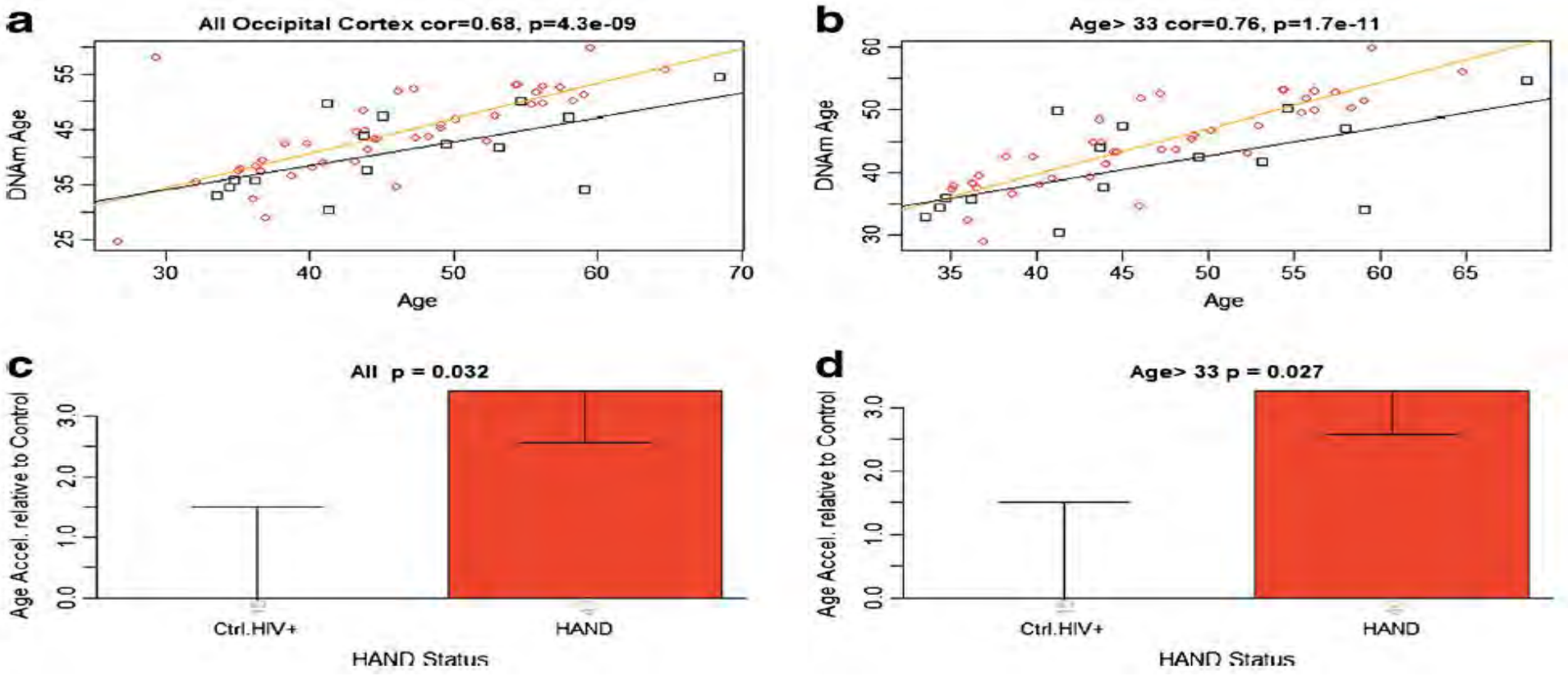
NMM Method is Also Associated with Older Predicted Brain Age



Underwood et al, CROI 2018, Abstract 125

HIV may Accelerate Aging to a Greater Extent in the Brain

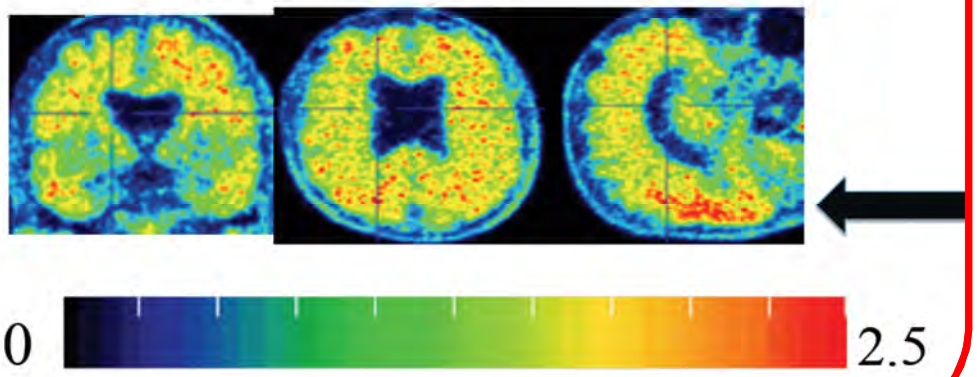


Levine et al, J Neurovirol 2015, Epub ahead of print

Amyloid Uptake is Greater in HIV+ Adults in Their 50s

Standardized uptake value ratio (SUVR) generated from 20 min scans (50-70 min post tracer injection) dynamic [18F]AV-45 PET

Positive Amyloid uptake in a 64 year old HIV+ individual with ANI



SUVR regional uptake by HIV serostatus and decade

Age (years)	50-59		60-69	
	HIV+	HIV-	HIV+	HIV-
Prefrontal	1.48	1.28*	1.32	1.40
Superior frontal	1.48	1.26*	1.38	1.44
Posterior Cingulate	1.62	1.43*	1.48	1.63
Parietal	1.61	1.34*	1.38	1.43
Precuneus	1.52	1.28*	1.38	1.32
Putamen	1.47	1.28*	1.38	1.42

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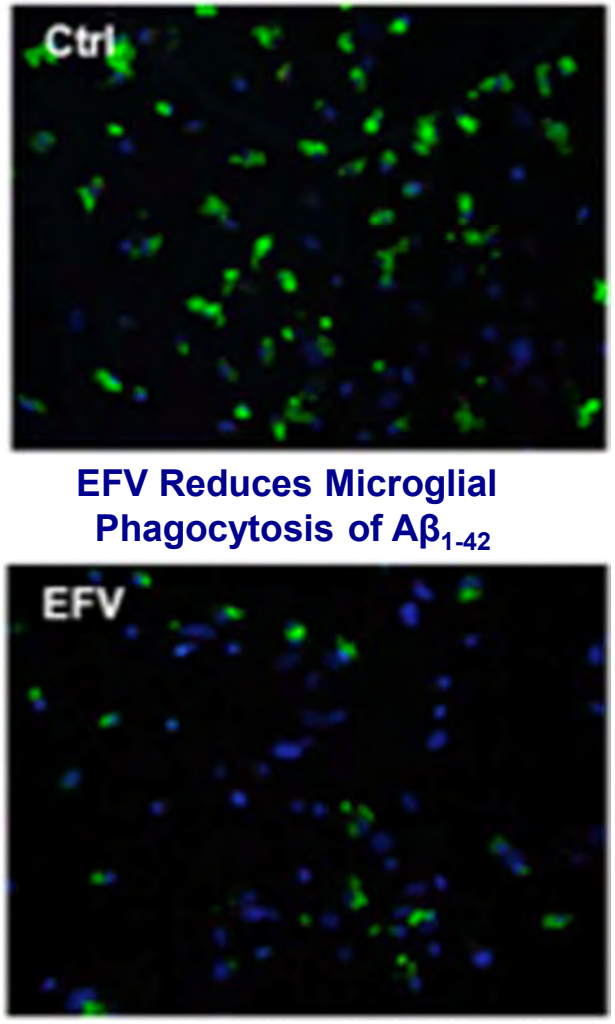
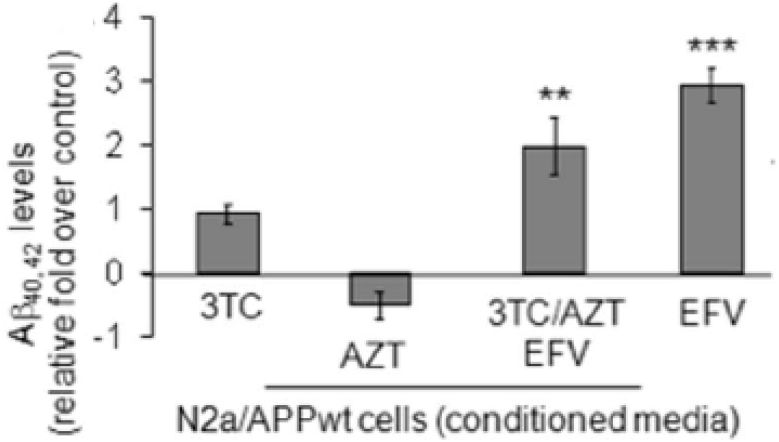
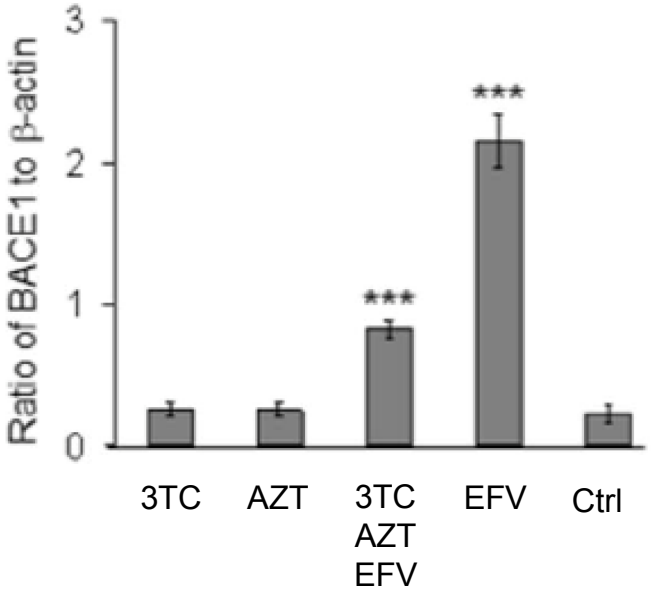
Sacktor et al, CROI 2018, Abstract 438

ART Drugs May Alter Amyloid Processing



EFV Reduces Microglial Phagocytosis of $A\beta_{1-42}$





Brown et al, PLoS ONE 2014, 9(4): e95500

HIV-Associated Global and Thalamic Hypometabolism on FDG-PET

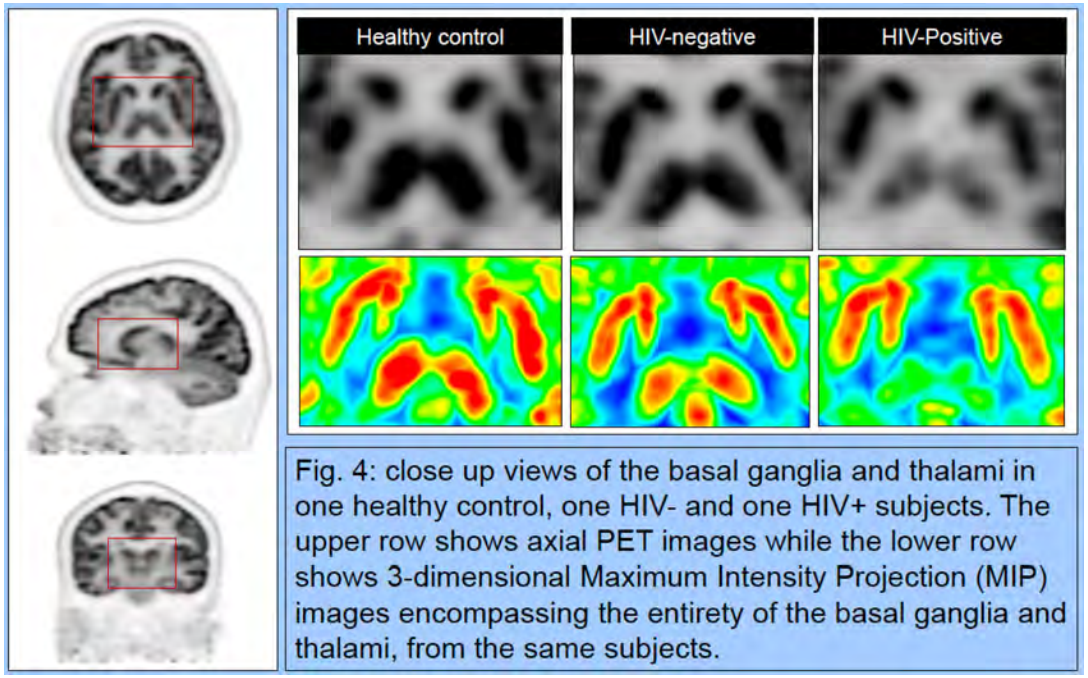
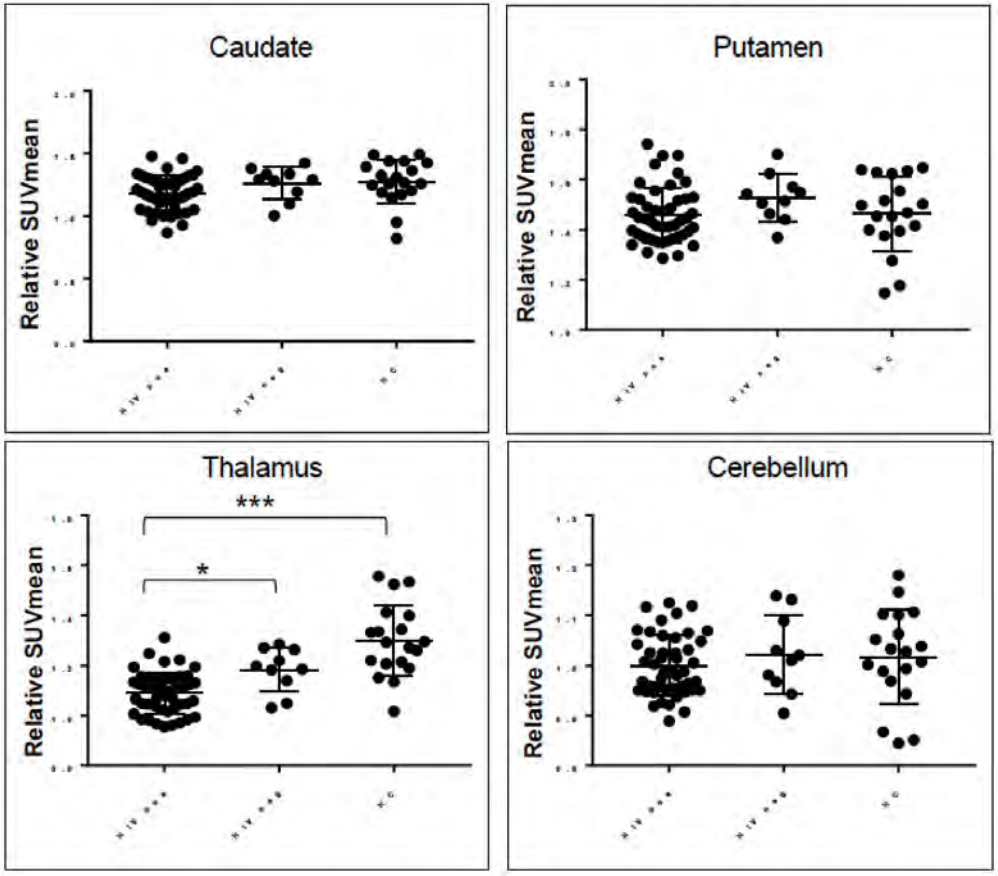


Fig. 4: close up views of the basal ganglia and thalami in one healthy control, one HIV- and one HIV+ subjects. The upper row shows axial PET images while the lower row shows 3-dimensional Maximum Intensity Projection (MIP) images encompassing the entirety of the basal ganglia and thalami, from the same subjects.



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Hammoud et al, CROI 2018, Abstract 440

Neurocognitive Decline Associated with Evidence of Insulin Resistance

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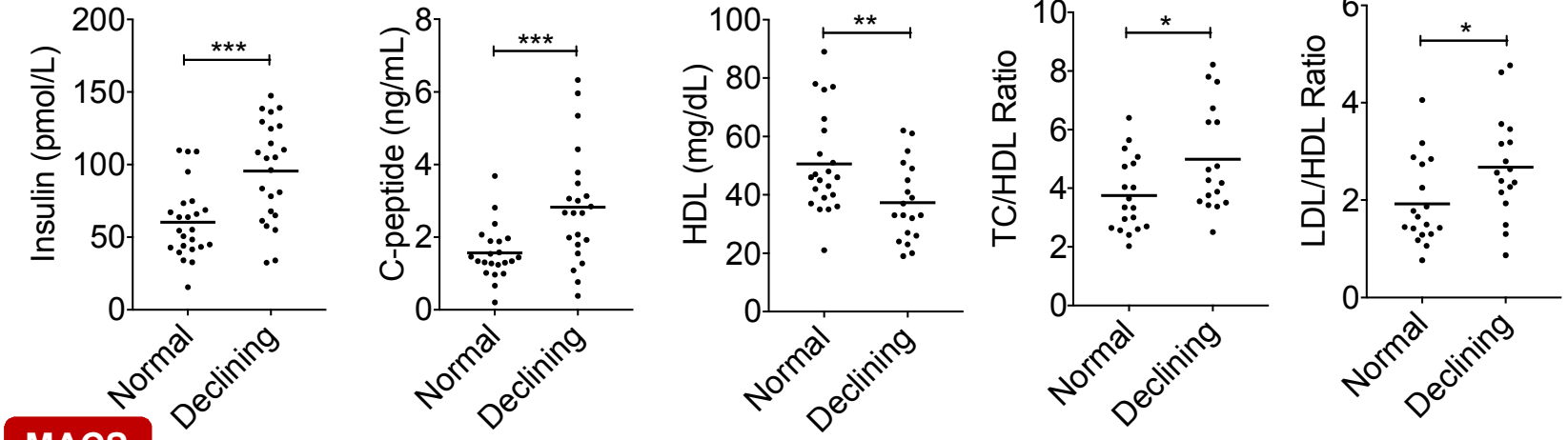
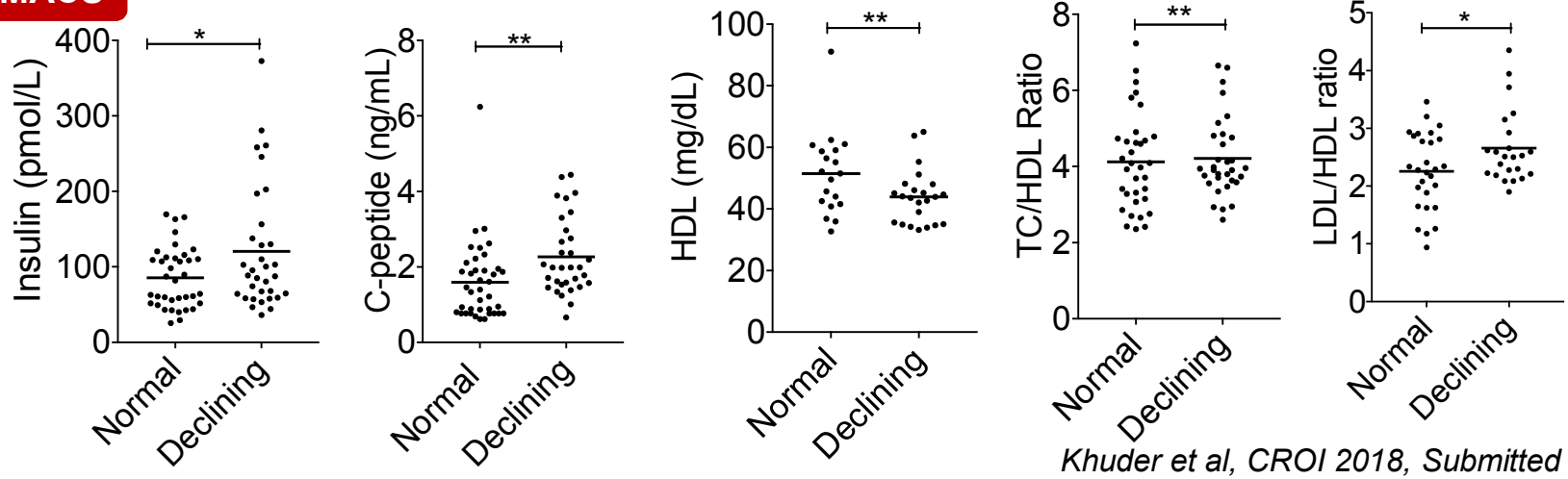
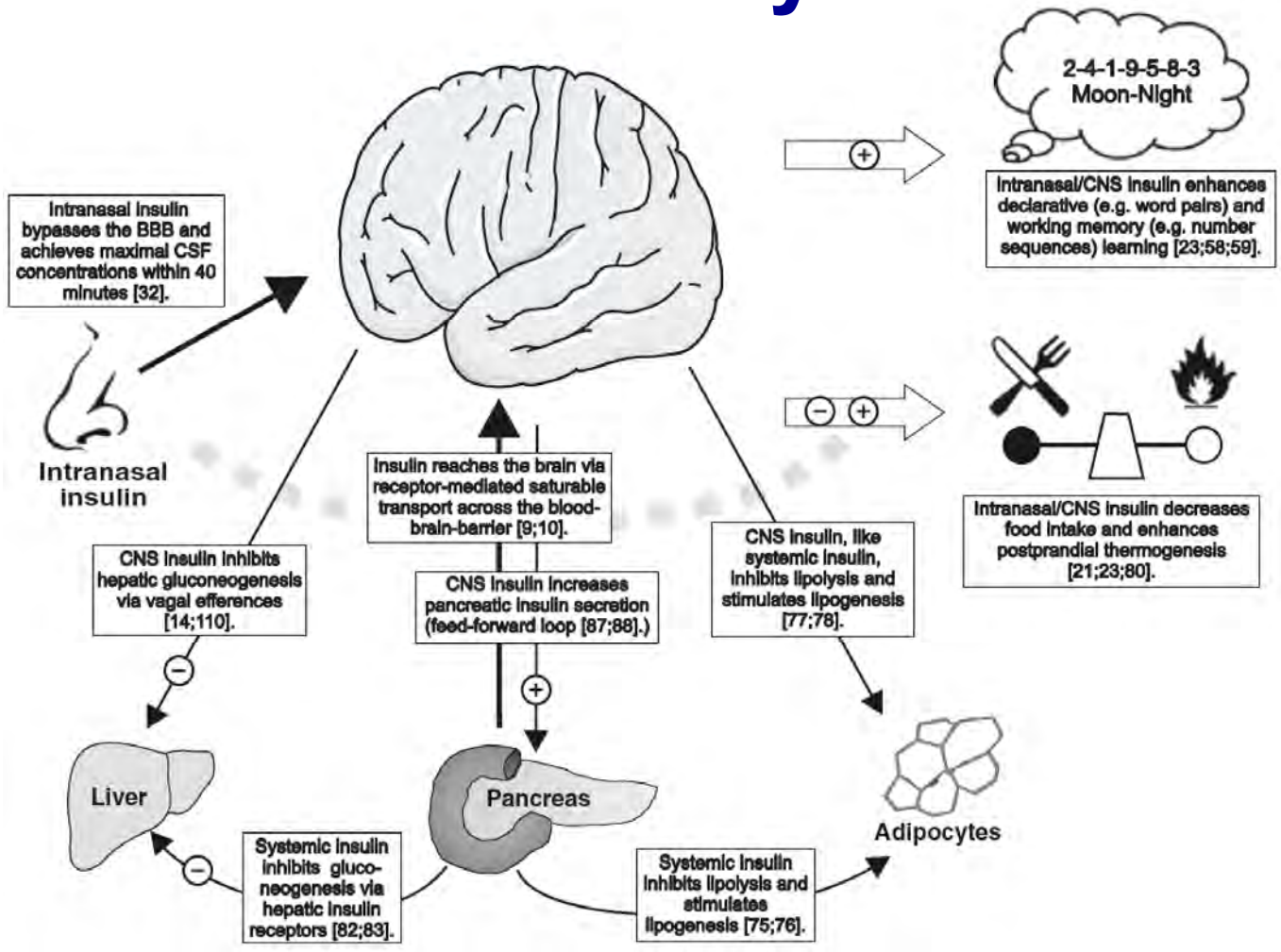


MACS



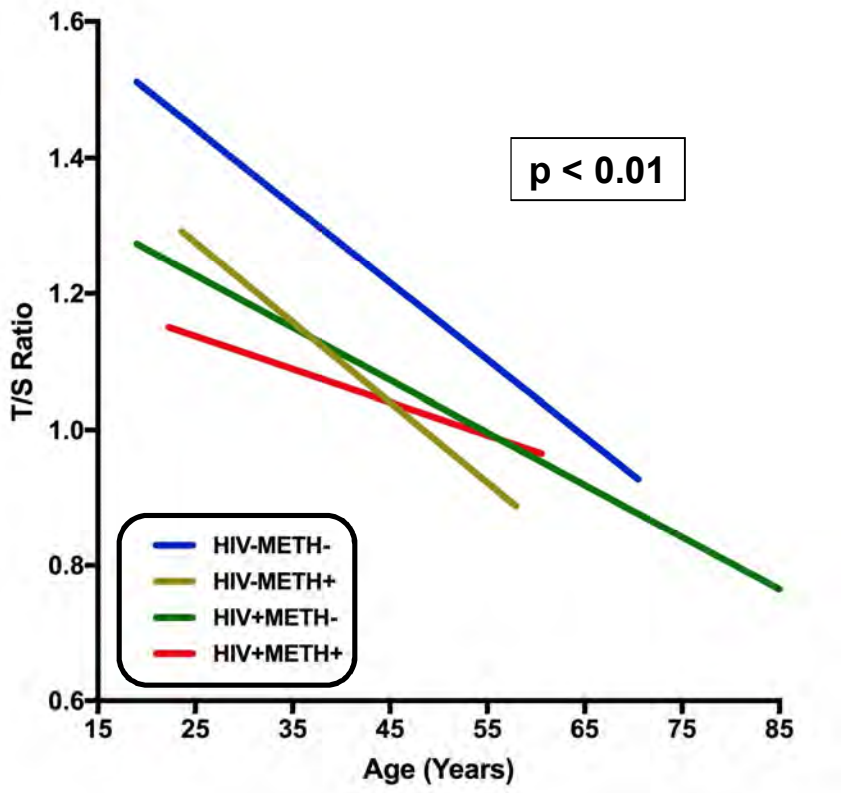
Khuder et al, CROI 2018, Submitted

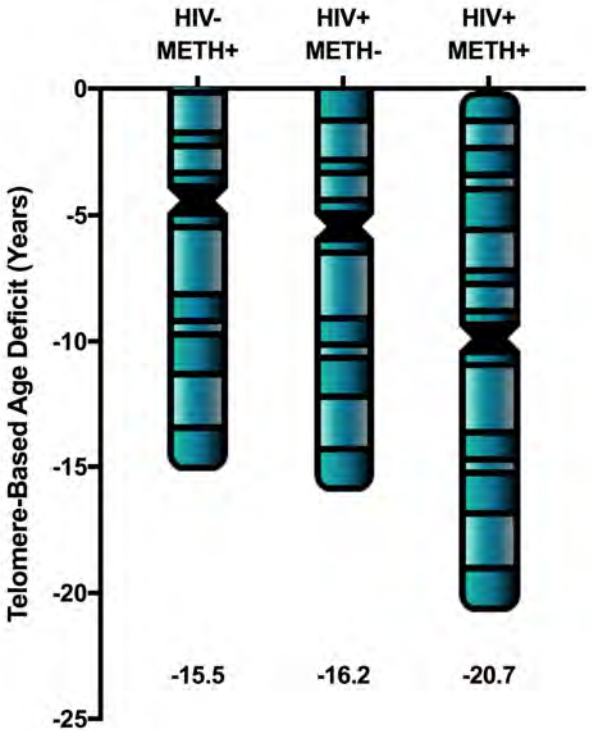
Intranasal Insulin May be Beneficial



Ott et al, Diabetes, Obesity and Metabolism 2012, 14: 214–221

HIV and Methamphetamine May Shorten Telomeres





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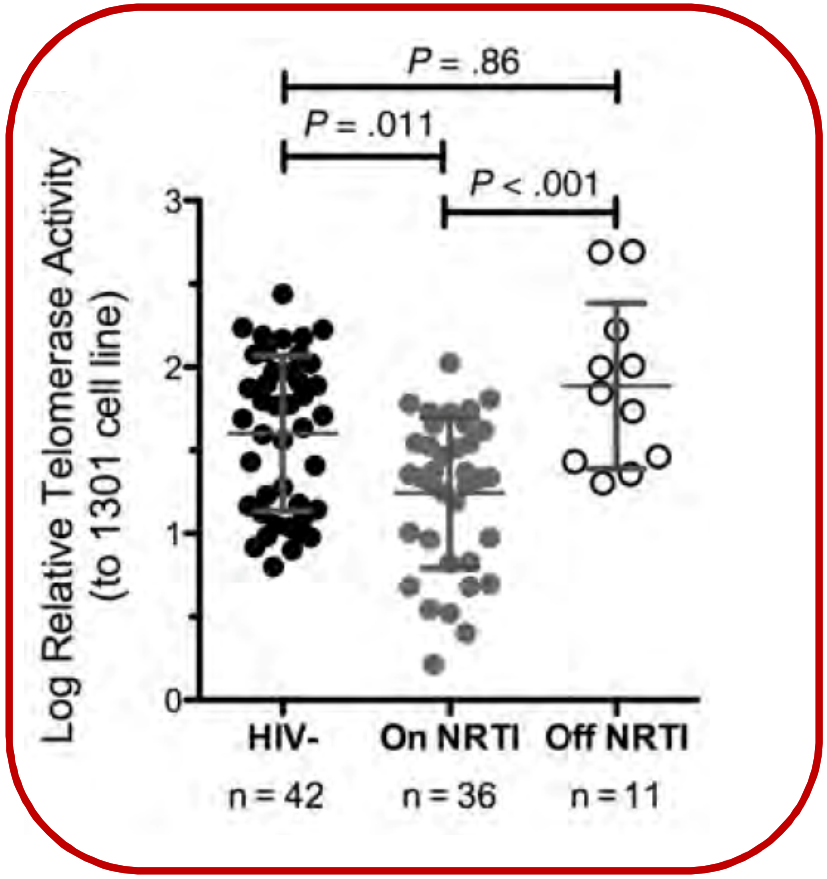
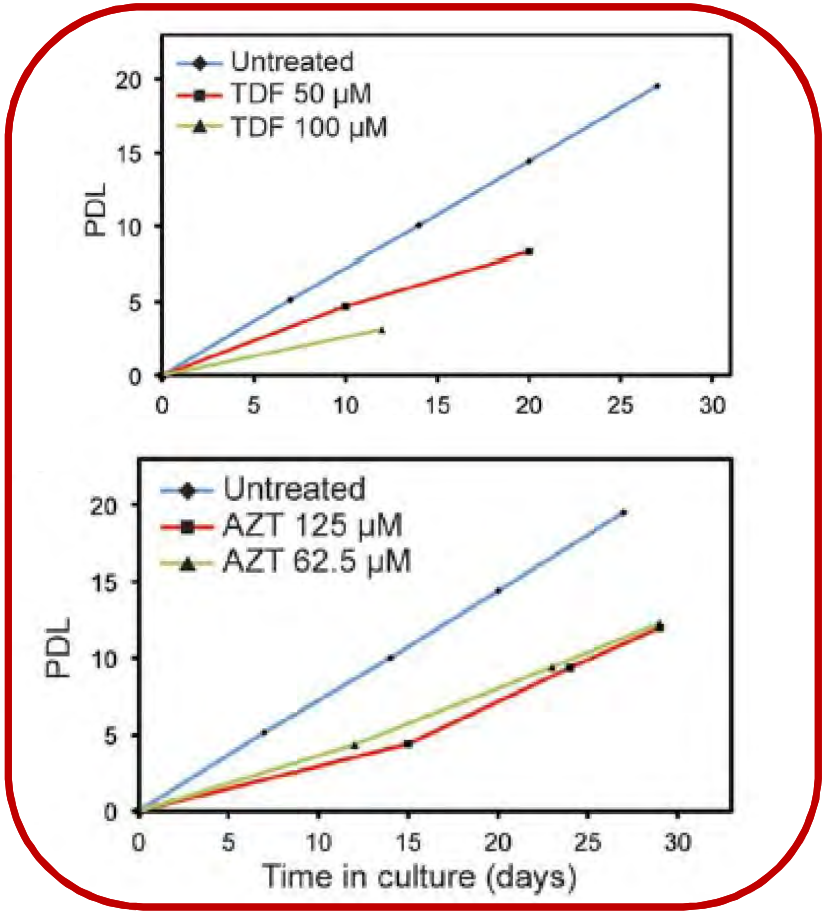
Mehta et al, CROI 2018, Abstract 760

NRTIs May Inhibit Telomerase, Which is a Reverse Transcriptase



Leeansyah et al, J Infect Dis 2013; 207:1157



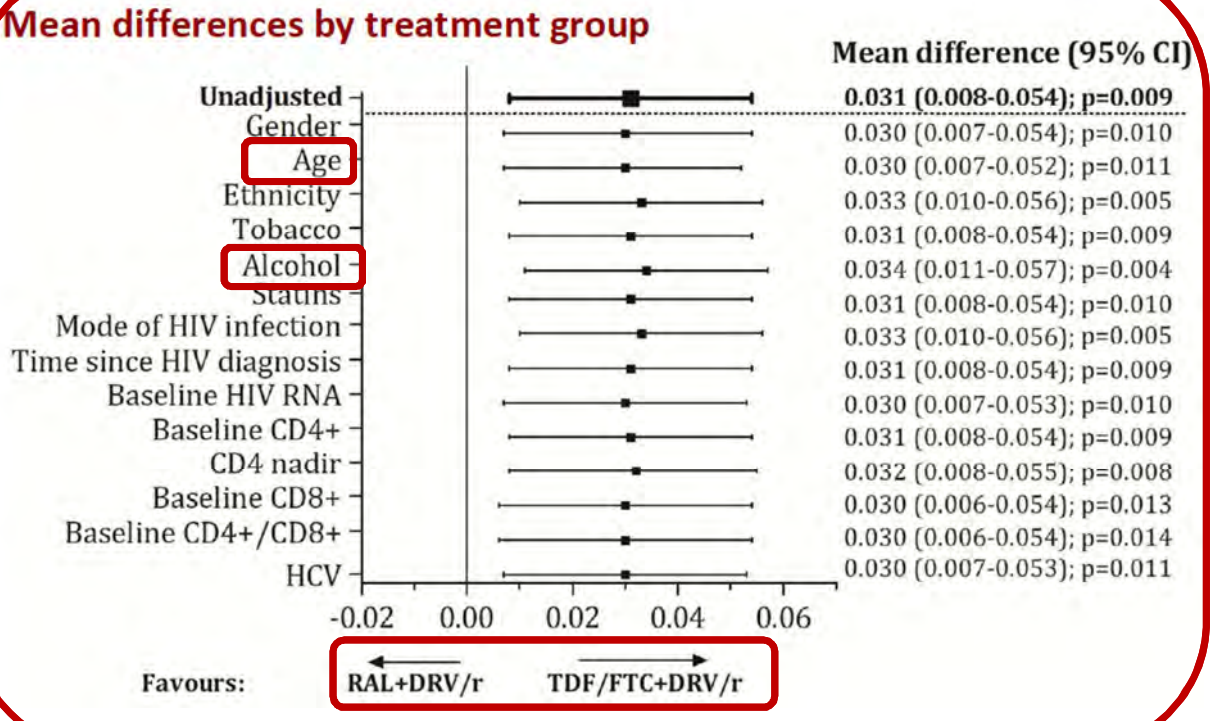
Hukezalie et al, PLoS ONE 7(11): e47505. doi:10.171

PDL = Population Doubling Level

Inconsistent Clinical Evidence of ART Effects on Telomere Length

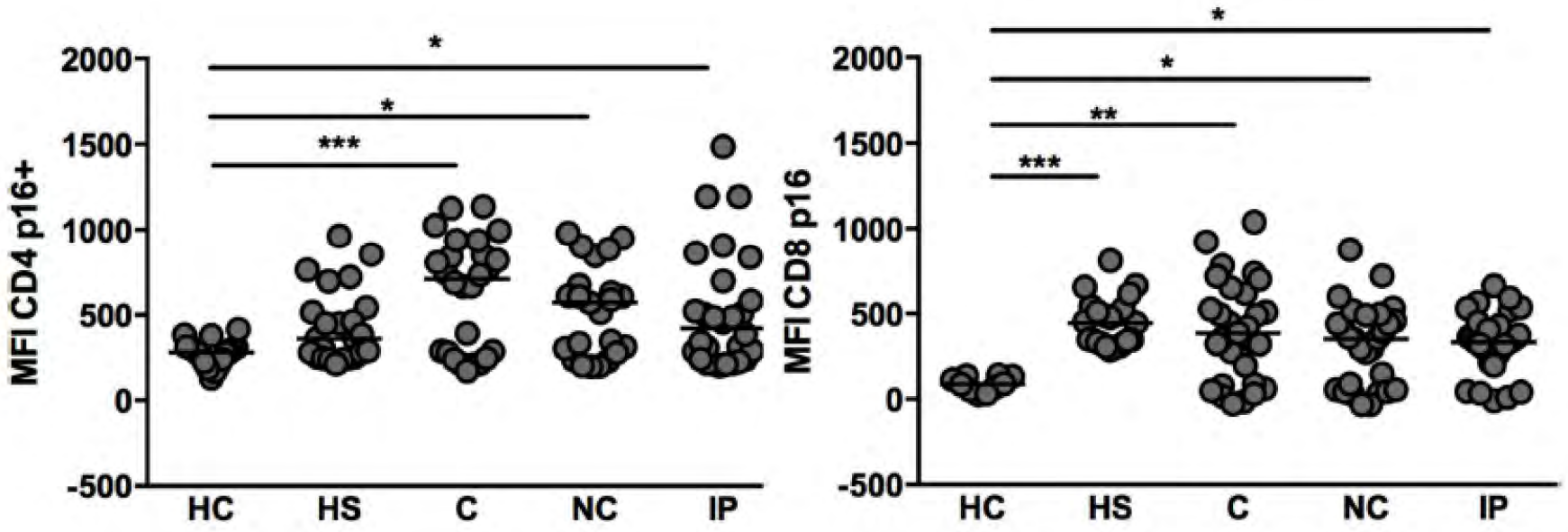
Variable	TDF Exposed	
	Exp(coef.) CI (95%)	*P*
Age (Ref. <45 yrs)		
≥45/50	0.99 (0.90 to 1.10)	0.908
≥50	0.92 (0.83 to 1.01)	0.074
Father's age at birth (per yr)	—	
Race (Ref. Caucasic)		
Other	—	
Education (Ref. Primary)		
Secondary	1.12 (1.03 to 1.22)	0.006
University	1.10 (1.00 to 1.21)	0.044
Income (Ref. Low)		
High	0.92 (0.86 to 0.99)	0.031
Time with HIV infection (Ref. <10 yrs)		
≥10–20	—	
≥20	—	
Time on ART (Ref. <10 yrs)		
≥10–20	0.89 (0.82 to 0.98)	0.017
≥20	0.91 (0.80 to 1.03)	0.120

Montejano et al, J Acquir Immune Defic Syndr 2017;76:102–109



Stella-Ascariz et al, CROI 2018, Abstract 758

$p16^{INK4a}$ is a Marker of Cellular Senescence and Does Not Normalize in CD8+ T-Cells with Suppressive ART

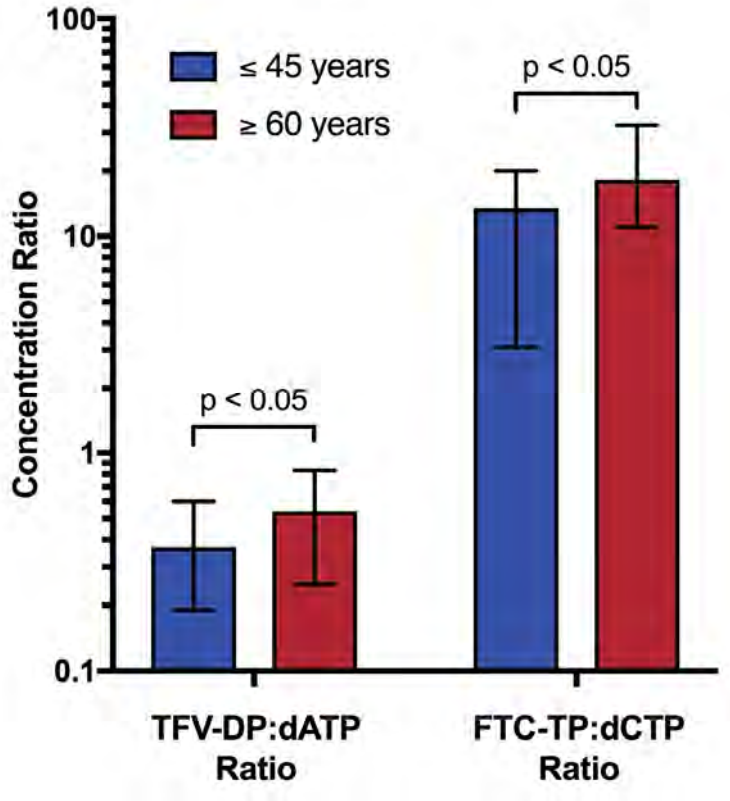


HC = HIV Negative Control
HS = HIV Suppressed on ART
C = HIV Controller off ART
NC = HIV Non-Controller off ART
IP = Immunologic Progressor off ART

Ribeiro et al, PLoS One. 2016;11(11):e0166759

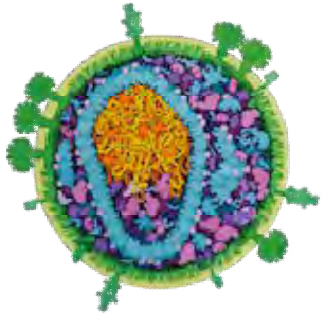
Age and NRTI Metabolite/ Endogenous Nucleotide Ratios

- Cellular senescence may alter intracellular metabolism of NRTIs
- The ratio of NRTI metabolites to their endogenous nucleotides may be a marker of toxicity
- Hypothesis: Older age will be associated with higher TFVdp:dATP and FTCtp:dCTP ratios



Dumond et al, CROI 2018, Abstract 464

Pathogenesis - Host



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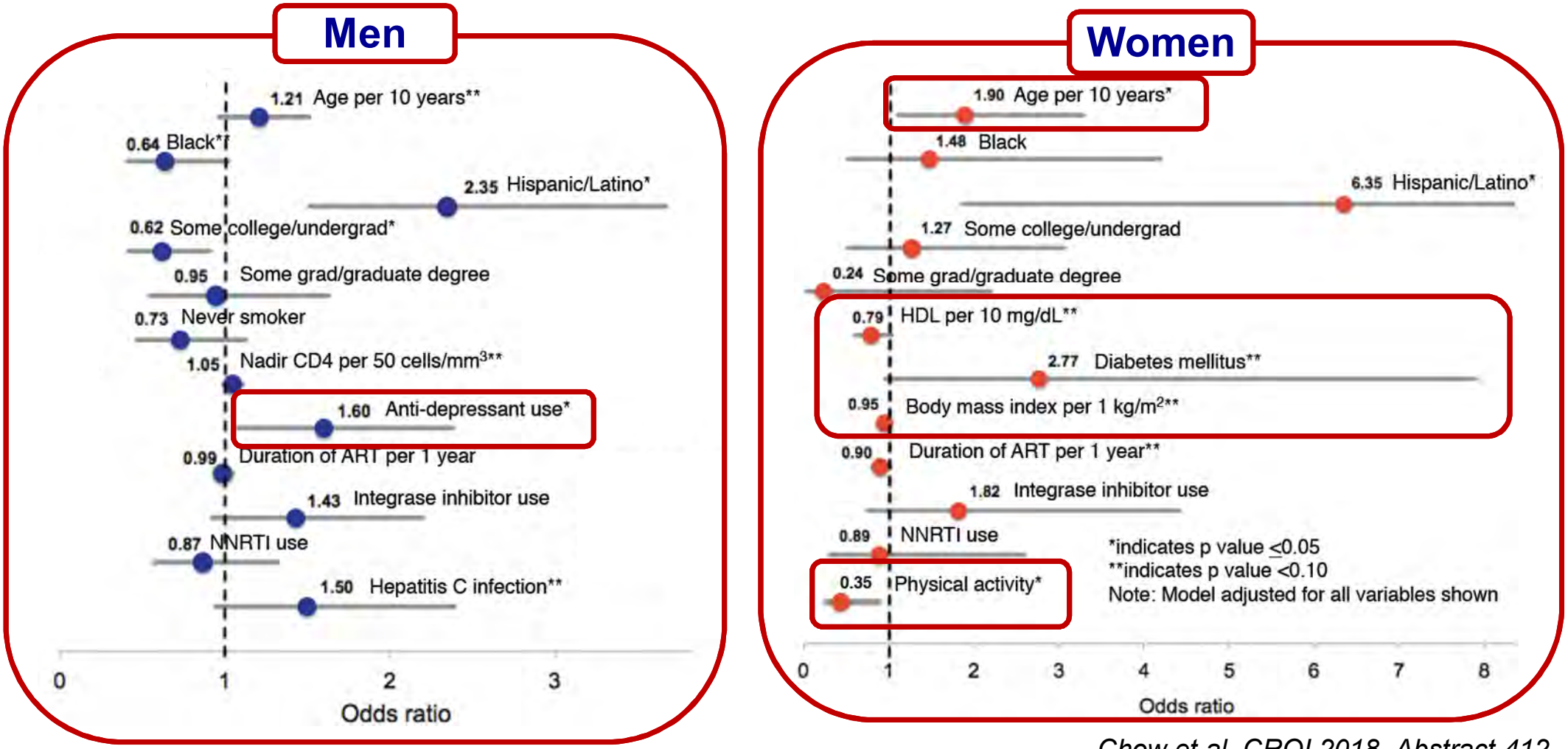
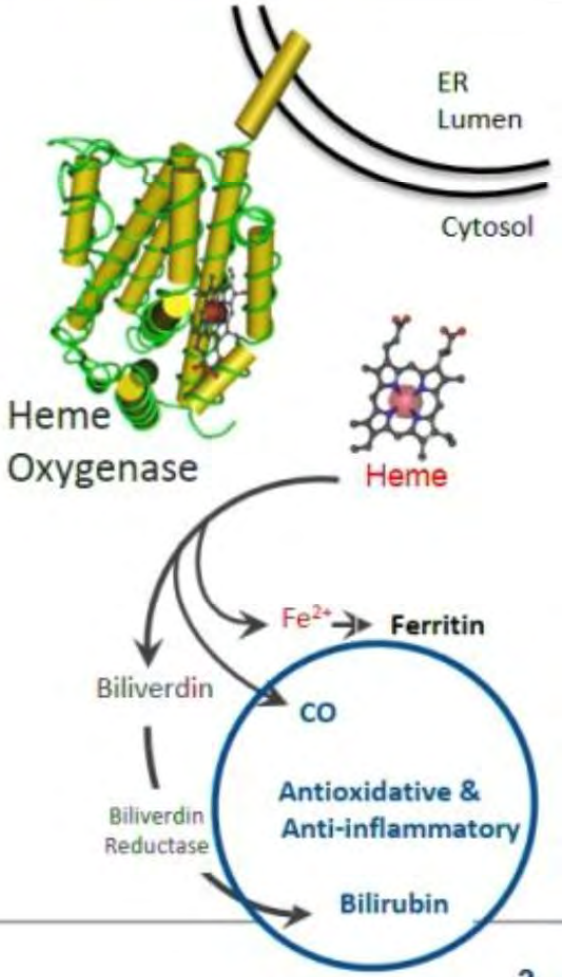
Sex-Based Differences in Correlates of NCI



Chow et al, CROI 2018, Abstract 412

Heme Oxygenase-1: A detoxifying and anti-inflammatory enzyme

- **Heme Oxygenase (HO-1)**
  - Highly inducible and ubiquitously expressed
  - Detoxifying and cytoprotective antioxidant enzyme
  - ↓ inflammation, oxidative stress, and cellular injury



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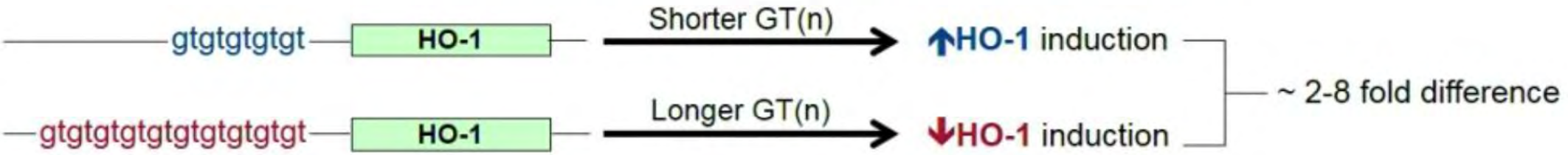
Gill et al, CROI 2018, Abstract 126

HO-1 promoter region (GT)n dinucleotide repeat microsatellite polymorphism



Diseases with IMPROVED clinical outcome associated with SHORTER HO-1 promoter region (GT)n repeats

- Cardiovascular disease (coronary artery disease, complications post angioplasty)
- Pulmonary disease (emphysema, acute chest syndrome)
- Neurological disease (ischemic stroke, cerebral aneurysm)
- Gastrointestinal disease (necrotizing acute pancreatitis)
- Infectious disease (sepsis, pneumonia)
- Immune disease (rheumatoid arthritis)

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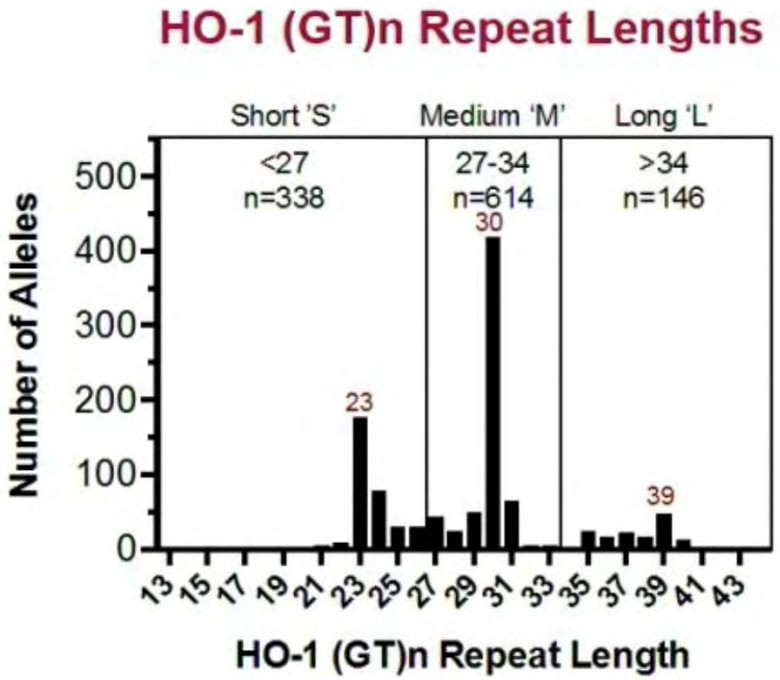
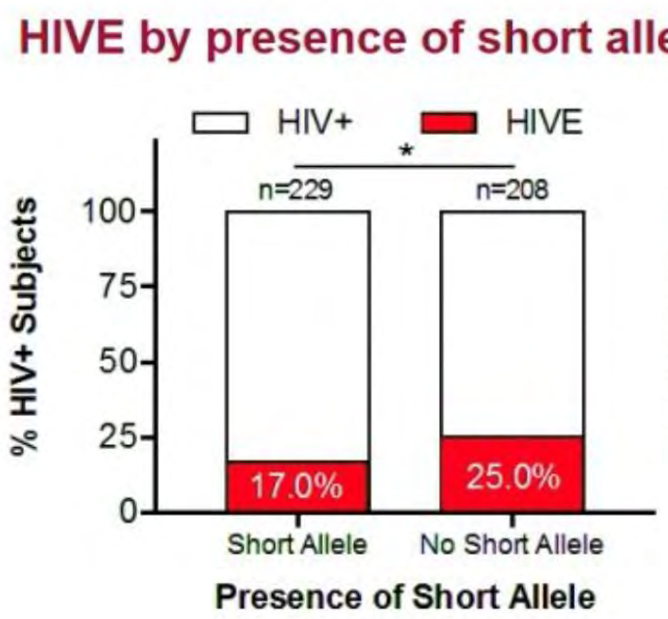
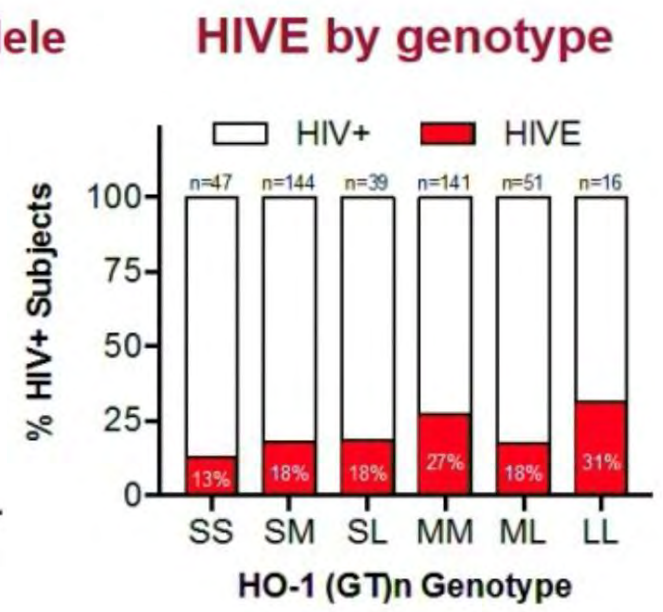
HO-1 Promoter Repeats in Brain Tissue Are Associated with HIV Encephalitis







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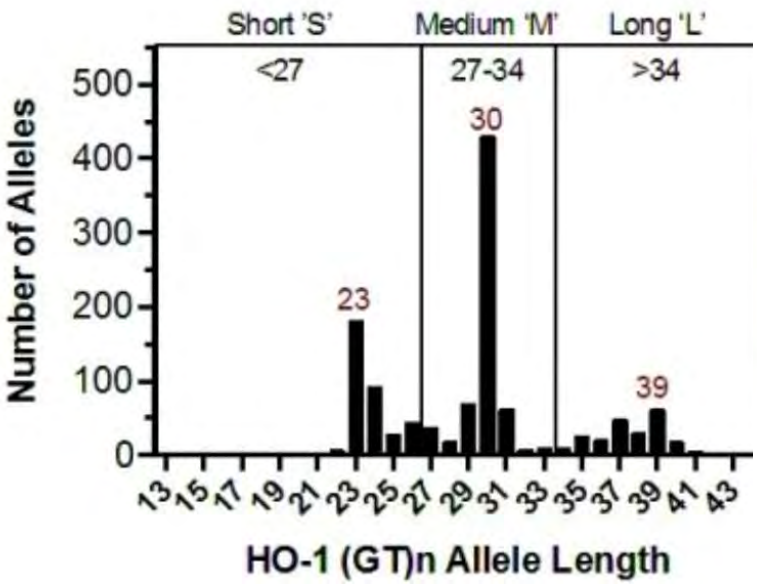
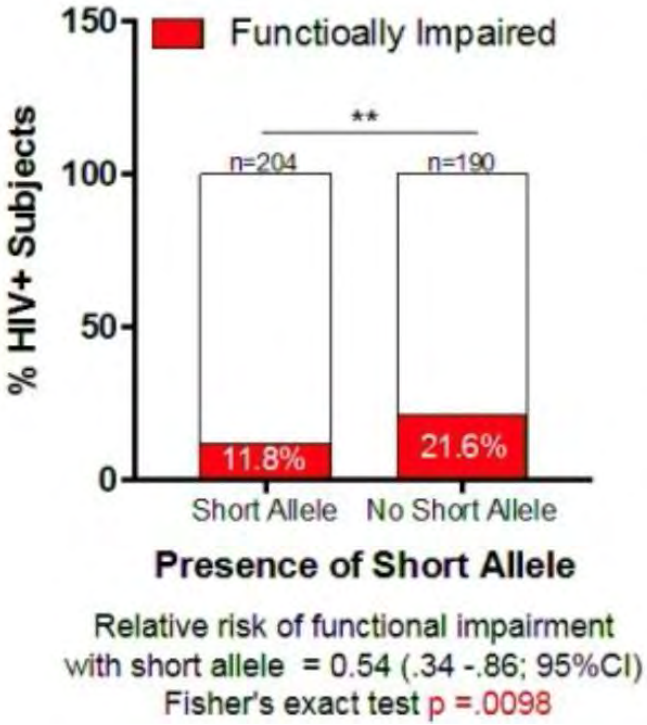
nntc
National NeuroAIDS Tissue Consortium

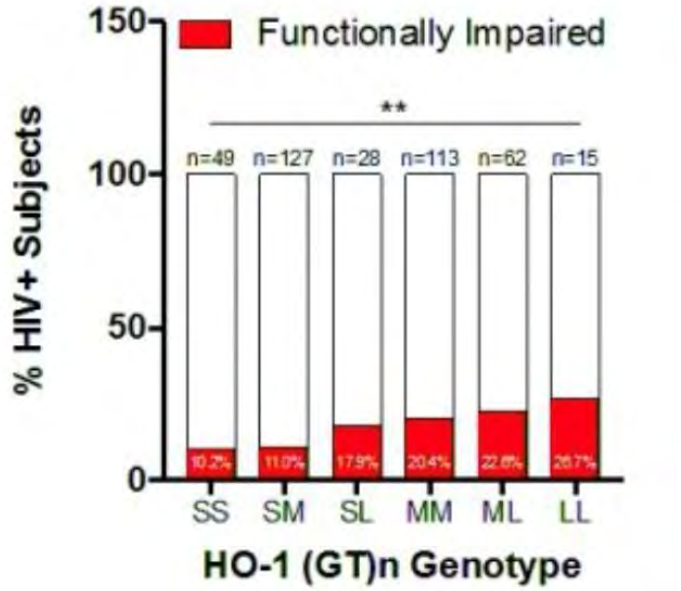
Gill et al, CROI 2018, Abstract 126

HO-1 Promoter Repeats in Blood-Derived DNA Are Associated with Symptomatic HAND





Relative risk of functional impairment with short allele = 0.54 (.34 -.86; 95%CI)
Fisher's exact test p =.0098



Chi-square test for Linear Trend p =.0088

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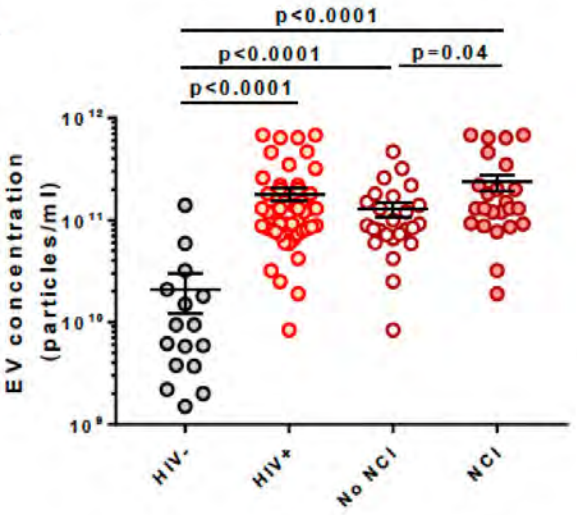
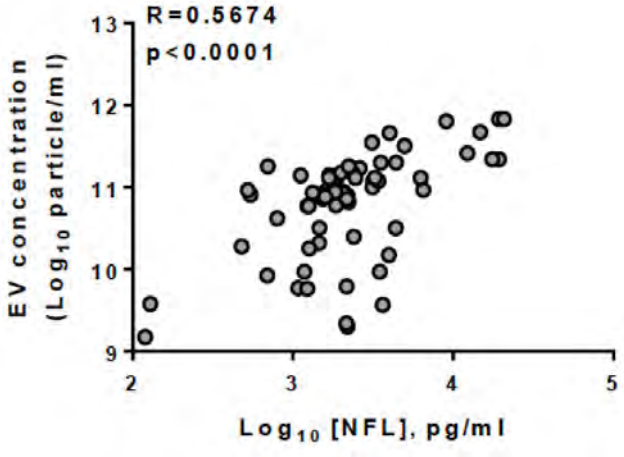
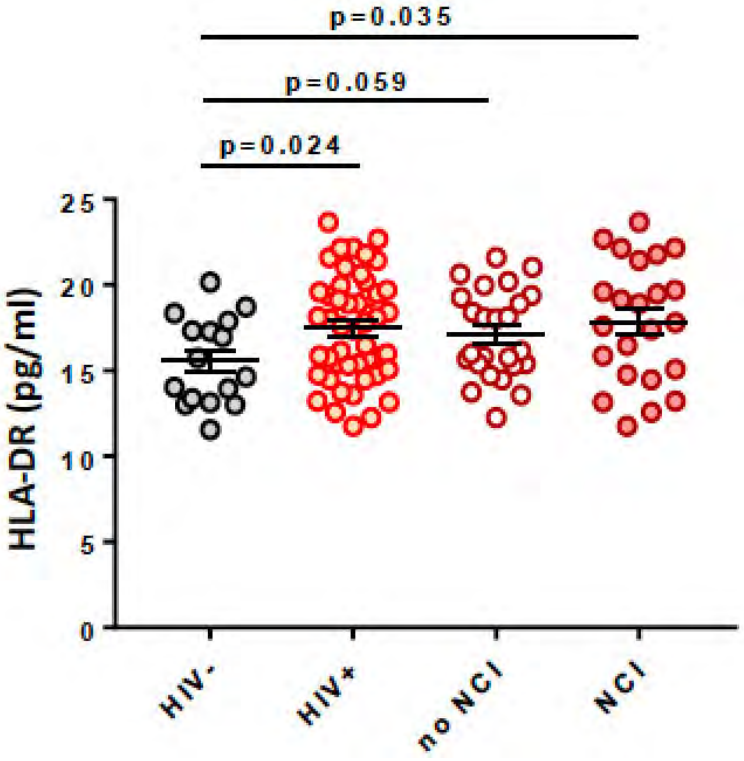
CHARTER

Gill et al, CROI 2018, Abstract 126

Exosome Discovery in CSF







Guha et al, CROI 2018, Abstract 453

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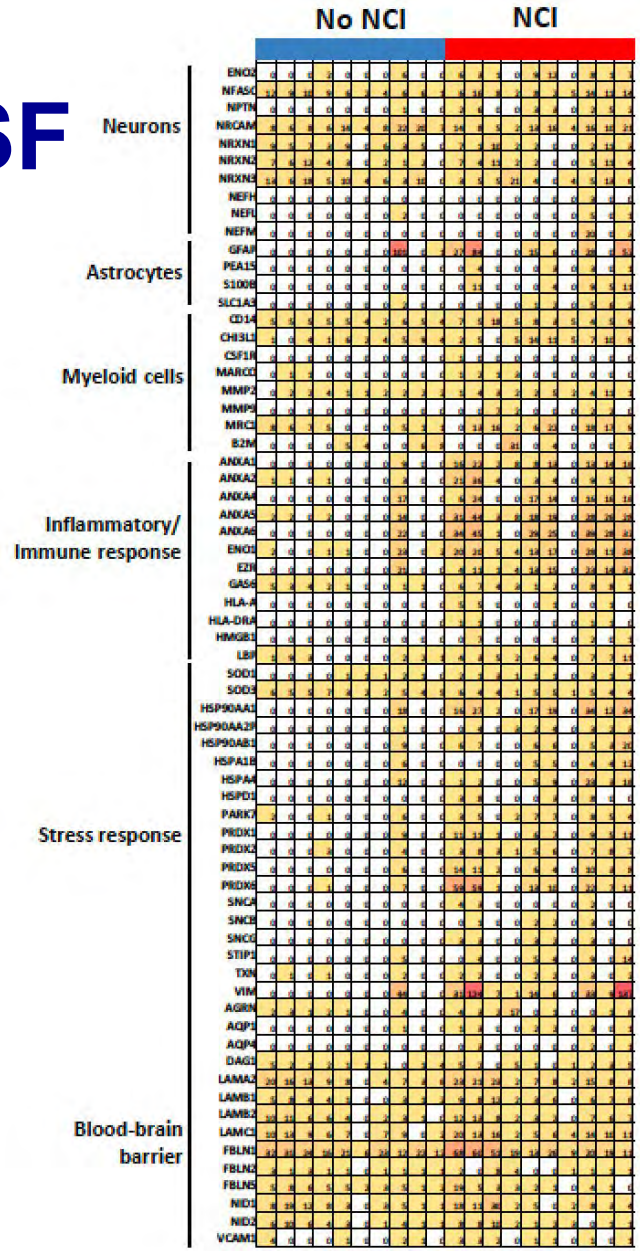
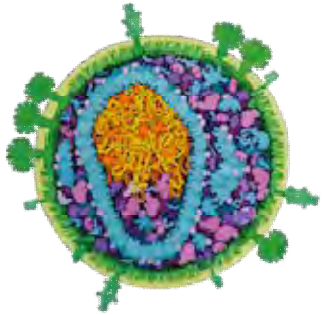


Pathogenesis - HIV



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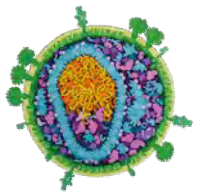
Study methods

- Cross sectional CSF and blood from participants with HIV on ART in A5321 at 19 ACTG sites; participants without HIV in New Haven, CT, USA.
- HIV persistence measures:

  HIV RNA from cell free samples: single copy assay sensitivity in CSF supernatant (3-5 ml) and blood plasma (5 ml).[1]

  HIV DNA and **RNA from cells (cell-associated)**: qPCR assays in PBMC and in cell pellets derived from ~13 mls of CSF. Measures were normalized for amplifiable CCR5 copies.[2]

- Inflammation biomarkers: (IL-6, IP-10, neopterin, MCP-1, sCD14, sCD163, TNF-α) by ELISA in cell-free CSF and plasma.



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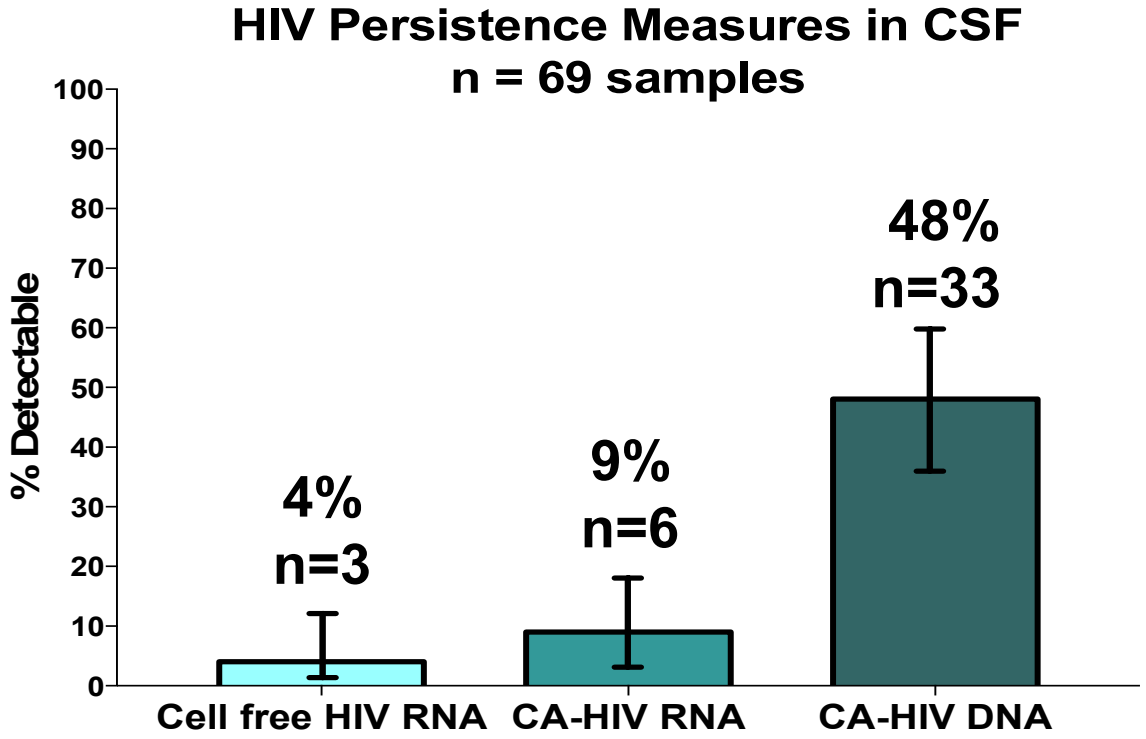
Spudich et al, CROI 2018, Abstract 119

[1] Cillo AR, et al., *J Clin Microbiol* 2014; [2]Hong F, et al., *J Clin Microbiol* 2016.

HIV detection in CSF in participants on suppressive ART



Boxes indicate % positive; bars represent 95% confidence intervals

Among those with detected CSF cell-associated HIV DNA, median level:
2.1 copies/10^3 cells
(range 0.1 - 7.0)

CA-HIV = cell-associated HIV

Spudich et al, CROI 2018, Abstract 119

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HIV DNA detection in CSF cells did not significantly associate with the level of PBMC HIV DNA or persistent viremia

Blood HIV Measures	CSF CA-HIV DNA Not Detected (n=36)	CSF CA-HIV DNA Detected (n=33)	P value*
Blood CA-HIV DNA (cps/10^6 CD4+ T cells)	375 (215-909)	723 (147-1209)	0.33
Blood CA-HIV RNA (cps/10^6 CD4+ T cells)	42 (13-145)	37 (11-156)	0.85
Plasma HIV RNA by iSCA (cps/ml)	<0.4 (<0.4-1.9)	0.4 (<0.4-3.3)	0.46

*Exact Wilcoxon test

- **Detection of CSF CA-RNA also did not associate with blood HIV measures.**

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Spudich et al, CROI 2018, Abstract 119

HIV DNA detection in CSF cells did not significantly associate with pre-ART measures or duration of ART

Characteristic (median (IQR))	CSF CA-HIV DNA Not Detected (n=36)	CSF CA-HIV DNA Detected (n=33)	p value
Pre-ART blood CD4+ T cell count (cells/mm^3)	300 (193-385)	285 (129-335)	0.27
Pre-ART CD4:CD8 ratio	0.4 (0.2-0.5)	0.2 (0.1-0.5)	0.09
Pre-ART plasma HIV RNA level (log_{10} cps/ml)	4.6 (<0.4-1.9)	4.7 (<0.4-3.3)	0.15
Duration of ART (years)	4.6 (4.2-4.9)	4.7 (4.5-5.2)	0.95

*Exact Wilcoxon test

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Spudich et al, CROI 2018, Abstract 119

HIV RNA detection in cell-free CSF did significantly associate with plasma viremia

Blood HIV Measures	CSF HIV by iSCA Not Detected (n=66)	CSF HIV by iSCA Detected (n=3)	P value*
Blood CA-HIV DNA (copies/10^6 CD4+ T cells)	530 (188-1129)	1136 (188-129)	0.62
Blood CA-HIV RNA (copies/10^6 CD4+ T cells)	37 (13-143)	297 (5-503)	0.39
Plasma HIV RNA by iSCA (copies/ml)	<.4 (<0.4-2.2)	5.9 (2.9-23.1)	0.007

*Exact Wilcoxon test

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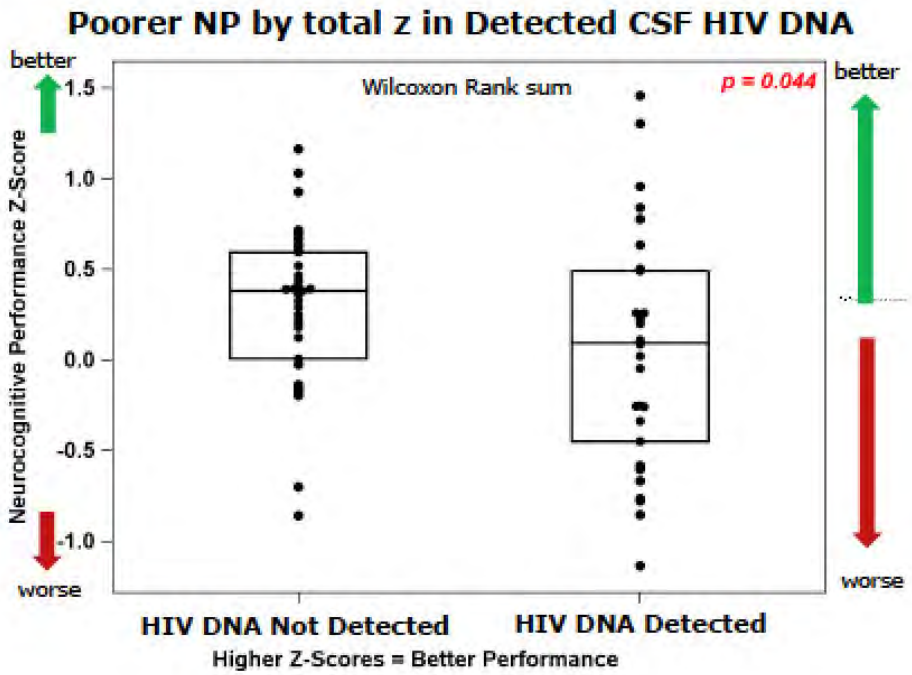
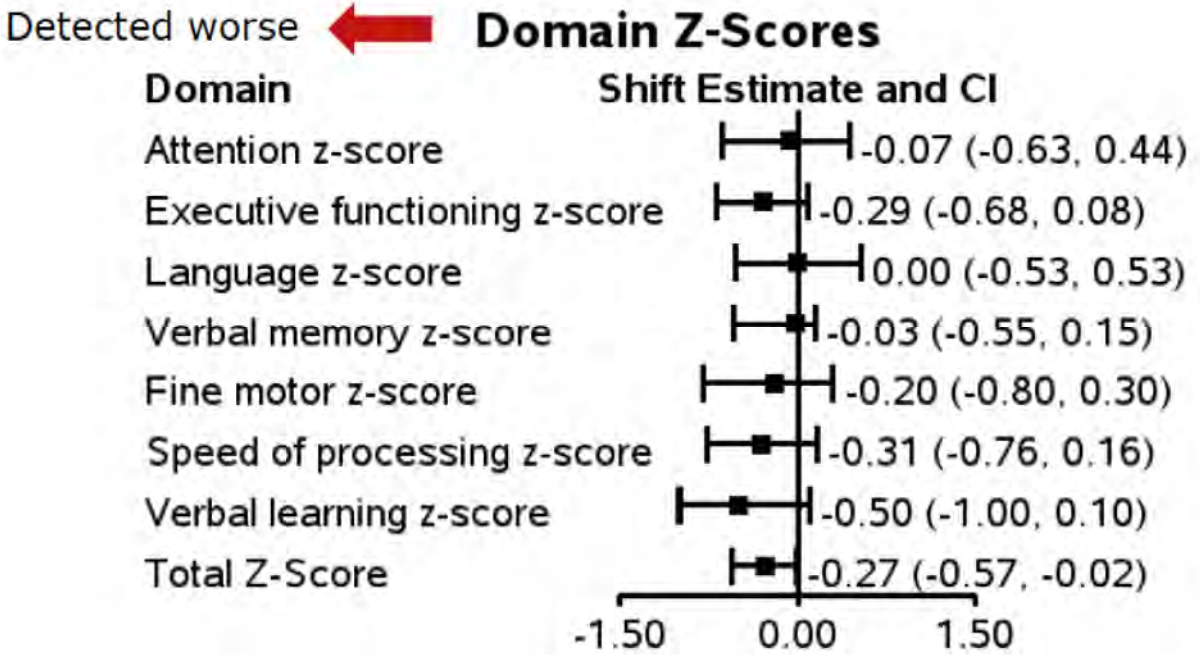
Spudich et al, CROI 2018, Abstract 119

Poorer Neurocognitive Performance Associated with CSF HIV DNA Despite Long-Term ART





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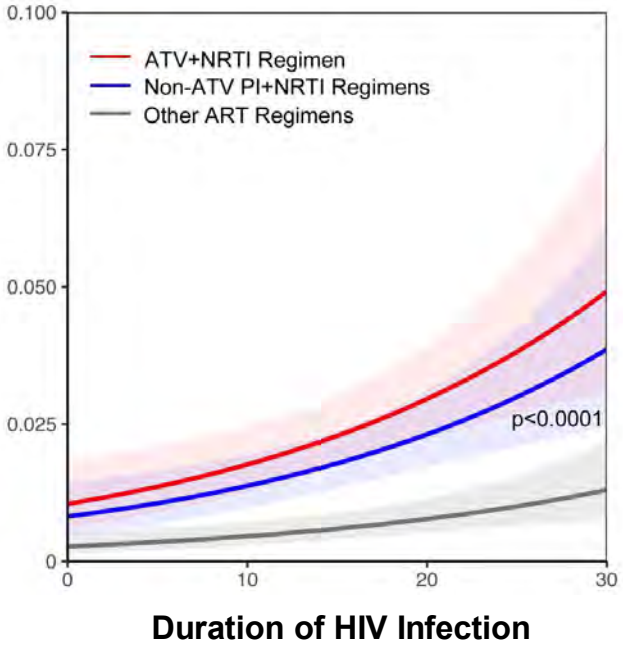
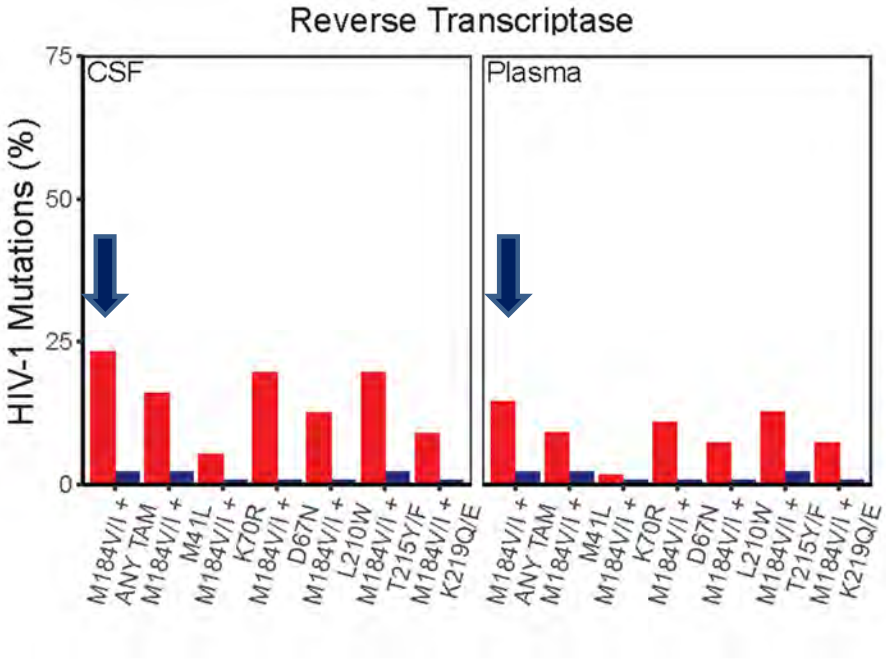
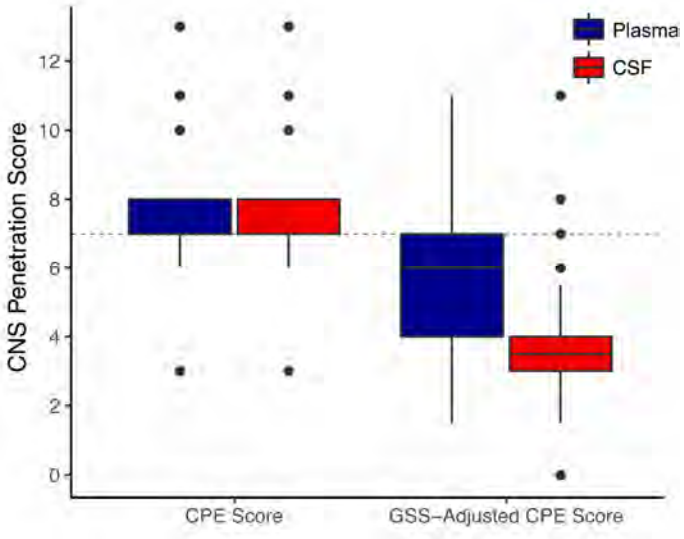
Robertson et al, CROI 2018, Abstract 403LP

CSF Viral Escape May Result From the Combination of Drug Resistance and Poor Drug Distribution







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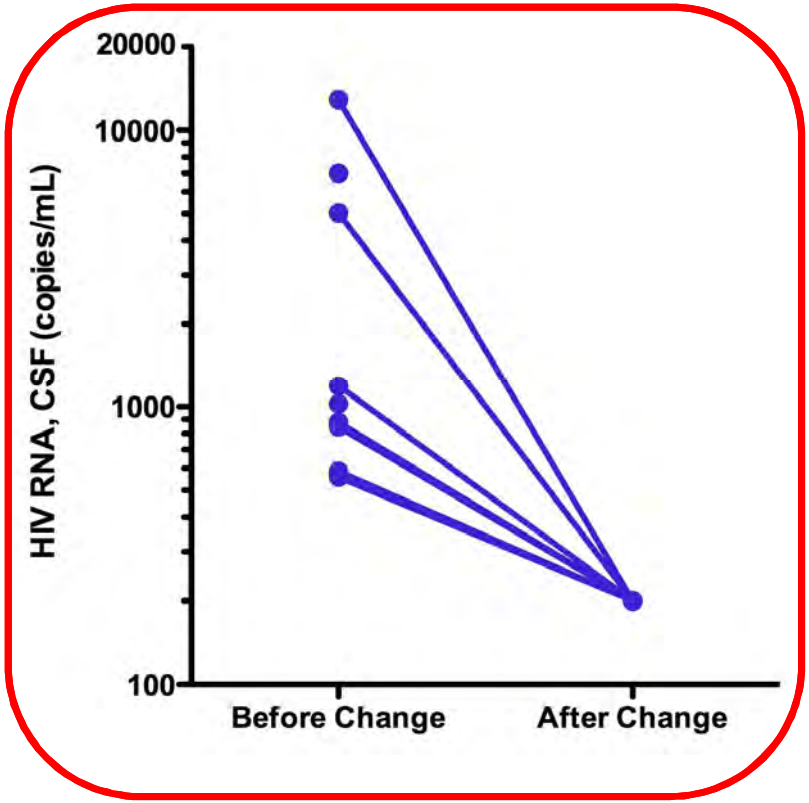
Mukerji, et al. CROI 2018, Abstract 123

Drug Resistance, CSF Viral Escape, and Adjusted CPE



Canestri et al, Clinical Infectious Diseases 2010, 50: 773–778

Score	Cutoff	Impaired < cutoff versus ≥ cutoff	*P*-value
$CPE\text{-}GSS_{ANRS}$	≥5	51.7% versus 27.4%	0.015
	≥5.5	45.7% versus 27.8%	0.057
	≥6	47.2% versus 27.4%	0.031
$CPE\text{-}GSS_{HIVDB}$	≥5	47.1% versus 27.6%	0.040
	≥5.5	43.6% versus 27.8%	0.082
	≥6	42.9% versus 27.7%	0.086
$CPE\text{-}GSS_{REGA}$	≥5	51.6% versus 27.2%	0.012
	≥5.5	45.9% versus 27.5%	0.044
	≥6	43.9% versus 27.6%	0.064

Fabbiani et al, Antiviral Ther 2015, 20: 441-7

Correlates of Symptomatic and Asymptomatic CSF Viral Escape Differ

Asymptomatic

	AOR	95% CI		p
Age (10 yrs increase)	**1.88**	**1.03**	**3.42**	**0.039**
Nadir CD4<200 cell/mmc	**3.69**	**1.85**	**7.37**	**<0.001**
CD4 at LP, cell/mmc				
<200	1.00			
201-350	1.42	0.30	6.63	0.656
350 or more	1.42	0.19	10.56	0.732
CPE score	0.75	0.48	1.18	0.217
Calendar year of LP				
1999-2003	1.00			
2004-2008	-	-	-	-
2009-2014	**0.08**	**0.02**	**0.37**	**0.001**
BBB dysfunction	**5.06**	**1.26**	**20.28**	**0.022**

Symptomatic

	AOR	95% CI		p
Male gender	**0.37**	**0.15**	**0.89**	**0.026**
CSF number of cells>5/mmc	**4.95**	**1.97**	**12.41**	**0.001**
CSF proteins >50 mg/dl	1.65	0.65	4.18	0.289

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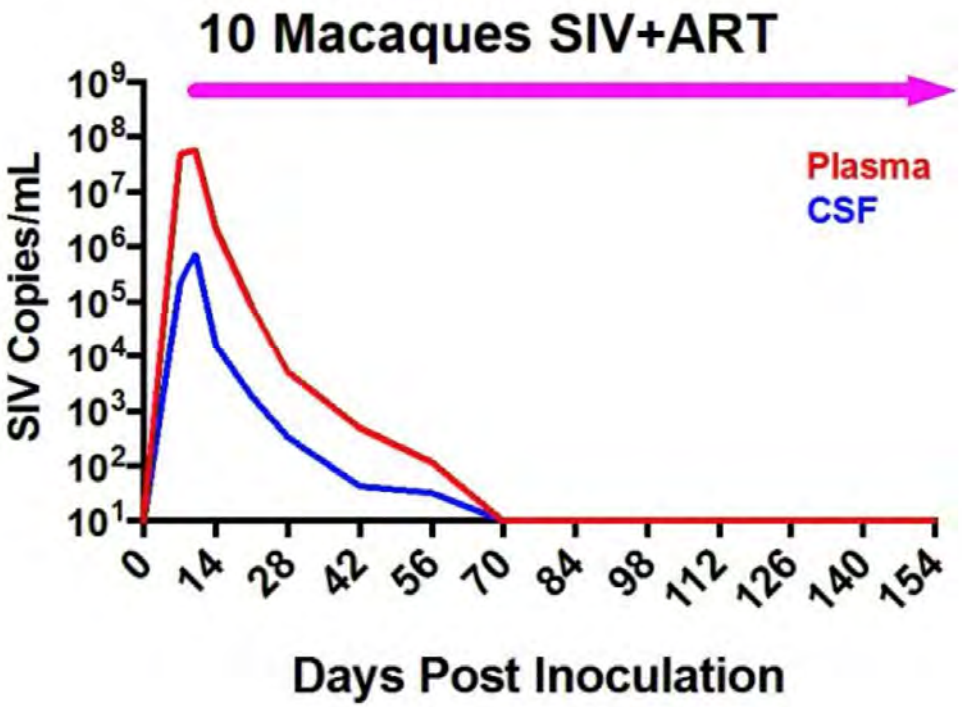
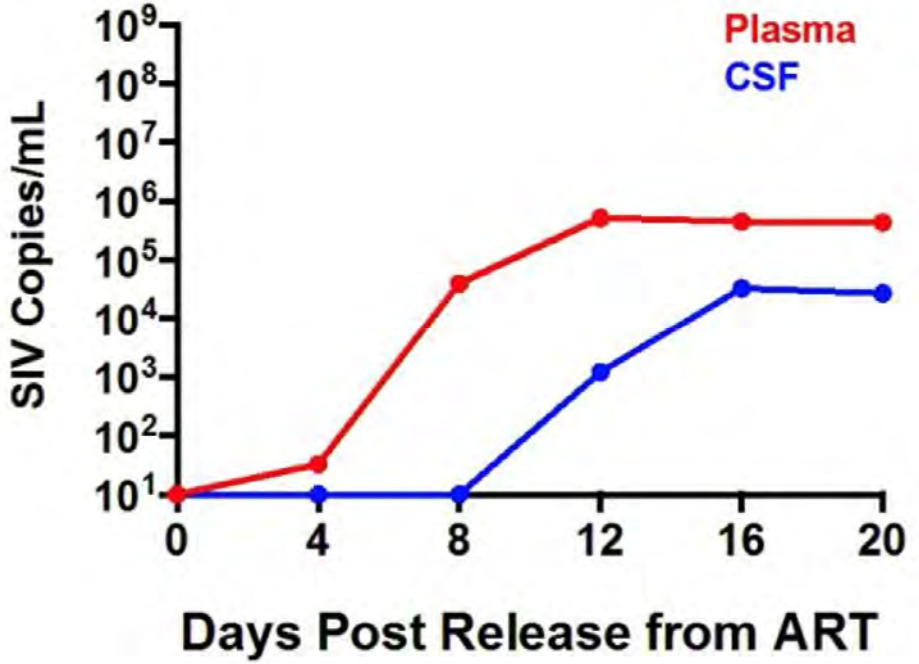
Pinnetti, et al. CROI 2018, Abstract 447

Spinal Cord May be an Independent Compartment from the Brain and CSF





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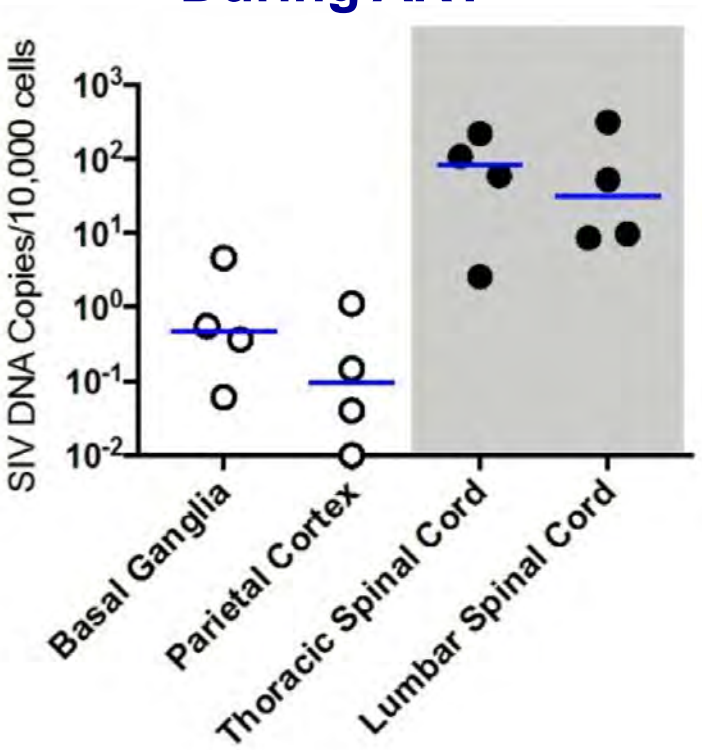
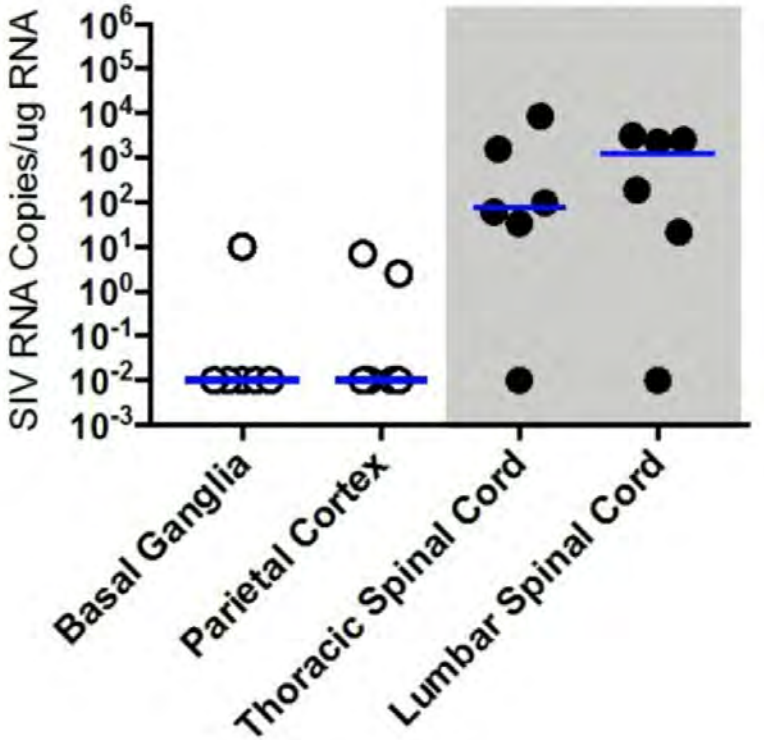
Mankowski, et al. CROI 2018, Abstract 124

SIV DNA and RNA were Higher in Spinal Cord Than in Brain

During ART



After ART Discontinuation



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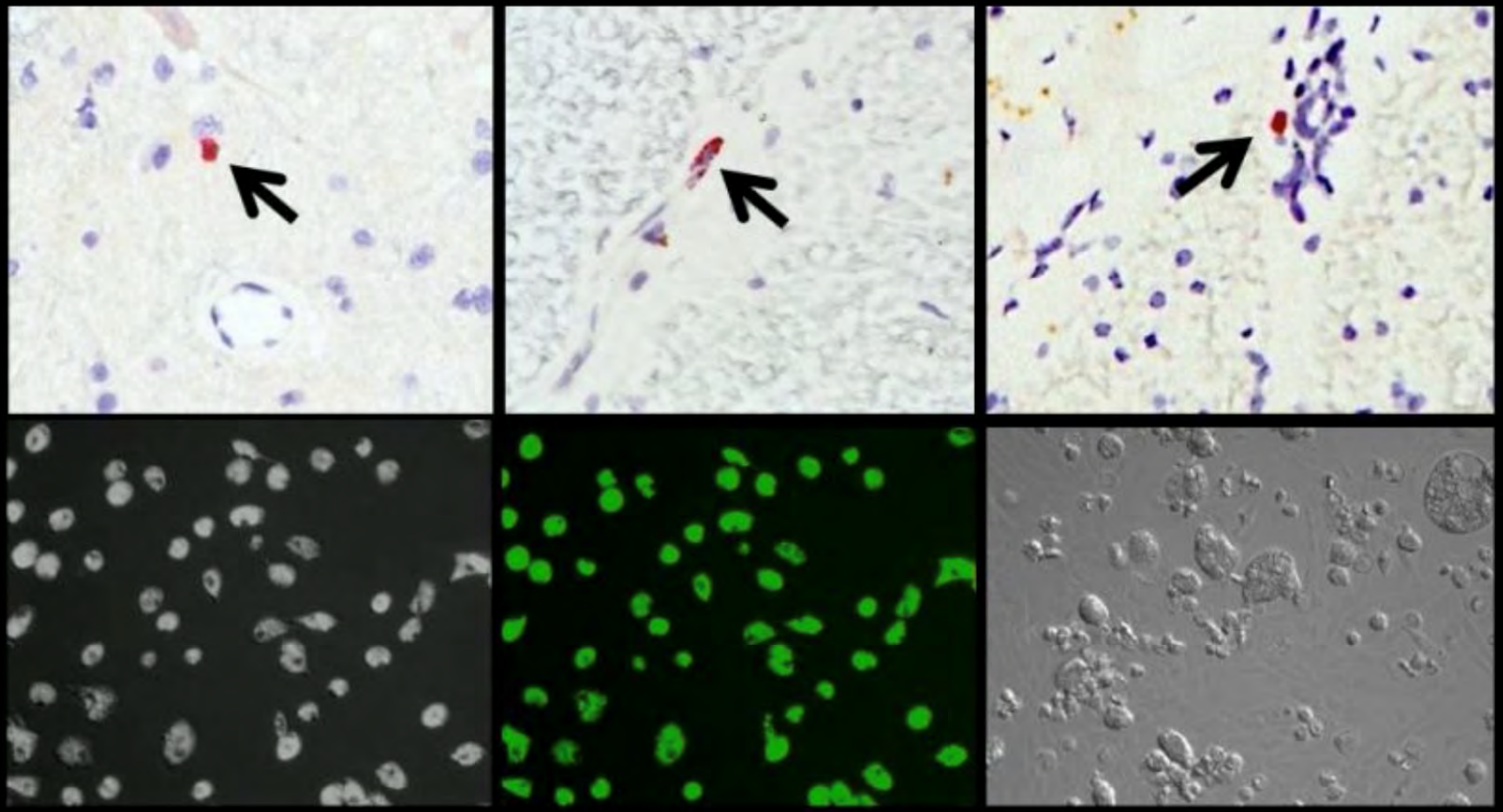
Mankowski, et al. CROI 2018, Abstract 124

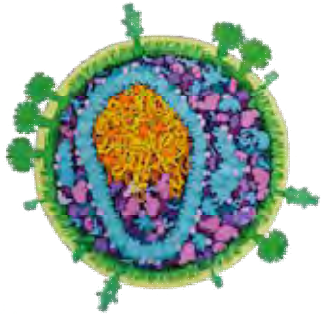
SIV RNA ISH



6/6 primary cultures SIV RNA+ by qRT-PCR

Mankowski, et al. CROI 2018, Abstract 124

Treatment



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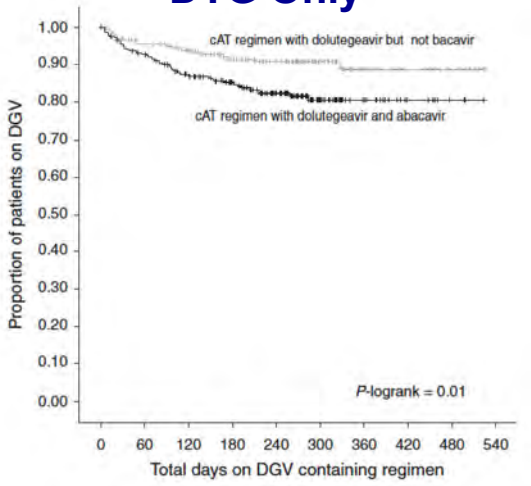
DTG and CNS Adverse Events

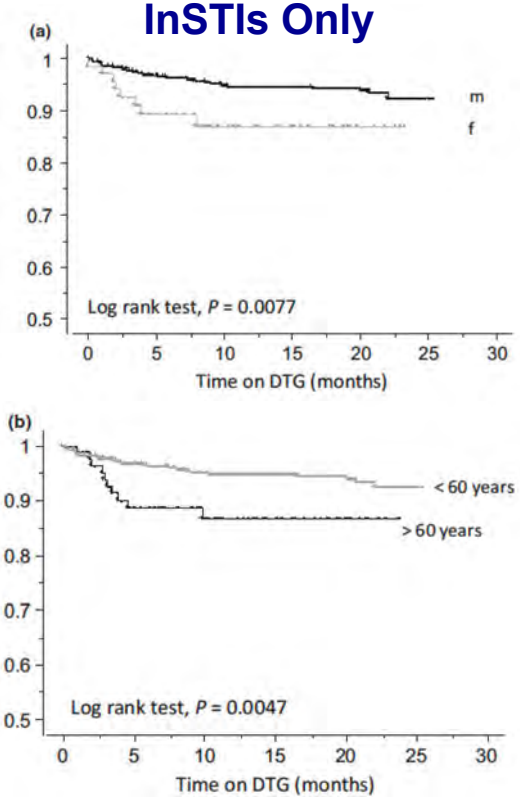
N=565
DTG Only



Adverse drug reaction	*n* (%)
Sleep disturbance, insomnia	31 (5.6)
Gastrointestinal complaints	21 (3.8)
Joint, tendon and/or muscle pain	11 (2.0)
Psychological/psychiatric symptoms[b]	14 (2.5)
Neurologic symptoms	10 (1.8)
General malaise (headache and severe fatigue)	24 (4.3)
Respiratory tract complaints	5 (0.9)
Other	9 (1.6)

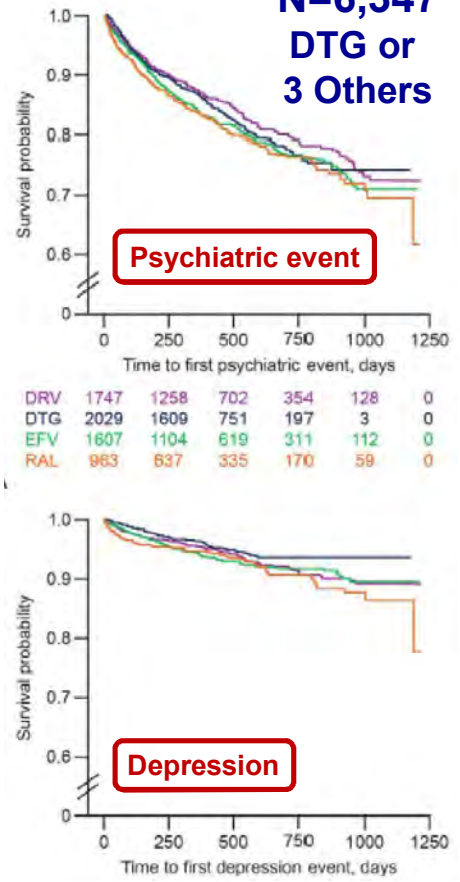
de Boer et al, AIDS 2016, 30:2831–2834

N=1,950
InSTIs Only



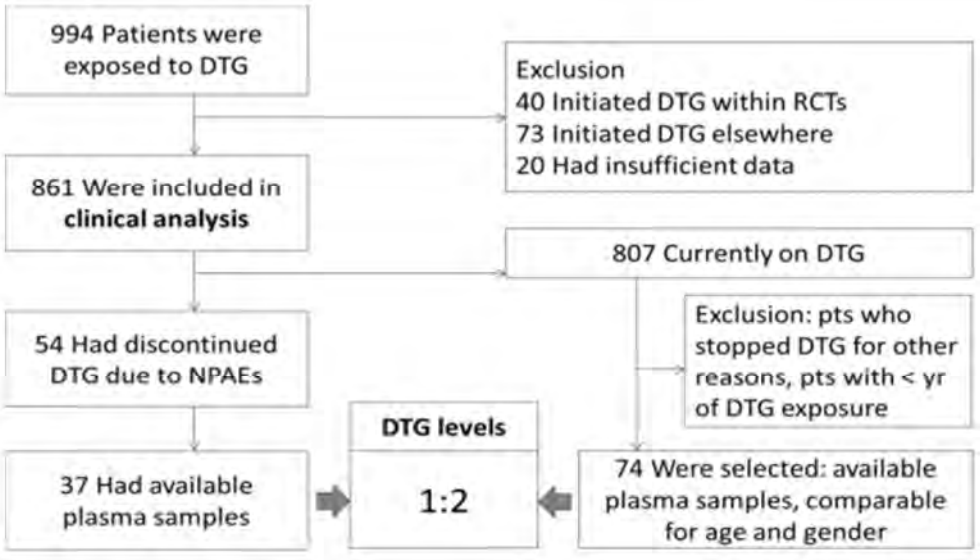
Hoffmann et al, HIV Medicine 2017, 18, 56--63

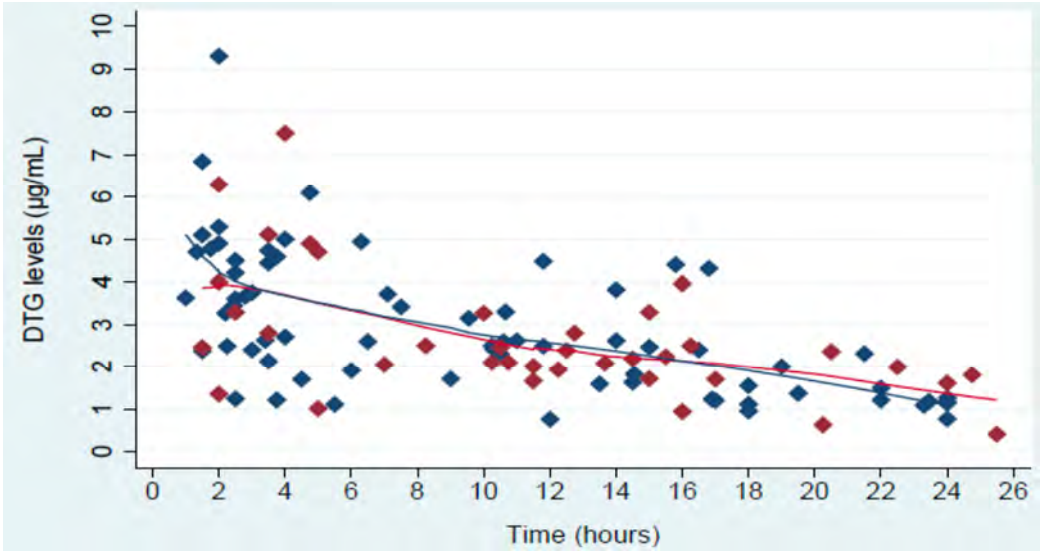
N=6,347
DTG or 3 Others



Fettiplace et al, J AIDS 2017;74:423–431

DTG Discontinuation Not Concentration-Dependent





Risk factors for NPAEs leading to DTG discontinuation	RH	95 % CI	p
Female, versus male gender	2.31	1.12-4.74	0.03
Older age (> 60 years), versus younger age	2.14	1.10-4.18	0.025
Depressive disorders, versus no	1.00	0.54-1.88	0.952
Other neuropsychiatric diagnoses, versus no	0.93	0.29-3.00	0.896

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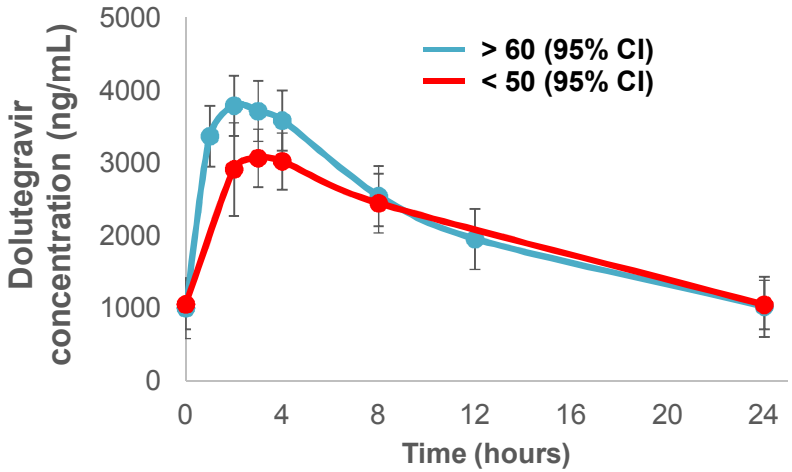
Hoffmann, et al. CROI 2018, Abstract 424

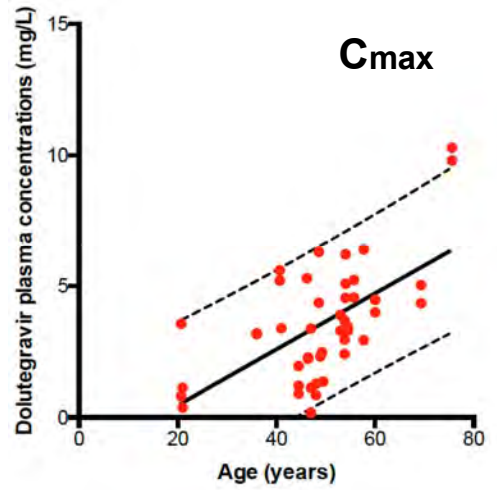
Dolutegravir, Age, Sleep, & Mood

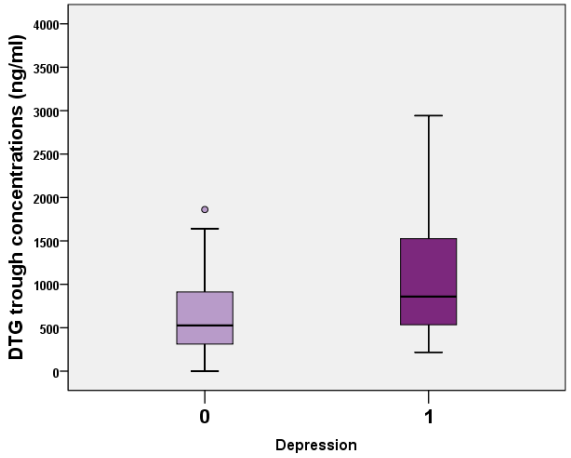
Courtesy Andrea Calcagno and Marta Boffito



	C_{max}	AUC_{0-24}
Pittsburgh Sleep Quality Index		
Duration of sleep (n=36)	**0.330 (0.05)**	**0.353 (0.03)**
Sleep disturbance (n=38)	-0.100 (0.55)	-0.121 (0.47)
Sleep latency (n=37)	-0.247 (0.14)	-0.053 (0.75)
Day dysfunction (n=37)	-0.181 (0.28)	-0.206 (0.22)
Sleep efficiency (n=35)	0.120 (0.49)	0.032 (0.86)
Sleep quality (n=38)	-0.212 (0.20)	0.207 (0.21)
Medication (n=37)	0.016 (0.92)	0.021 (0.90)
PSQI total (n=32)	0.074 (0.69)	-0.042 (0.82)

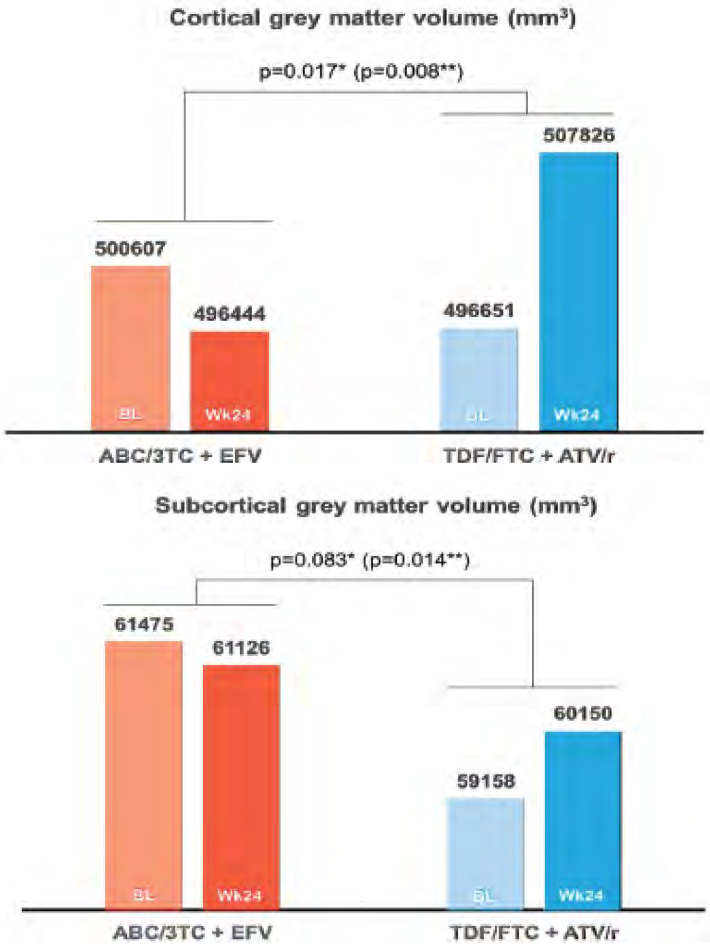
Elliot et al, 18th International Workshop on Clinical Pharmacology of Antiviral Therapy, 2017





Borghetti et al, Italian Conference on AIDS and Antiviral Research, 2017

ART Regimens Differ in Imaging Findings After 24 Weeks



	LEFT SIDE		p value	RIGHT SIDE		p value
	ABC/3TC+EFV	TDF/FTC+ATV/r		ABC/3TC+EFV	TDF/FTC+ATV/r	
THALAMUS	-18.5	153.6	0,4009	77.6	226.1	0,1558
CAUDATE	-7.8	16.1	0,1734	-132.9	14.2	**0,019**
PUTAMEN	8.6	165.9	0,4689	36.3	68.8	0,3692
PALLIDUM	-108.8	-5.6	0,235	-13.9	47.7	0,3106
HIPPOCAMPUS	-12.1	21.2	0,6639	-40.8	108.2	**0,0257**
AMYGDALA	31.5	69.2	0,4341	-63.0	126.1	**0,0034**
ACCUMBENS AREA	-23.7	2.2	0,4009	-7.9	17.5	0,2838

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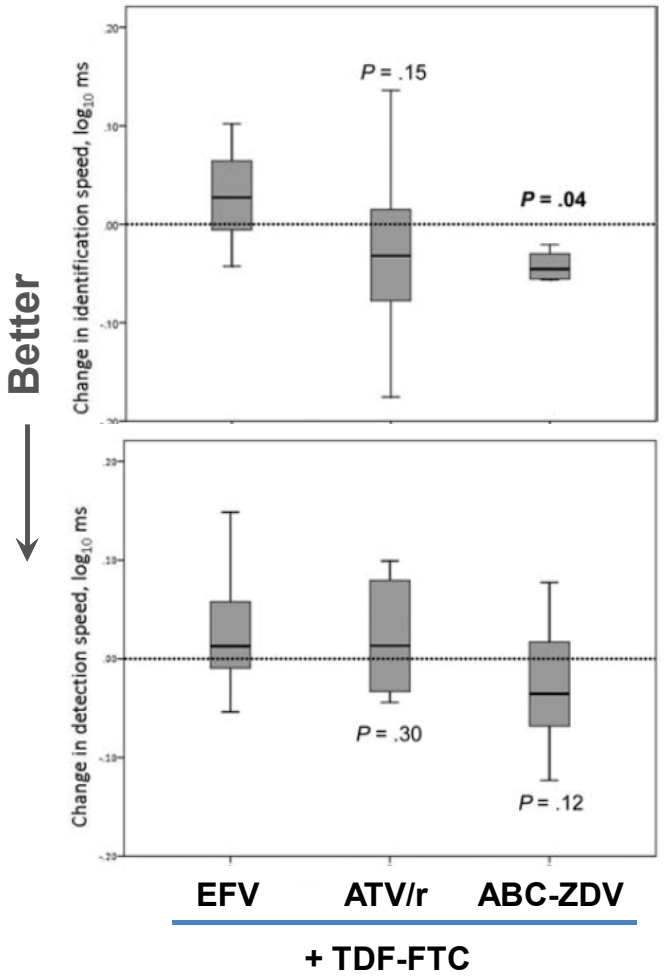
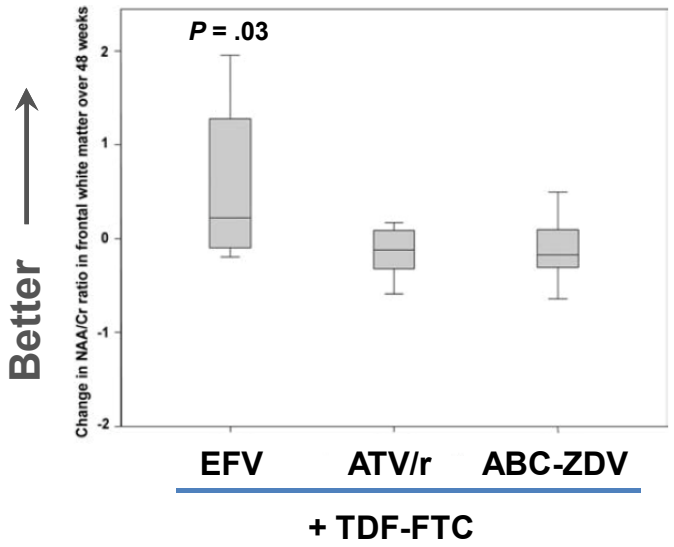
Perez Valero, et al. CROI 2018, Abstract 425

ALTAIR: Neurocognitive and Neuroimaging Responses Differed Between 3 Regimens

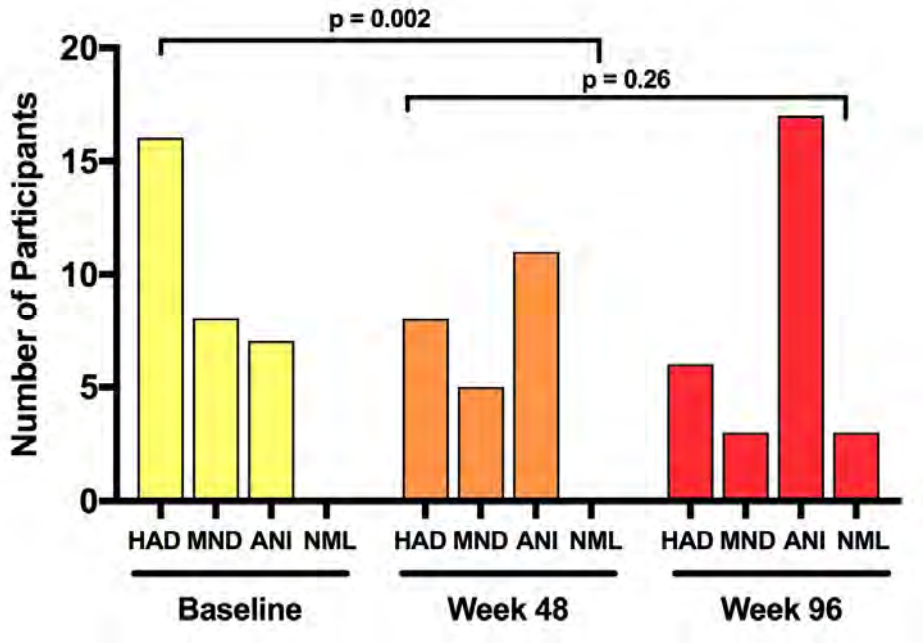




- **30 HIV+ ART-naive adults randomized to 1 of 3 regimens for 48 weeks**
- **ABC-ZDV-TDF-FTC: greater improvement in reaction time and executive function**
- **EFV-TDF-FTC: greater NAA/Cr increase**

Winston, et al. Clinical Infectious Diseases 2010; 50: 920–929
Winston et al, HIV Medicine 2012, 13: 245–251

ART Intensification May Benefit HAND



Graph adapted from poster

Table 3: Cognitive and biologic markers evolution according CPE ≥9 or not

Median [IQR]	Evolution at W96/D0 with CPE ≥9 (n=22)	Evolution at W96/D0 with CPE <9 (n=9)	p
Δ GDS	-0,4 [-0,8;-0,1]	0 [-0,2;+0,2]	**0,018**
Δ BDI II score	-5 [-11;-1]	1 [-1;+5]	**0,029**
Δ CCQ score	-1,5 [-4;0]	-2 [-2;-1]	1,0
Δ Altered domain	-1 [-3;0]	0 [-1;+1]	**0,025**
Δ Neopterin (PI ; CSF)	0 [-2;+2]; -0,3 [-2;0,8]	1,3 [-1;5]; -0,4 [-1;0,3]	0,18; 0,86
Δ sCD14 (PI ; CSF)	510[250;763]; -9[-35;1]	430[313;628];-4[-28;0]	0,64; 0,70
Δ MCP-1 (PI ; CSF)	-18[-48;21]; -39[-50;38]	41 [-6;146]; 9[-75;84]	0,06; 0,78
Δ IP-10 (PI ; CSF)	-28[-105;1];-78[-122;56]	57[7;211];-7[-131;280]	**0,028**; 0,31
Δ NFL (PI ; CSF)	2,6 [1;6] ; 50 [-84;137]	2,9 [1-6]; 112 [54;311]	0,60; 0,27

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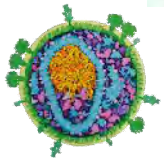
Force, et al. CROI 2018, Abstract 415

Cross-Sectional or Cumulative CPE Not Associated with HAND

	Unadjusted			Adjusted [a]		
CPE scores ANI, MND, HAD, Other						
Cross-sectional analysis (at the time of neurocognitive assessment)						
N		909			900	
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Continuous	1.03	0.96 – 1.11	0.408	1.04	0.94 – 1.14	0.441
≥ 7	1.13	0.81 – 1.57	0.476	1.22	0.81 – 1.83	0.347
≤ 5	0.89	0.45 – 1.75	0.735	0.82	0.35 – 1.92	0.646
6 – 8 (Ref.)	R	0.77 – 1.45	0.713	R	0.80 – 1.69	0.433
≥ 9	1.06			1.16		
Cumulative analysis (entire cART duration) [b]						
N		909			900	
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Continuous / T	1.04	0.95 – 1.14	0.360	1.02	0.89 – 1.16	0.812
≥ 7 / T (%)	1.02	0.98 – 1.06	0.347	1.03	0.97 – 1.10	0.323
≤ 5 / T (%)	0.98	0.93 – 1.04	0.494	0.99	0.90 – 1.10	0.885
≥ 9 / T (%)	1.01	0.96 – 1.06	0.649	1.00	0.94 – 1.07	0.959



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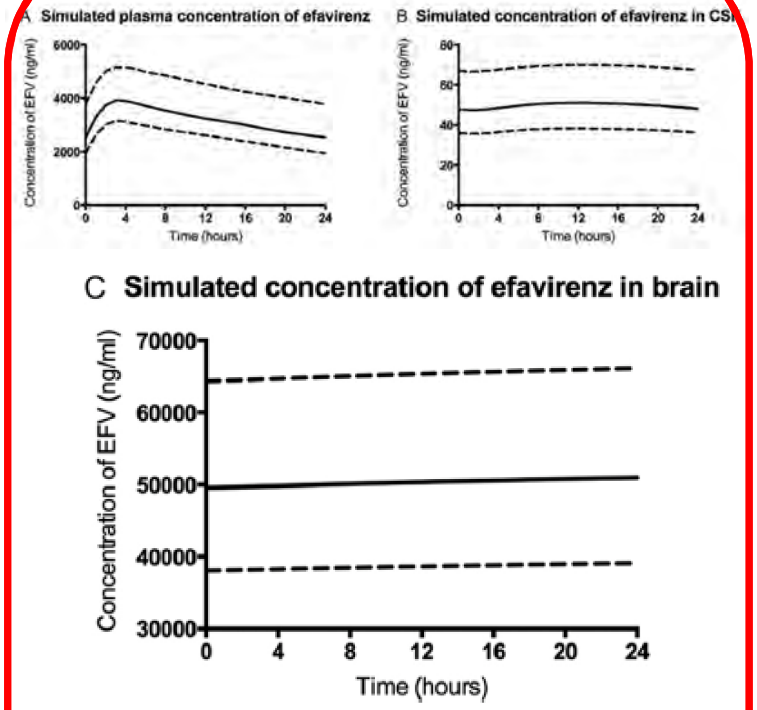
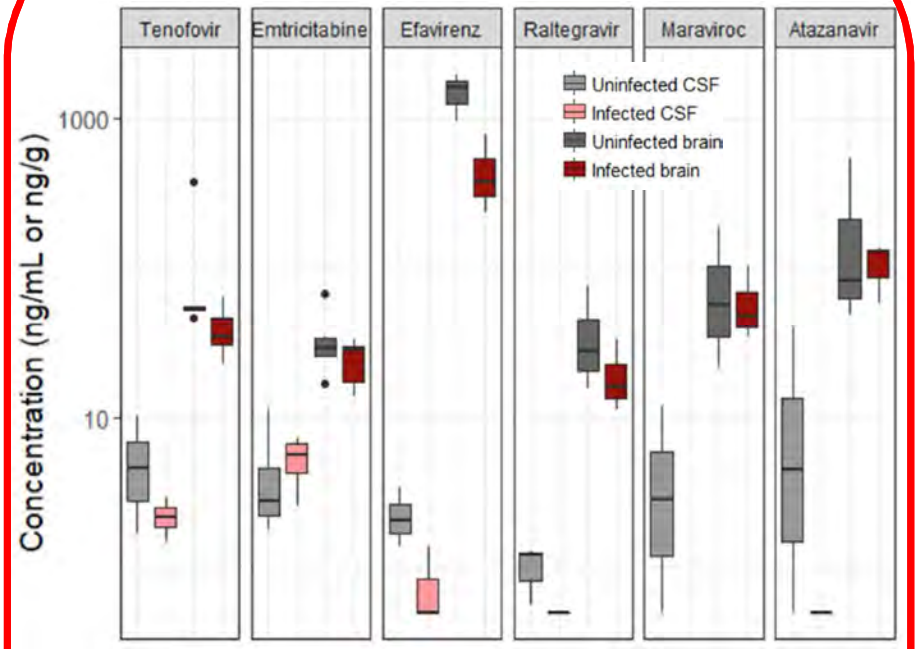
Darling, et al. CROI 2018, Abstract 416

Animal Models Also Support Higher ART Concentrations in Brain Tissue

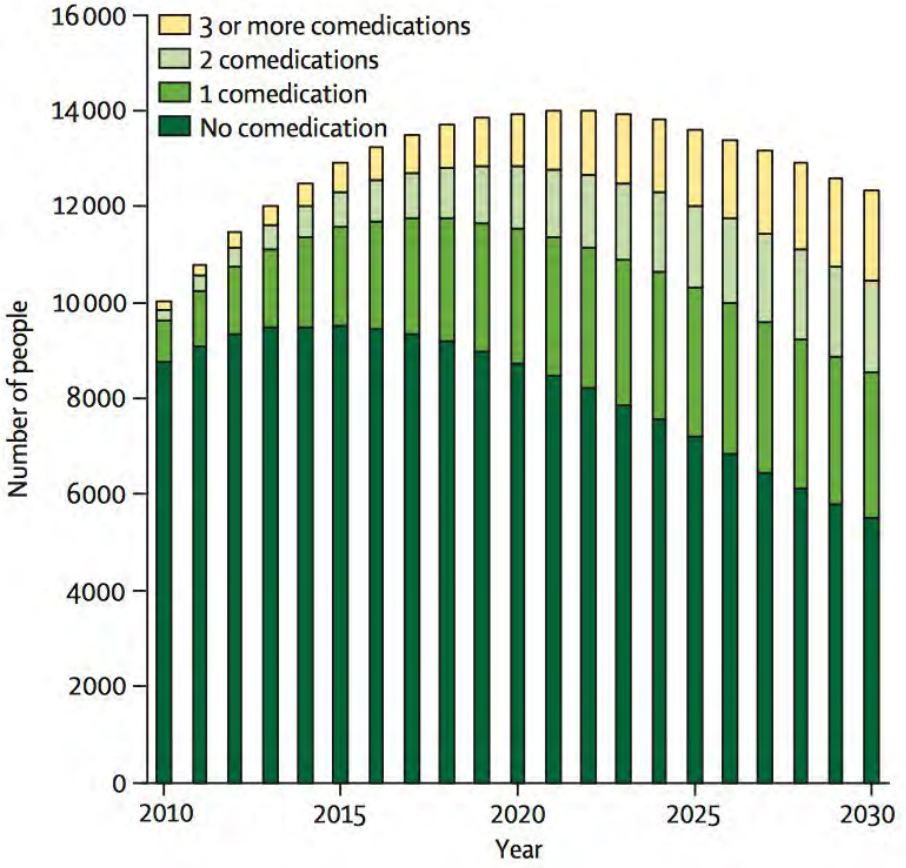


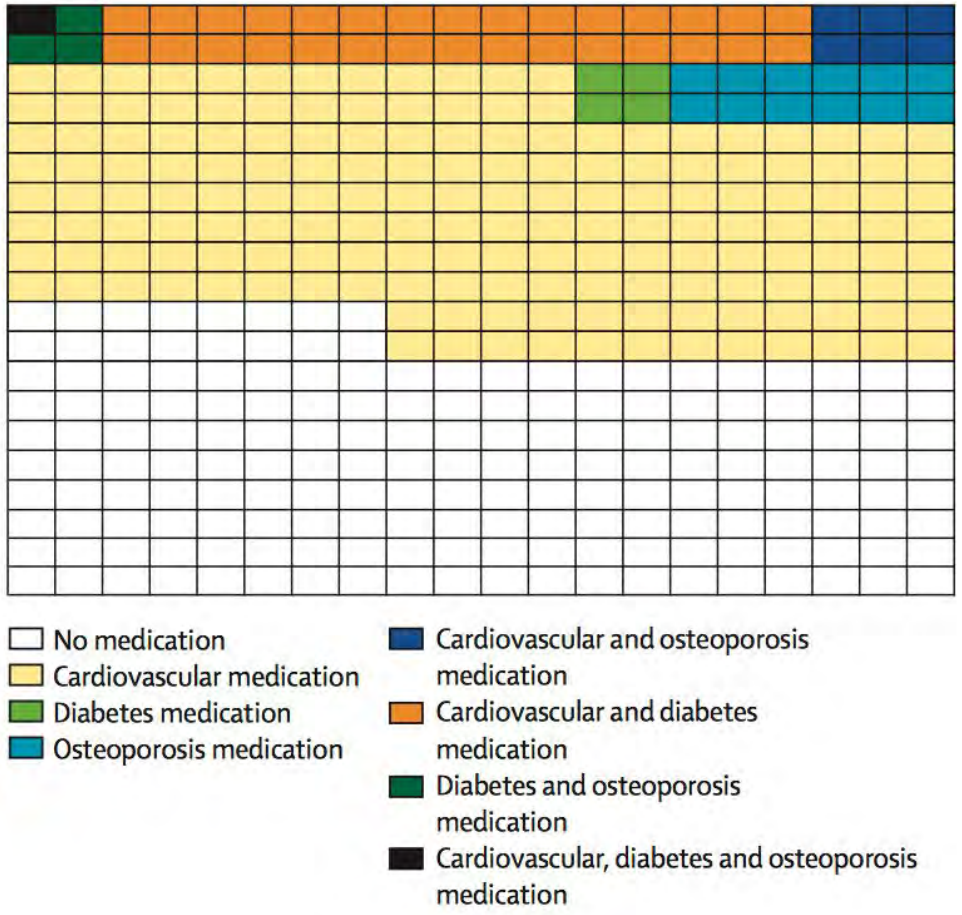
Curley et al, AAC 2017, 61(1): e01841-16



Srinivas et al, IAS 2017, Abstract WEAB0105

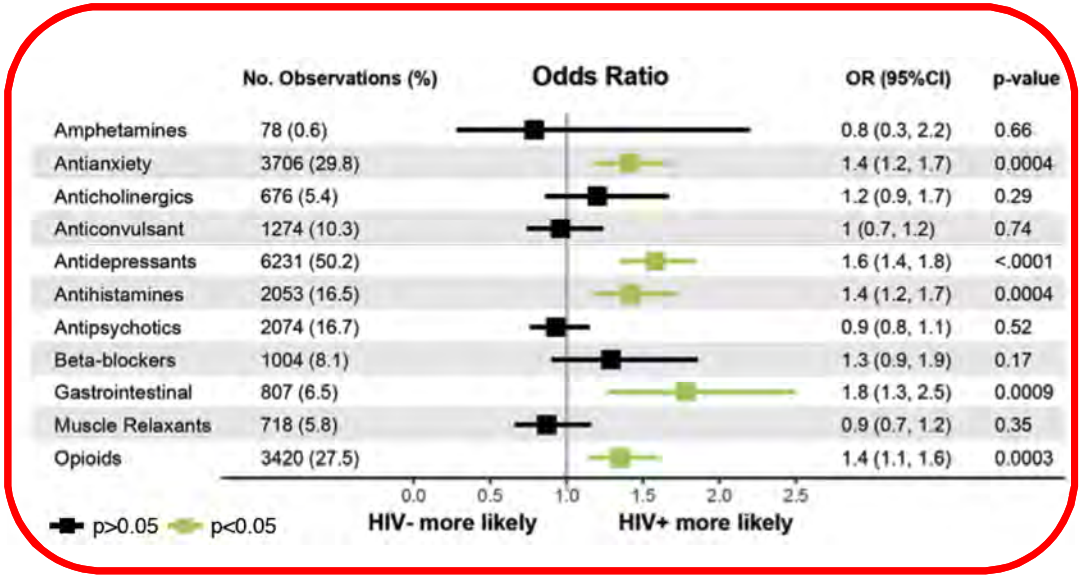
Increasing Polypharmacy in Aging HIV+ Adults

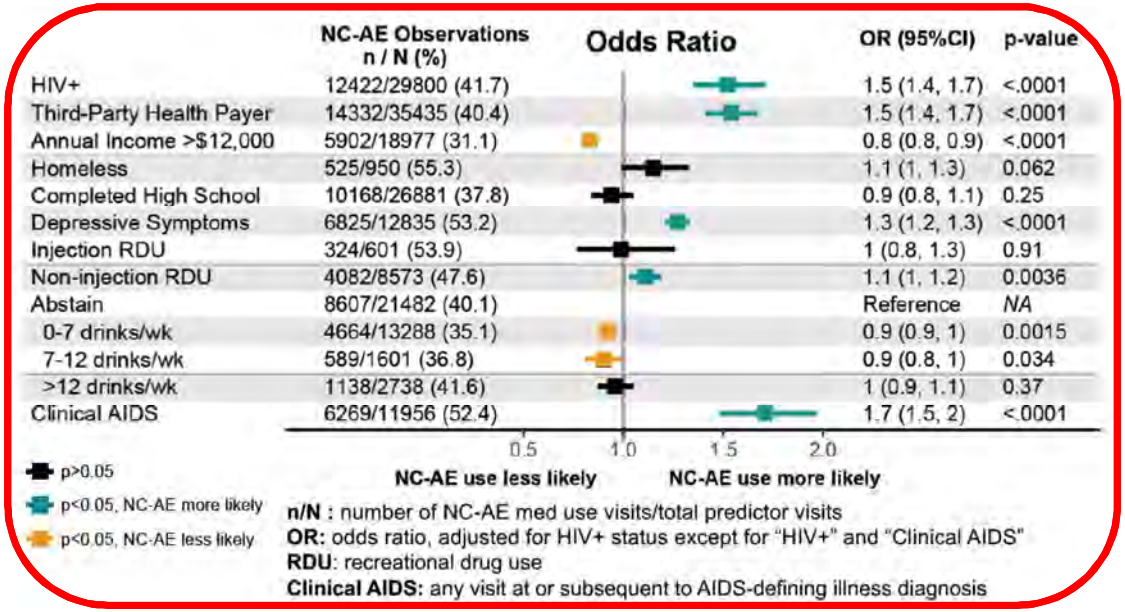




Smit, Lancet Inf Dis 2015, 15(7):810-8

Women with HIV are More Likely to Use Other Medications Associated with NC-AEs





NC-AE Drug Use and ART

Outcome	OR (95% CI)	p-value
cART use	1.46 (1.35-1.57)	<0.0001
cART adherence	1.03 (0.95-1.12)	0.45
Undectable viral load	1.12 (1.05-1.19)	0.0008

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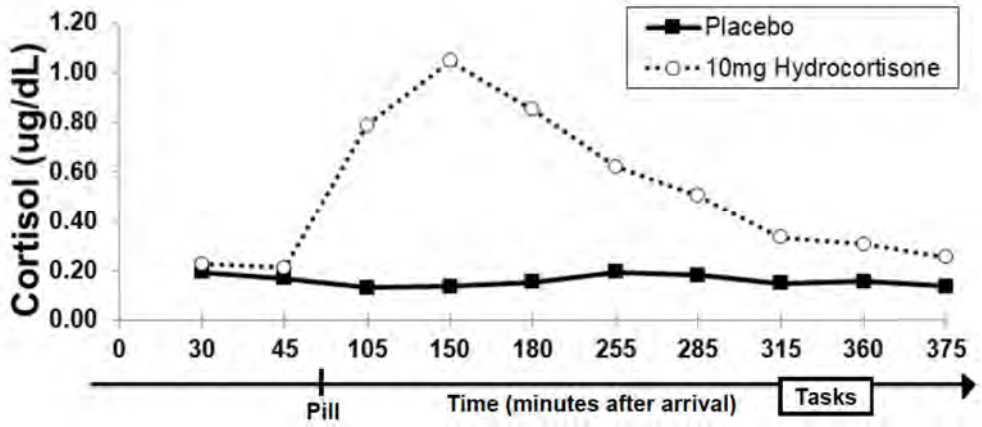
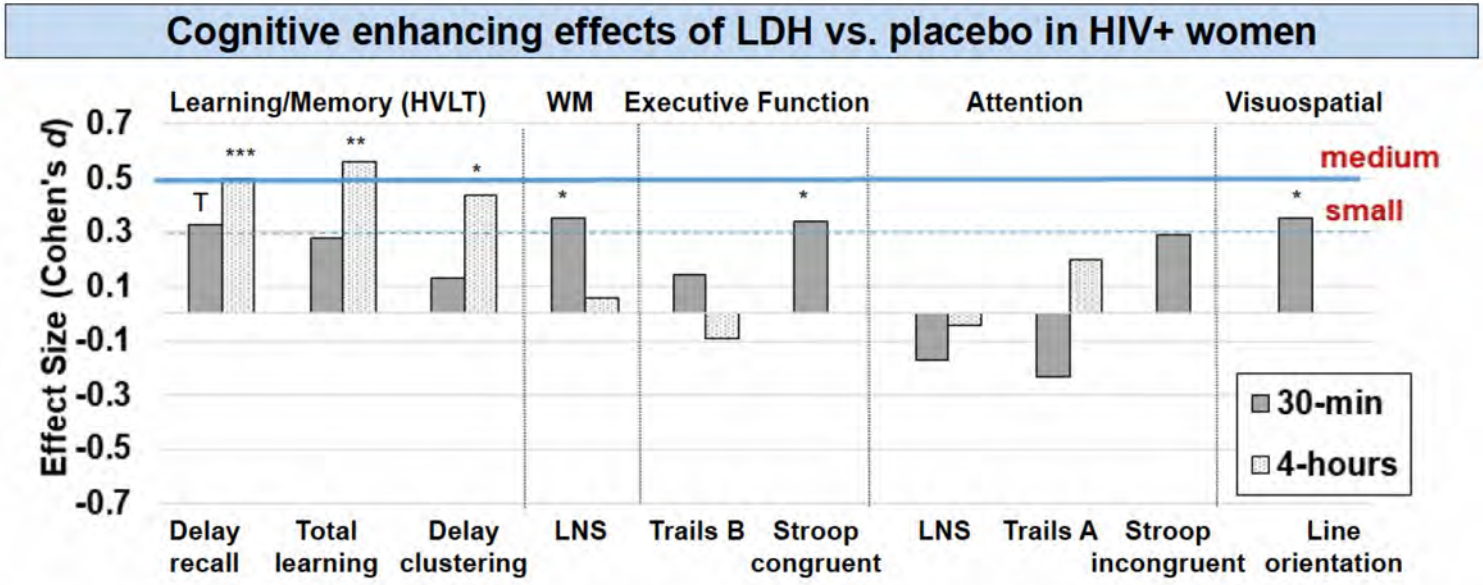
Radtke, et al. CROI 2018, Abstract 401

Benefits of Low Dose Hydrocortisone in Women with HIV





***p<0.001; **p<0.01; *p<0.05. T=0.06. WM=working memory. Analyses controlled for order of cognitive tests.

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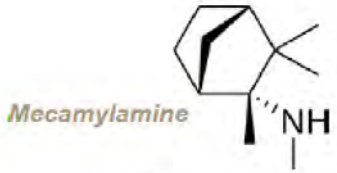
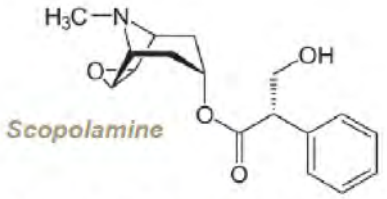
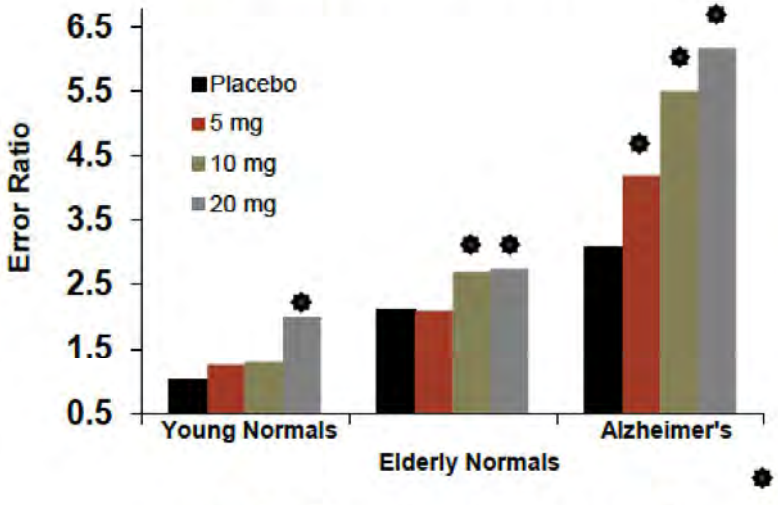
Rubin, et al. CROI 2018, Abstract 420

Anticholinergic Probe for Cholinergic Responsive Impairment

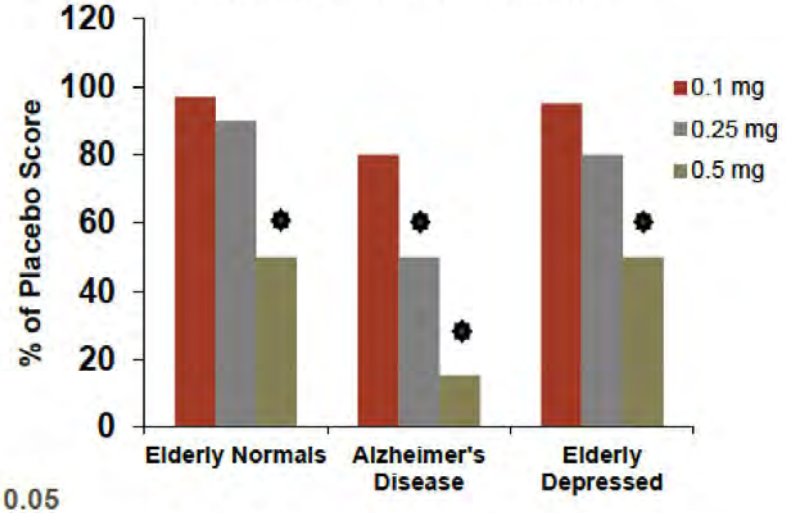




Mecamylamine's effect on Repeated Acquisition Task Performance



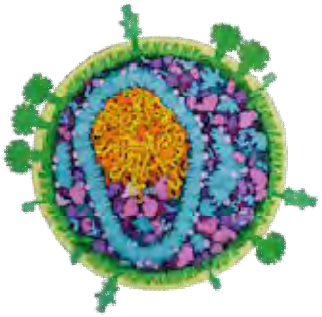
Scopolamine's effect on Verbal Free Recall Performance



* $p < 0.05$

By looking at differences in how these drugs affect different groups, we can determine ***relative differences*** in baseline cholinergic function

Newhouse et al. (2001), Sunderland, Tariot, & Newhouse, (1988)



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- **HAND Diagnosis-Related**
  - Novel Multivariate Method
  - Depression
- **Pathogenesis**
  - Host (Aging)
  - HIV
- **Treatment**

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