Update on risk factors, detection, and management of neurocognitive impairment in HIV-infected persons

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HIV
Neuropsychiatry

Disclosures

Funds for investigator-initiated research were paid to University of California, San Diego:

- Abbvie
- Gilead Sciences
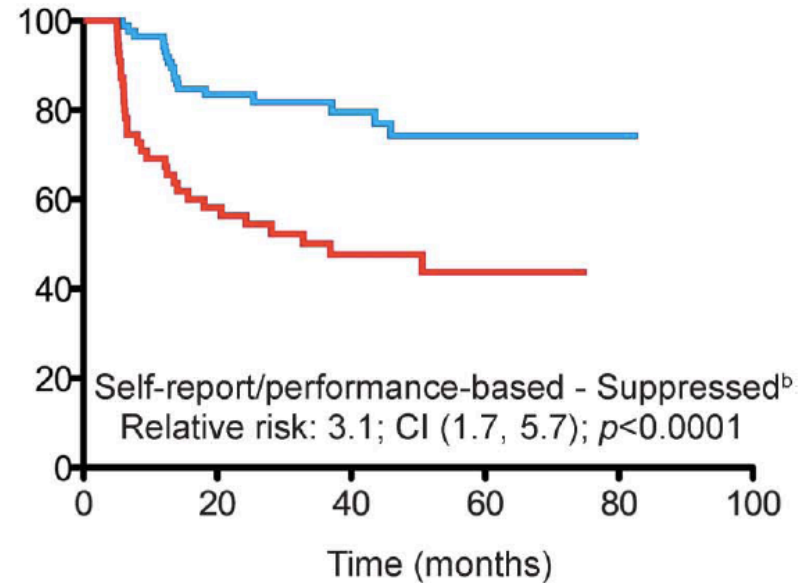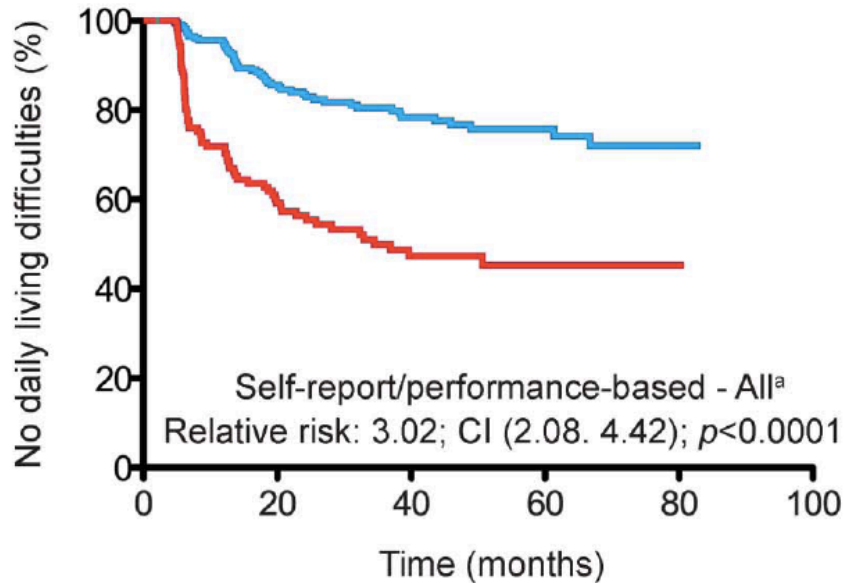- Merck & Co., Inc.
- ViiV Healthcare

Honoraria for advisory boards or lectures were paid to Dr. Letendre:

- Abbvie
- Cipla
- Janssen
- Merck & Co., Inc.
- ViiV Healthcare

HIV
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Updated research nosology for HIV-associated neurocognitive disorders

	Acquired Impairment in ≥ 2 Cognitive Abilities	Interferes with Daily Functioning	No Cause Prior to HIV	No Current Strongly Confounding Condition
Asymptomatic Neurocognitive Impairment (ANI)	✔	No	✔	✔
Mild Neurocognitive Disorder (MND)	✔	Mild	✔	✔
HIV-Associated Dementia (HAD)	Marked	Marked	✔	✔

HIV Neuropsychiatry

Antinori et al, Neurology 2007, 69: 1789-99

Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline

Self-report/performance-based - All[a]
Relative risk: 3.02; CI (2.08. 4.42); p<0.0001

Self-report/performance-based - Suppressed[b]
Relative risk: 3.1; CI (1.7, 5.7); p<0.0001

- 347 adults who were either unimpaired (n = 226) or had ANI (n = 121)
- Assessed every 6 months with median follow-up of 45.2 months
- Symptomatic decline was based on self-report or objective, performance-based problems in everyday functioning
- Current CD4 and depression were significant time-dependent covariates

Grant et al, Neurology 2014;82:1–8

More Subjects Meet Criteria for Symptomatic HAND if the Requirement for Attribution of Problems to a Cognitive Disorder is Eliminated

With Attribution*

ANI MND HAD

Without Attribution*

ANI MND HAD

With Attribution: ANI 47 %, MND 44 %, HAD 8 %
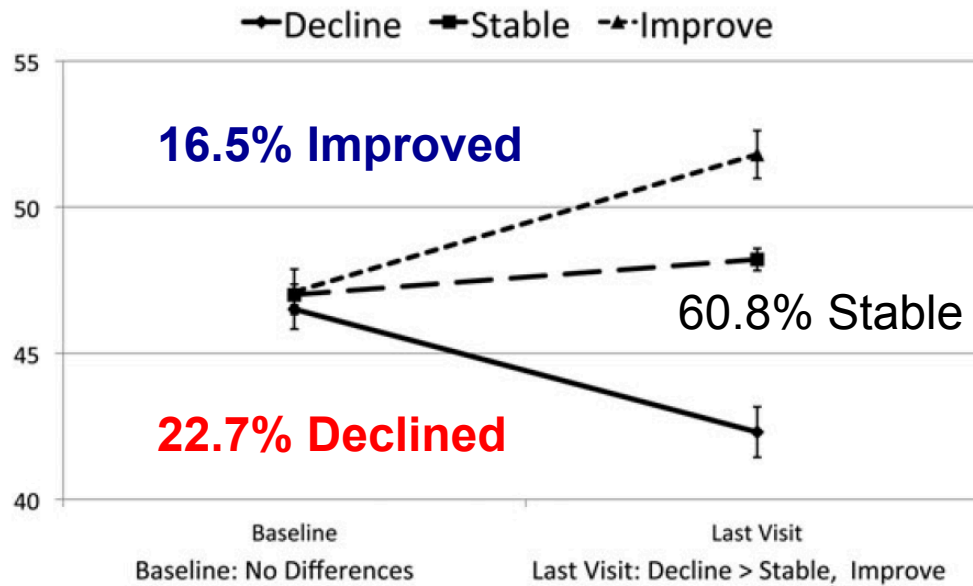
Without Attribution: ANI 33 %, MND 55 %, HAD 12 %
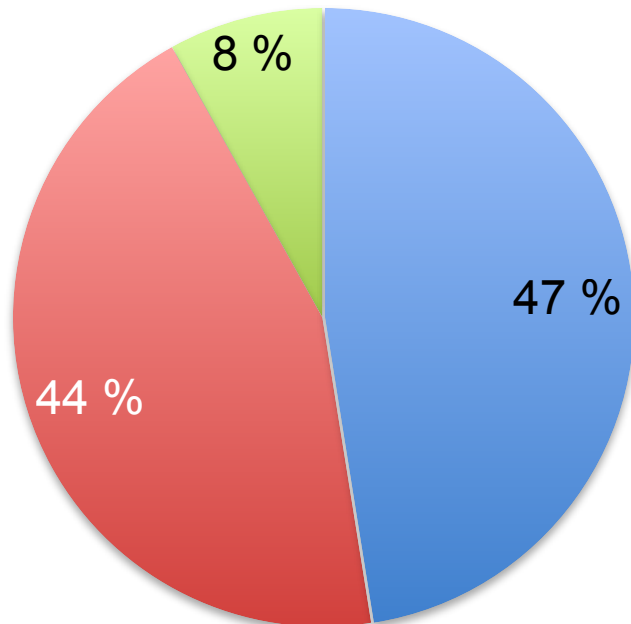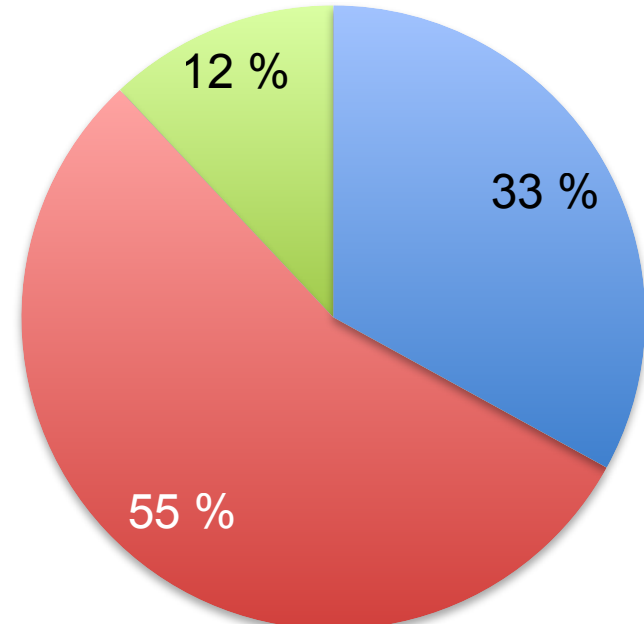
*Attribution regarding physical vs. cognitive causes
Diagnoses made by combination of self-report and performance based measures

Heaton et al, Unpublished CHARTER Data

Neurocognitive Change in the Era of HIV Combination Antiretroviral Therapy: The Longitudinal CHARTER Study

- Analyzed incidence and predictors of neurocognitive change over mean 35 months in 436 HIV+ adults who were assessed every 6 months

Heaton et al, Clinical Infectious Diseases 2015; 60(3):473–80

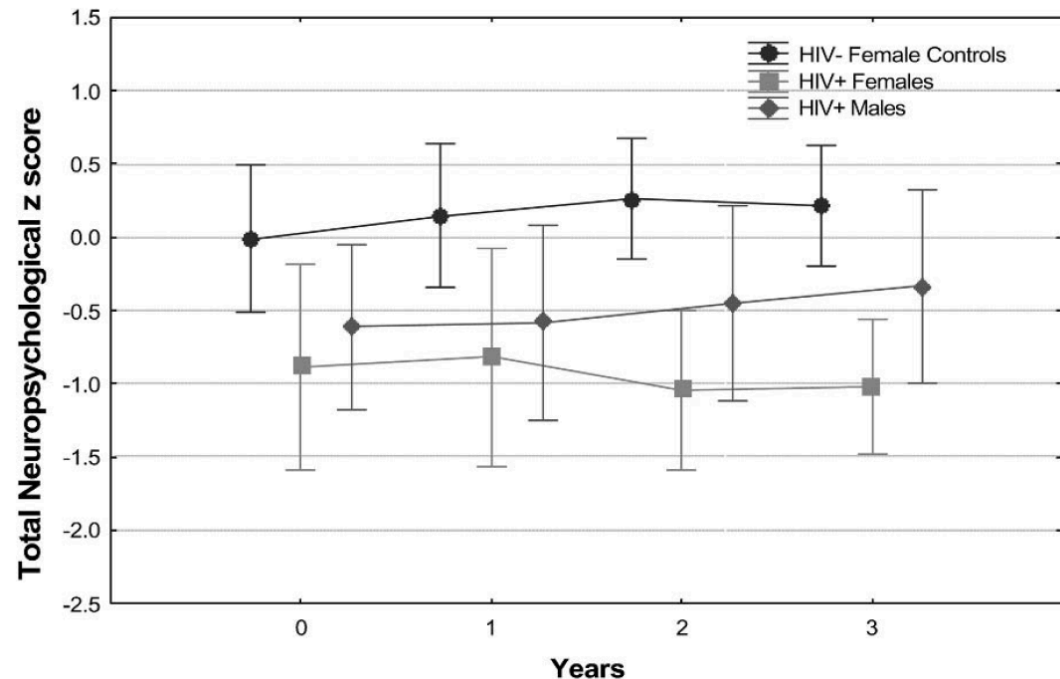|	**Decline**			**Improvement**	
	Risk	**RR**		**Risk**	**RR**
Sex	Female	1.76*	**Sex**	-	-
Ethnicity[1]	Hispanic	2.35**	**Education**	Higher†	1.10
ART Use[1]	Off ART	1.91**	**Est. IQ Before HIV[1]**	Higher†	1.02*
Current CD4 Count	Lower†	1.14**	**HIV RNA in CSF**	Lower†	1.47*
HIV RNA in Plasma	Higher†	1.26**	**HIV RNA in Plasma**	Lower†	1.27*
Serum Albumin[1]	Lower†	2.36***	**Serum Total Protein[1]**	Lower†	1.96***
Hematocrit[1]	Lower†	1.10***	**Hematocrit**	Higher†	1.06*
Neuropsychiatric Comorbidities[1]	Severe	2.47**	**Serum Hepatic AST[1]**	Lower†	1.01*
Lifetime Methamphetamine Diagnosis[1]	Present	1.81*	**Lifetime Substance Use Diagnosis**	Absent	1.63
Beck Depression Inventory[1]	Higher†	1.03	**Lifetime Major Depression Disorder[1]**	Absent	1.63*

*p < 0.05, **p < 0.01, ***p < 0.0001
†CD4: per 100 cells; HIV RNA: per 1 $\log_{10}$ c/mL; Albumin, Hematocrit, Total Protein, AST: Per 1 "unit"; Beck Depression: Per 1 unit; IQ: Per 1 unit; Education: Per year; Hepatic AST: Per 1 mg/dL; Total Protein: Per 1 g/dL
[1]Included in the final multivariable model (in red)

As the US Incidence of HIV in Women Rose, Early Findings Were Mixed

- An early pilot study published of HIV+ women identified that women performed worse than men on tests of neurocognitive functioning

- A subsequent larger, prospective study found no difference

Robertson K, et al. J Neuro-AIDS. 1996;1: 166;
Robertson K, et al, J Acquir Immune Defic Syndr 2004;36:817–822

Pattern of Impaired Cognitive Abilities May Differ Between Women and Men

- 122 adults who differed by HIV serostatus and sex

- HIV was associated with impairment to a similar extent in men (52%) and women (55%) but the pattern of impairment differed
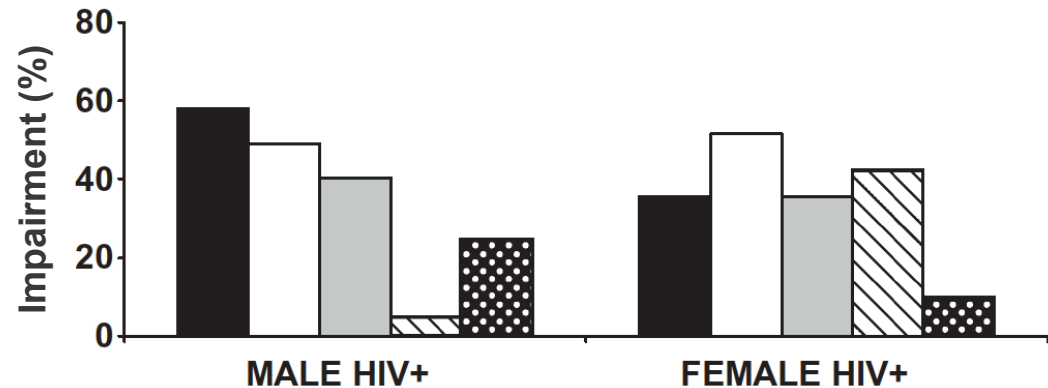
Figure 2. Type of impairment. ■ Visual memory; □ Attention/Psychomotor speed; ▨ Abstract reasoning/Verbal intelligence; ◳ Verbal memory for texts; ▨ Verbal memory for digits and words.

Interaction of Cognitive Functioning and Mood Symptoms

- 708 HIV+ and 278 HIV- women from the WIHS
- HIV, but not menopausal stage, was associated with worse performance on all cognitive measures

	Verbal Learning	Memory	Executive Function
HIV Serostatus	$p < 0.01$	$p < 0.05$	$p < 0.05$
Depressive Symptoms	$p < 0.05$	$p < 0.05$	$p < 0.05$
Anxiety Symptoms	$p < 0.05$	$p < 0.01$	-
Sleep Disturbances	-	-	-
HIV x Anxiety Interaction*	$p < 0.001$	-	-

Anxiety was associated with worse learning only among HIV+ women

Rubin et al, Menopause 2014. 21(9): 997-1006
Also see: Giesbrecht et al, PLoS One 2014. 9(3): e89556

# Challenges to the Implementation of the Current Approach to HAND Diagnosis

- Screening instruments are not consistently sensitive between sites

- We do not routinely perform comprehensive neurocognitive testing in clinic

- Many of our patients are unemployed or have below average socioeconomic status, complicating assessment of daily functioning

- Confidently deciding that a condition confounds attribution of the cause of impairment to HIV can be difficult

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Soluble Biomarkers Identify a Preclinical Stage in Alzheimer's

*Sperling et al, Alzheimer's & Dementia 7 (2011) 280–292*
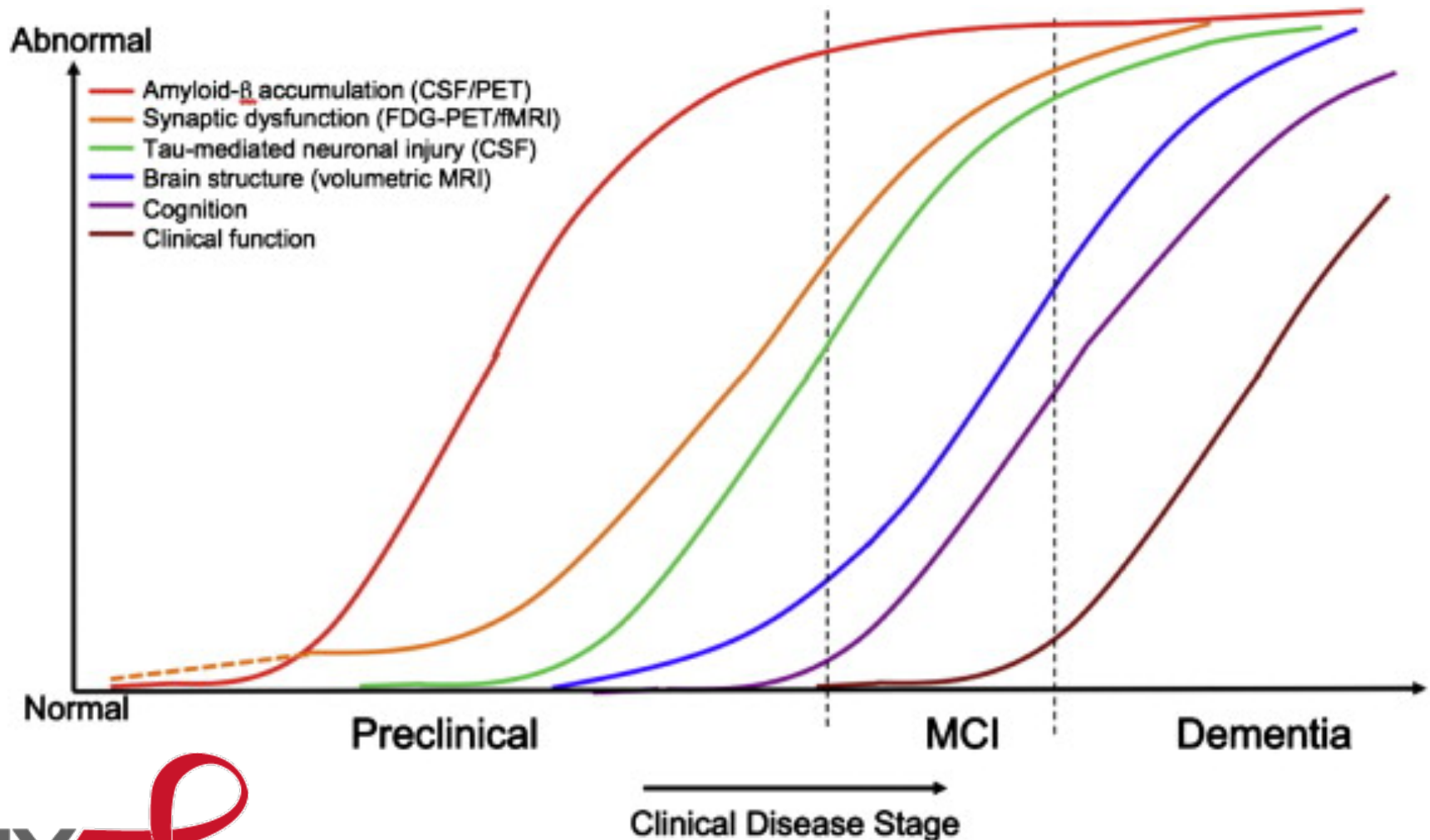
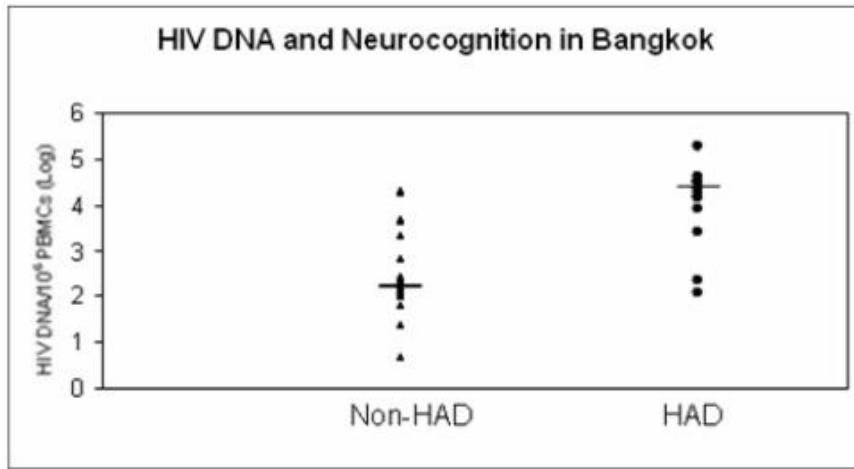# ANI and MND are Associated with Higher Neopterin but not NFL

- Cross-sectional analysis of 150 HIV+ subjects taking suppressive ART without significant neuropsychiatric confounds
- Subjects were classified as NP-normal (NPN, n=79) or NP-impaired (ANI, n = 38; MND, n=33)
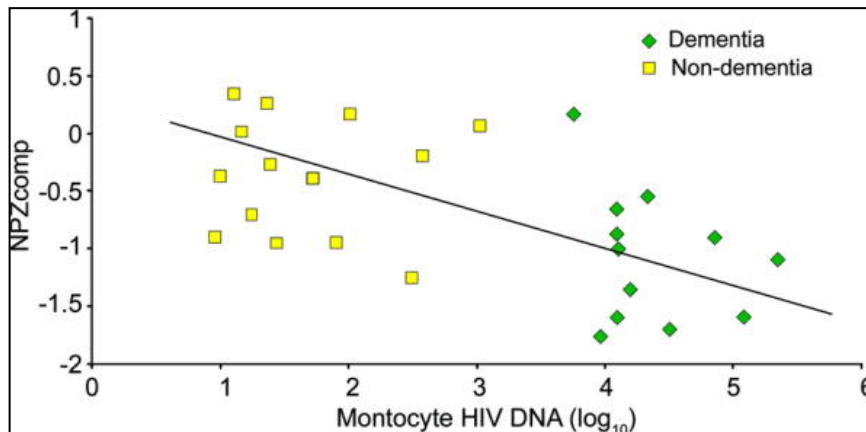

Edén et al, CROI 2014, Abstract 490
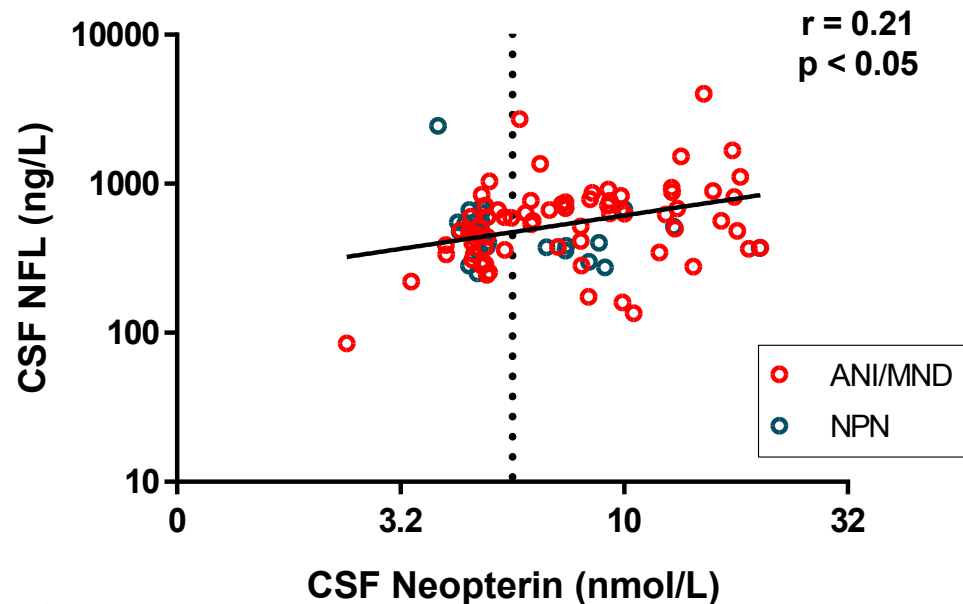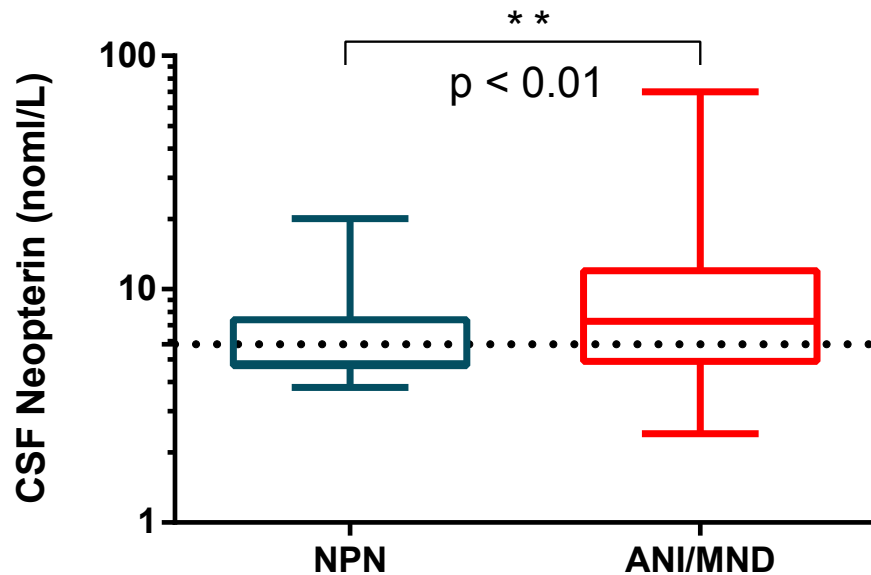
Higher Soluble CD163 in Plasma in MND but not ANI
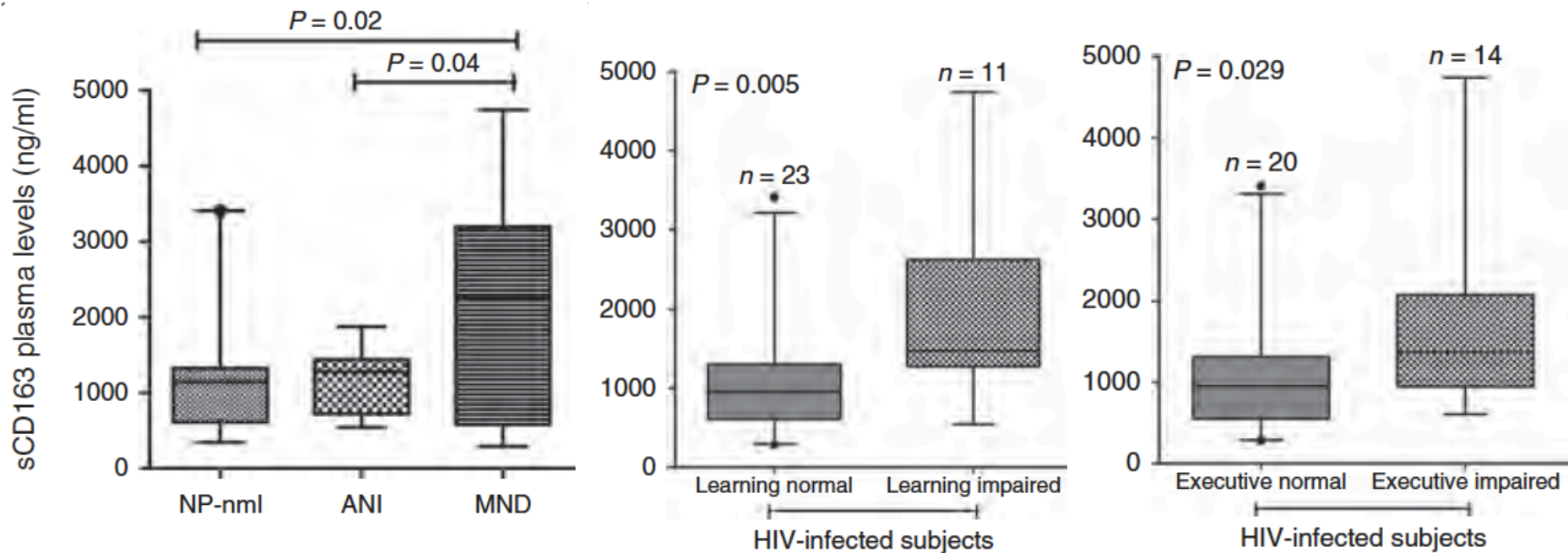
Higher HIV DNA Content is Associated with Worse Neurocognitive Performance

HIV DNA and Neurocognition in Bangkok

Shiramizu et al, Int J Med Sci 2006, 6;4(1):13-8

Valcour V et al, Neurology, 2009. 72(11):992-8

	Statistic	p (after EDI control)
Younger	- 0.200141	0.447789 (0.646705)
Older	0.546697	0.00492138 (0.0213879)

< 40 yo
> 50 yo
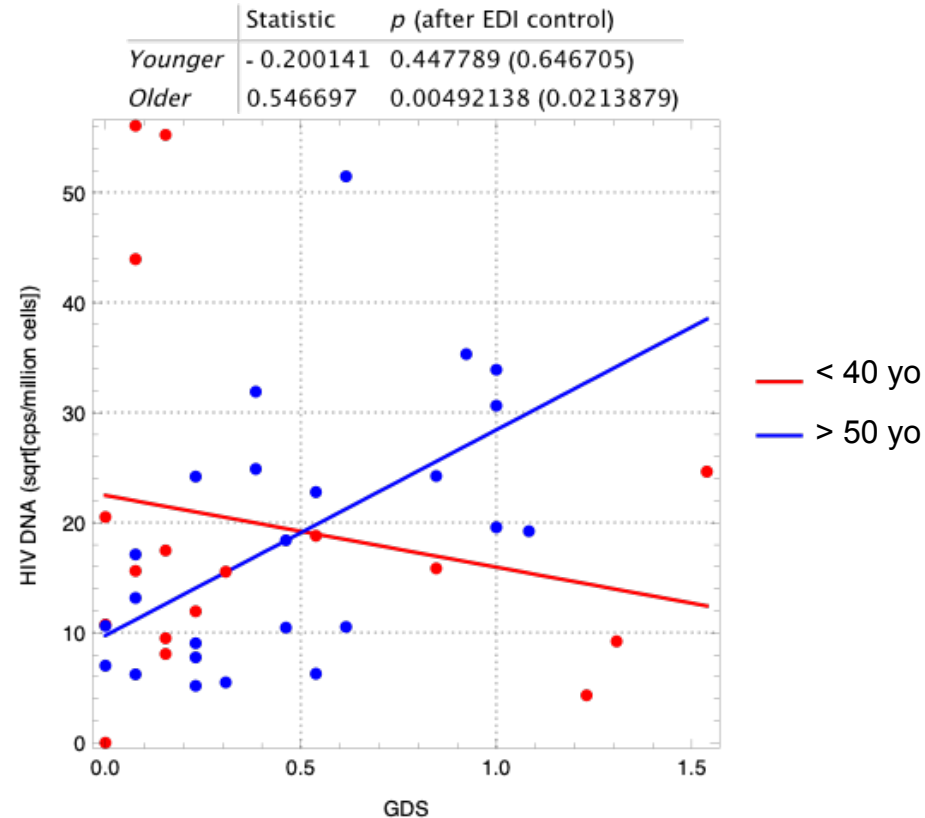
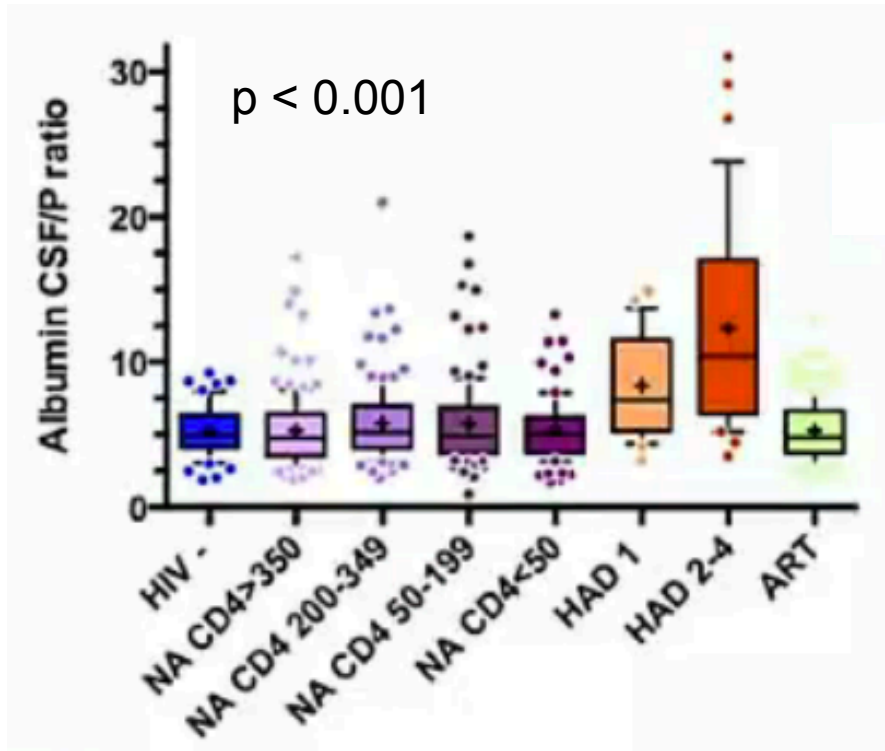*Oliveira et al, CROI 2015, Abstract 491*

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Possible Biological Classification of HAND

|	Higher HIV DNA	Higher sCD163	Higher Neopterin	Higher Neurofilament Light	Alternative Diagnosis on Imaging
	Blood	Blood	CSF	CSF	-
Asymptomatic Neurocognitive Impairment (ANI)	✔	No	✔	No	No
Mild Neurocognitive Disorder (MND)	✔	✔	✔	No	No
HIV-Associated Dementia (HAD)	✔✔	✔	✔✔	✔	No

Additional challenges:
- Clinical standardization of assays
- Identification of clinically relevant cutpoints
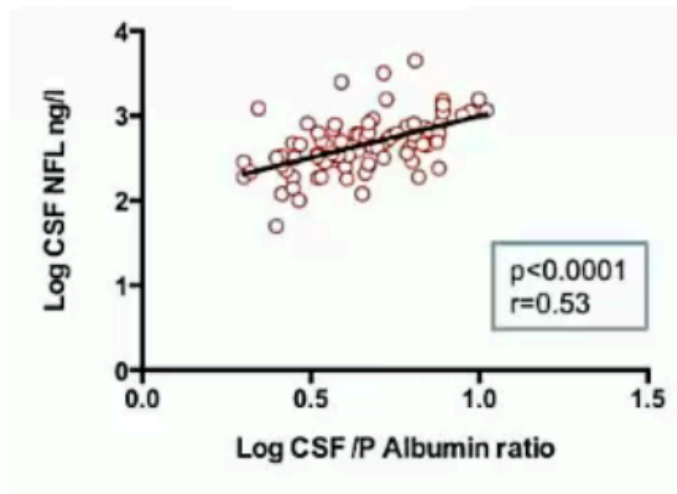
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CSF/Plasma Albumin Ratio is Elevated in HAND
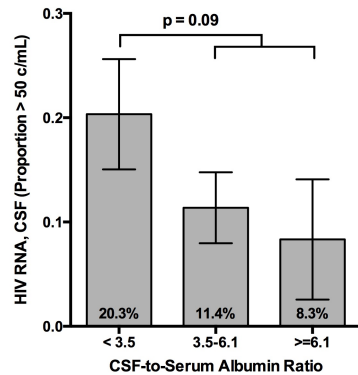

p < 0.001

Anesten et al, CROI 2015. Abstract 59

Neuroasymptomatic, off ART

p<0.0001
r=0.36

On ART

p<0.0001
r=0.53
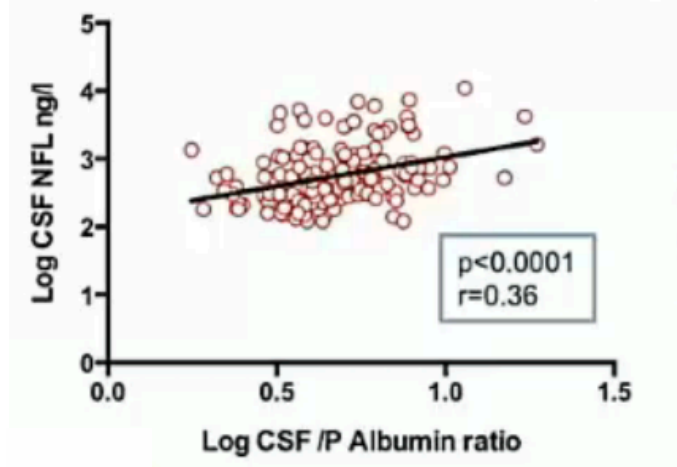
BBB Permeability During ART May Define Different HAND Phenotypes

CHARTER Data, Manuscript in Preparation
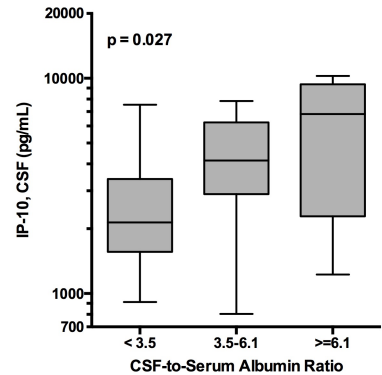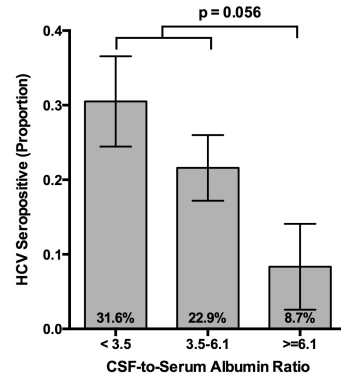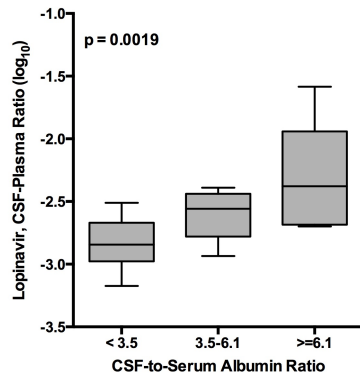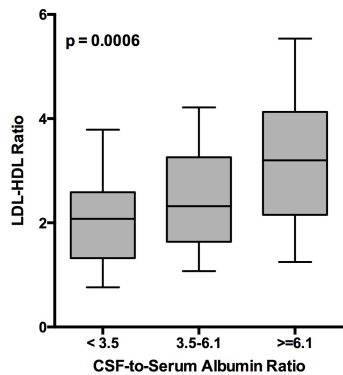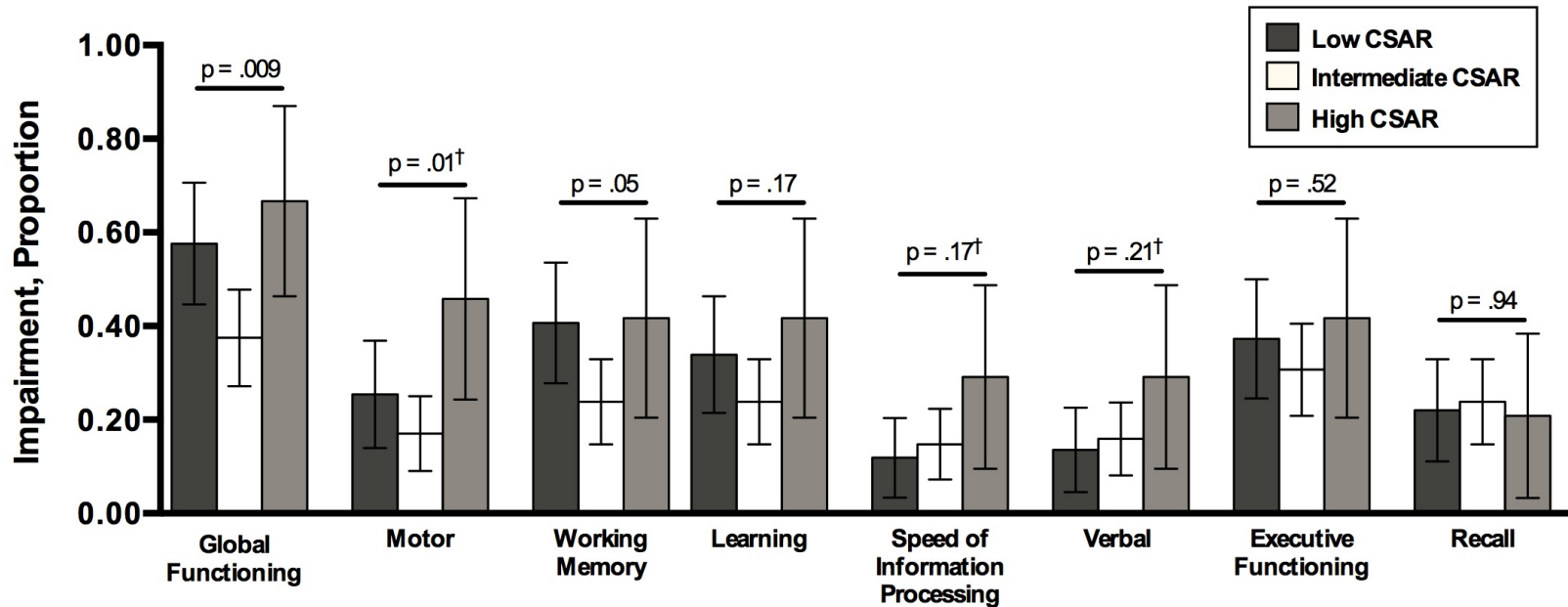
# Biomarkers of HAND May Differ in Younger and Older HIV+ Adults

- **Similar in older and younger adults**
  - HIV RNA (SCA)
  - Neurofilament light
  - sCD163
  - Neopterin
  - D-dimer, hsCRP

- **Stronger in older adults**
  - HIV DNA
  - Telomere length and other aging biomarkers
  - IL-6, MCP-1, sCD40L
  - Amyloid β1-42, p-Tau

	Correlation		Interaction
	Age	GDS	Age x Biomarker
Viral			
- HIV RNA (SCA)	✗	✗	-
- HIV DNA	-	-	✗
Neuronal			
- Phospho-Tau (181)	✗	✗	✗
- Total tau	✗	✗	-
- Neurofilament Light	✗	-	-
Aging			
- Telomere Length	✗	-	✗
- Mitochondrial Common Deletion	✗	✗	-
- Free Mitochondrial DNA	✗	-	✗
- 8-OHdG	✗	✗	✗
- Protein Carbonyls	✗	✗	✗
- F2-isoprostanes	✗	-	✗
Macrophage/Glial			
- MCP-1	✗	✗	✗
- sCD163	✗	✗	-
- Neopterin	✗	✗	-
- GFAP	✗	-	-
Metabolic/Vascular/Inflammation			
- IL-6	✗	✗	✗
- sCD40L	✗	-	✗
- D-dimer	✗	-	-
- hsCRP	-	-	-
- Amyloid β1-42	-	-	✗

Correlates of Shorter Telomere Length

	Risk	Effect size	P value	n
Sex	Male	d = 1.6	**0.005**	48
Ethnicity	White/Other	d = 1.0	**0.001**	48
Age	Older	r = -0.32	**0.03**	48
Est. Duration of HIV	Longer	r = -0.31	**0.06**	38
Duration of ART	Longer	r = -0.27	**0.08**	44
Plasma HIV RNA	> 50 c/mL	d = 1.0	**0.07**	34
Total Cholesterol	Lower	r = 0.33	**0.03**	43
Global Deficit Score		r = 0.04	0.80	47
GDS Impairment		X^2 = 0.09	0.76	47

Unpublished UCSD Data
Copyright S. Letendre 2015

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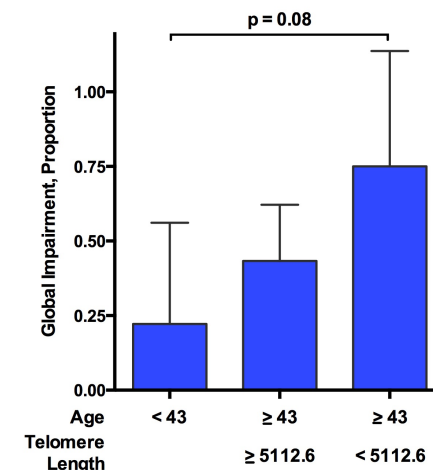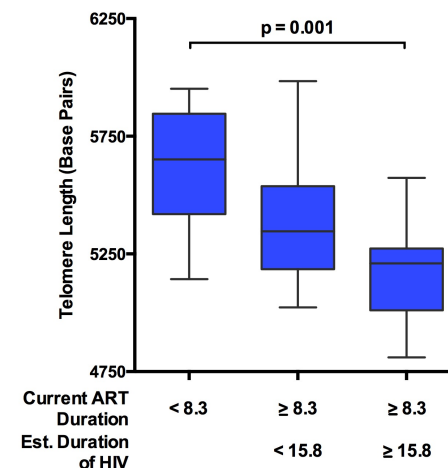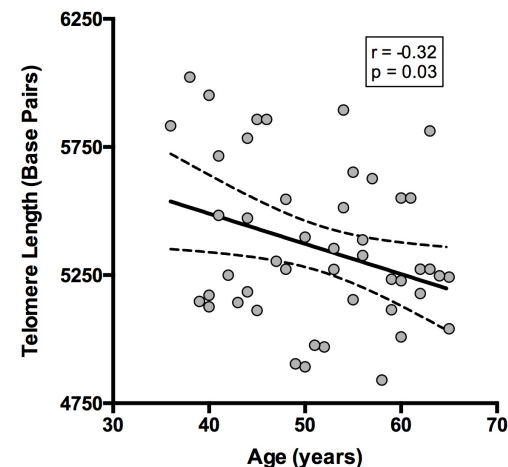
Higher *Lactobacillales* proportion in gut microbiome is associated with higher CD4 Count and CD4/CD8 ratio

Pérez Santiago et al, AIDS. 2013; 27(12):1921-31
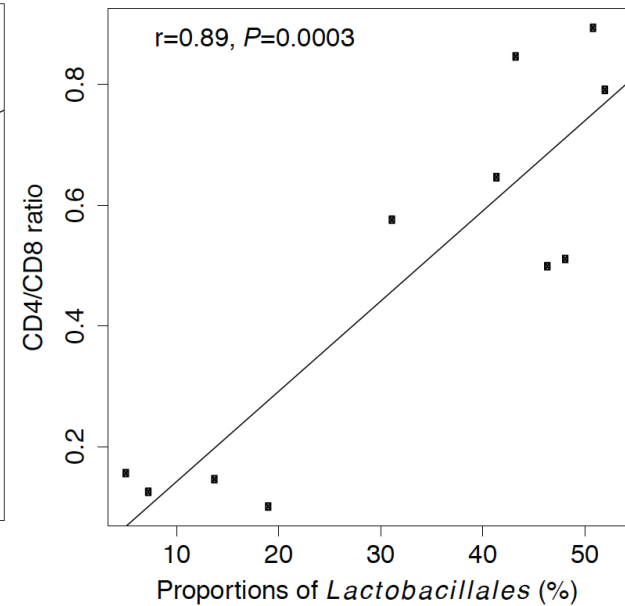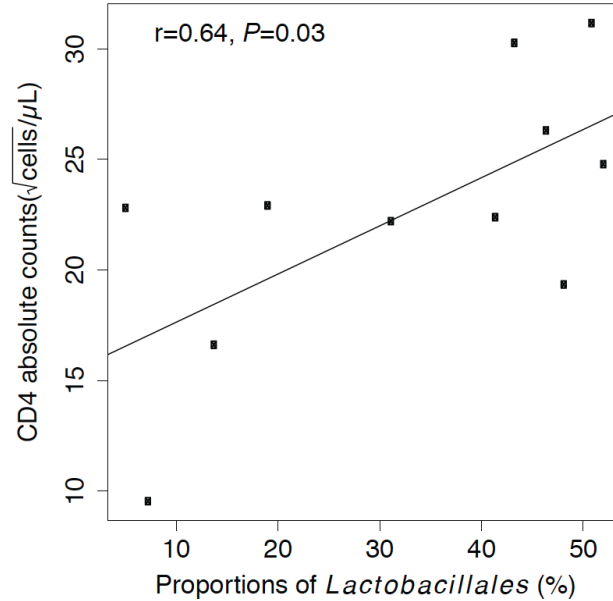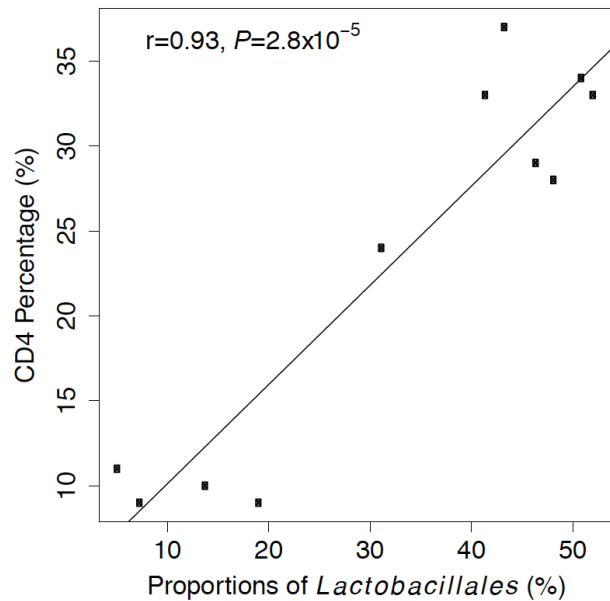
Gut Microbiome Clustered by Presence or Absence of Neurocognitive Impairment
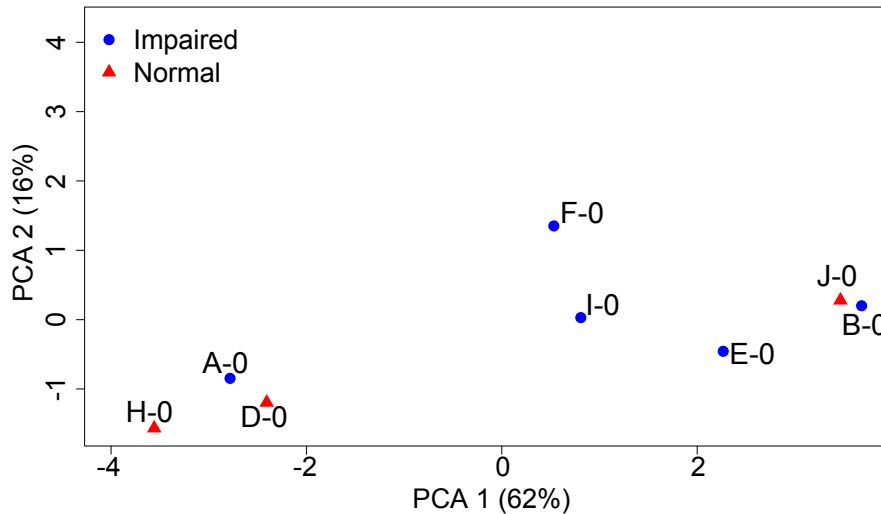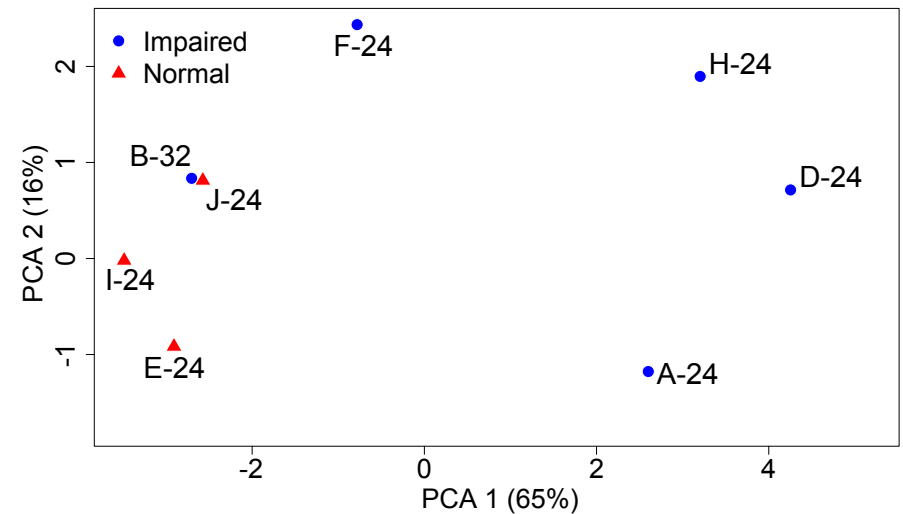
Pérez Santiago et al, International Symposium on Neurovirology 2015

Multiple Characteristics Can Influence the Effectiveness of ART in the CNS

- **Distribution of ART drugs into the brain**
  - CSF may not be equivalent to brain
- **Efficacy of the drugs**
  - Macrophages are the target cells in the brain
  - Drug resistance
- **Toxicity of the drugs**
  - Neurotoxicity
  - Metabolic and vascular disease

- **Timing of ART initiation**
  - Earlier ART initiation may better prevent HAND
- **Host factors**
  - Older age
  - Blood-brain barrier permeability
  - Coinfections and other comorbidities

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2,207 CSF Viral Loads in 413 Volunteers Over 30 months
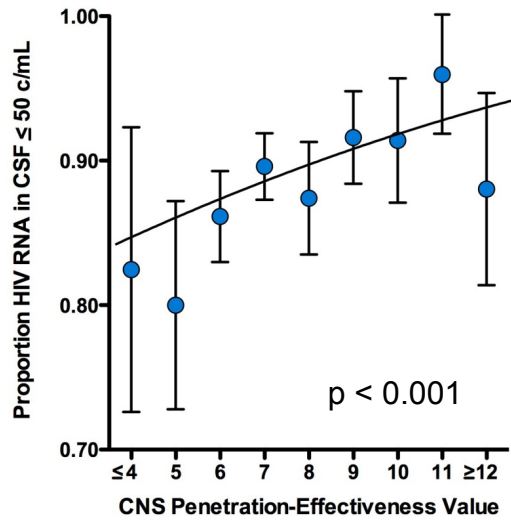
Letendre et al, 19th CROI, 2012, Abstract 473

CSF Inflammation Biomarkers in 394 Volunteers Taking Suppressive ART
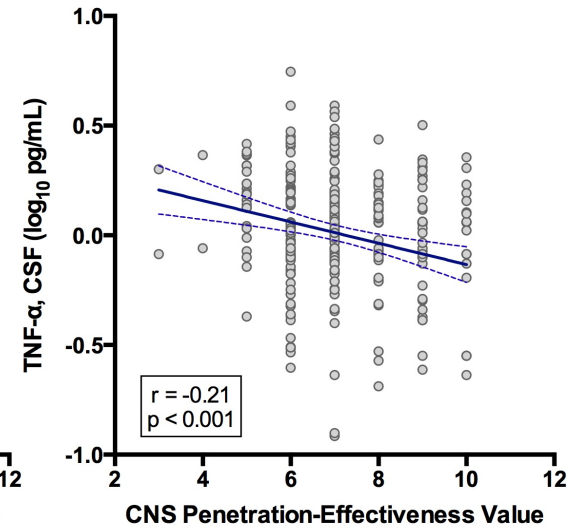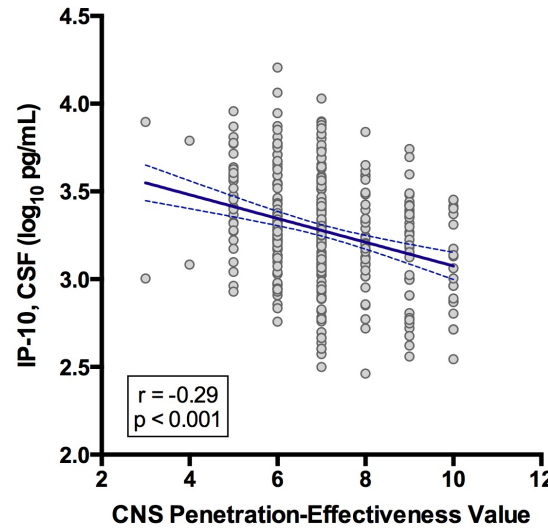
Single-Copy Assays in CSF in 283 Volunteers Taking Suppressive ART

Letendre et al, 16th CROI, 2009, Abstract 484b
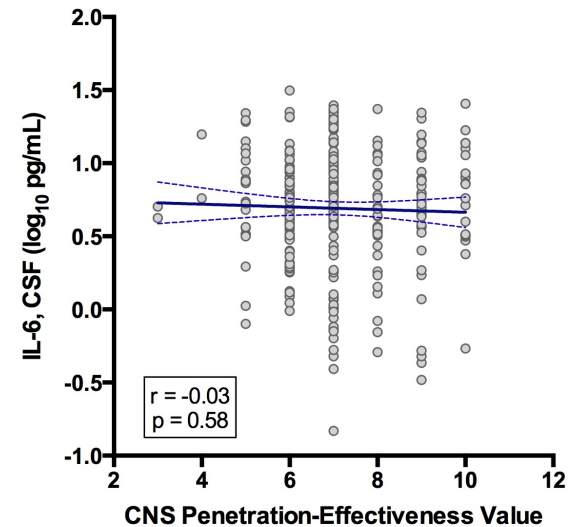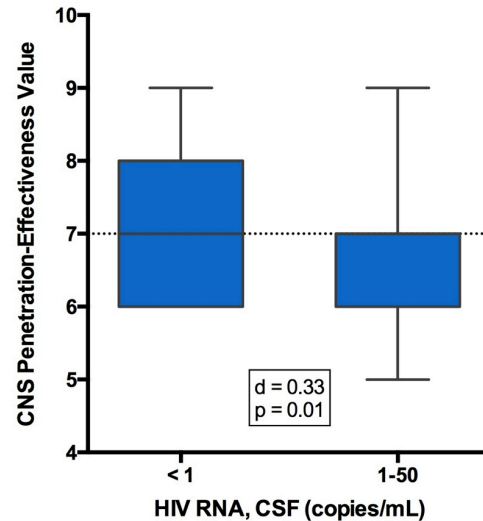
Letendre et al, In Preparation

Ideal Characteristics of Analyses of CNS Effectiveness of ART

- Studies should be randomized and longitudinal

- Power and duration should be sufficient

- Assessments should be standardized and comprehensive

- Drug regimen potency and toxicity should be similar

  – For those that focus on CPE, regimens should have the same number of drugs

Recent Reports Have Mixed Findings

		N	NP	Duration	Principal Finding	Notes
Ciccarelli[1]	C-S	101	C	-	Beneficial	2010 version stronger than 2008 version
Ciccarelli[2]	C-S	215	C	-	Beneficial	Adjusted CPE using GSS
Casado[3]	C-S	69	B	-	Trend toward benefit	Beneficial when CD4 < 200
Vassallo[4]	L	96	C	22 months	Beneficial	~25% were not virologically suppressed
Cross[6]	L	69	C	~1 year	No association	Binary transformation only
Ellis[5]	RCT	49	C	16 weeks	No association	Beneficial in subgroup
Wilson[7]	C-S	118	B	-	Detrimental on 2 tests	Binary transformation only Substance users only
Kahouadji[8]	C-S	93	B	-	Detrimental on 1 test	Methodological flaws
Caniglia[9]	L	61,938	N	-	Detrimental	Absolute risk 1.1% vs. 0.9%

C-S = Cross-sectional, L = Longitudinal, RCT = Randomized clinical trial, C = Comprehensive, B = Brief, N = None, GSS = Genotype Susceptibility Score

[1]Ciccarelli et al, Antiviral Therapy 2013, 18: 153-160; [2]Ciccarelli et al, 20th CROI 2013, Abstract 405; [3]Casado et al, J Neurovirol 2014, 20: 54-61; [4]Vassallo et al, AIDS 2014, 28(4):493-501; [5]Ellis et al, Clin Infect Dis. 2014;58(7):1015-22; [6]Cross et al, S Afr Med J 2013;103(10):758-762; [7]Wilson et al, J Clin Experim Neuropsych 2013, 35:915-25, [8]Kahouadji et al, HIV Medicine 2013, 14: 311-5.

Maraviroc Intensification May Be Beneficial
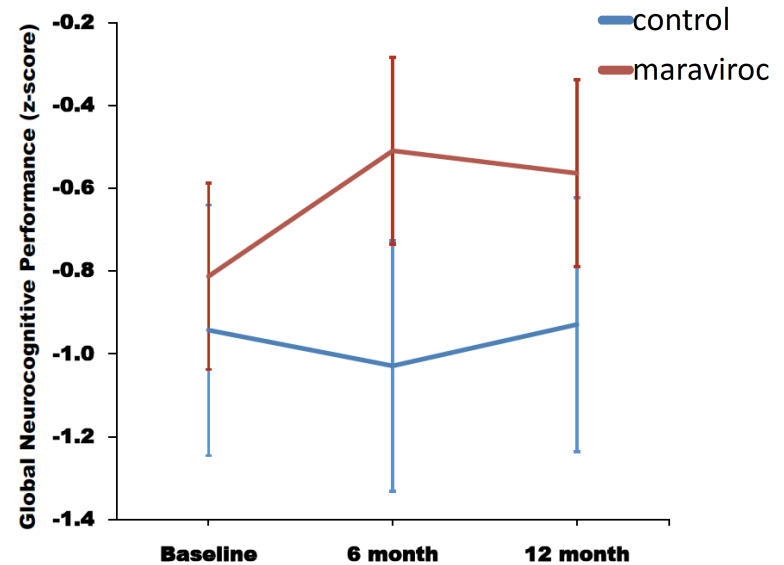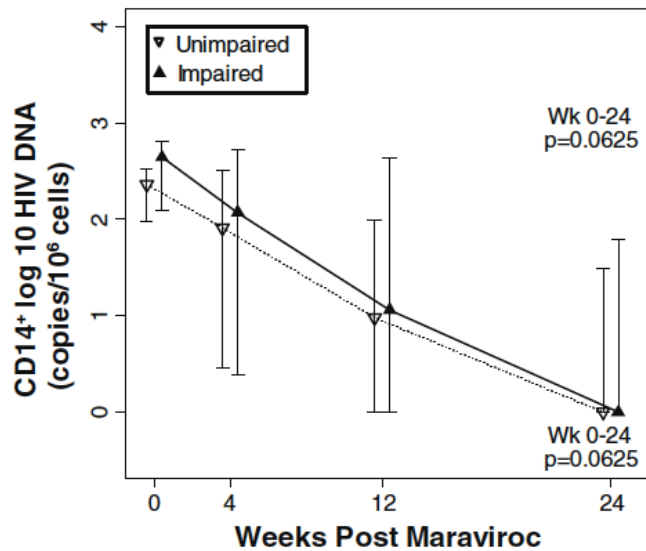
- Open-label, single-arm intensification trial with MVC In 12 adults on suppressive ART
- Reduced circulating intermediate and nonclassical CD16-expressing monocytes, monocyte HIV DNA content and sCD163 by 24 weeks
- This was associated with significant improvement in NP performance in the 6 subjects who had mild to moderate cognitive impairment.

- 12 month prospective open-label, randomized, placebo-controlled trial
- 14 adults on suppressive ART with recent progression to HAND completed the trial
- Large effect (d 0.77) at 6-months and moderate effect at 12-months (d 0.55)
  - Arm x Time interaction: $p < 0.05$
- Glutamate concentration in BG was stable in MA arm but increased in control arm at 12-months

Ndhlovu et al, J Neurovirol. 2014;20(6):571-82

Gates et al, CROI 2015. Abstract 441

Clinical Trial of CNS Penetrating ART to Prevent HAND in China

250 HIV+ Adults
ART Naive, CD4 < 350/mm^3
Normal **Neurocognitive Performance**

R → **Efavirenz + Tenofovir + Lamivudine**

Open-Label

R → **Nevirapine + Zidovudine + Lamivudine**
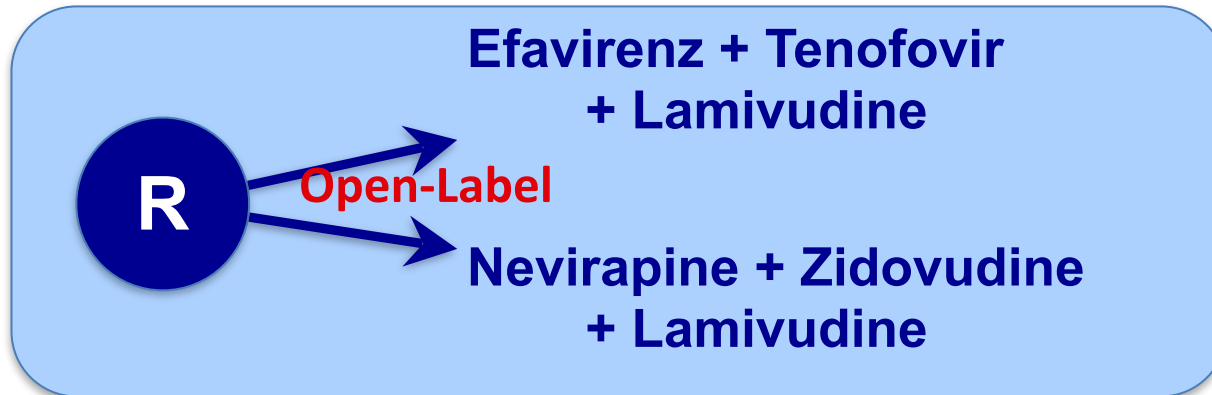
Blinded to Treatment Arm: Investigators from US, China CDC, and Beijing University Mental Health Institute

Follow-up: 96 Weeks at 2 Hospitals in Beijing
Safety Assessments & Data Safety Monitoring Board
Standardized Neurocognitive Testing
Functional Assessments
Targeted Pharmacogenetics
Inflammation Biomarkers in Blood

Neurocognitive Methods

- **An 8-test battery that assessed 5 cognitive abilities was administered at 48 and 96 weeks**

- **Cross-sectional & longitudinal normative data**
  - Adjust for effects of age, gender, and education using data from **HIV-adults in China**

- **Summary measures**
  - **Primary outcome:** Summary Change Score*
  - **Secondary outcomes:** Global neurocognitive impairment, Global deficit score

Neurocognitive Test Battery

- **Hopkins Verbal Learning Test-Revised - Total Learning**
- **Brief Visuospatial Learning Test-Revised - Total Learning**
- **WAIS-III Digit Symbol Test**
- **Grooved Pegboard Test**
- **WMS-III Spatial Span**
- **Action Fluency Test**
- **Paced Auditory Serial Addition Task (PASAT)-50**

Cysique et al, J Clinical Experimental Neuropsychology 2011. 33 (5), 505–522

Before Treatment, Arms were Comparable

	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	128	122	-
Demographic Characteristics			
Age (Years)	32.9 (7.7)	31.9 (8.3)	0.31
Sex (Men)	124 (97%)	122 (100%)	0.12
Ethnicity (Han)	121 (94.5%)	116 (95.1%)	0.84
Education (Years)	11.6 (3.6)	11.8 (3.9)	0.72
Body Mass Index	22.3 (2.9)	21.8 (2.5)	0.16
Disease Characteristics			
AIDS Diagnosis	42 (32.8%)	39 (32.0%)	0.89
HIV RNA, Plasma (log_{10} c/mL)	4.2 (0.8)	4.2 (0.9)	0.78
CD4+ T-cells (/mm^3)	235.1 (89.8)	222.1 (83.6)	0.24
CD8+ T-cells (/mm^3)	823.6 (355.7)	836.2 (439.0)	0.80
HCV Seropositive	3 (2%)	3 (2%)	0.99
HBV Surface Antigen	1 (0.8%)	1 (0.8%)	0.99

*Values are either mean (SD), median [IQR], or number (%)

Before Treatment, Arms were Comparable

	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	128	122	-
Neurocognitive & Mood Characteristics			
Global Deficit Score (GDS)	0.12 (0.15)	0.14 (0.14)	0.25
Beck Depression Inventory	9.8 (7.6)	9.7 (8.3)	0.92
Other Lab Characteristics			
Total WBC Count (x 10^9/L)	5.1 (1.5)	4.9 (1.3)	0.55
Hemoglobin (g/dL)	14.7 (1.1)	14.8 (1.2)	0.55
Platelets (x 10^9/L)	191 (51)	187 (46)	0.57
Alanine Aminotransferase, Serum	22.9 [16.0, 33.8]	21.1 [15.0, 30]	0.24
Total Bilirubin, Serum	0.12 (0.05)	0.12 (0.04)	0.46
Albumin, Serum	4.7 (0.3)	4.7 (0.4)	0.76
Total Protein, Serum	8.2 (0.5)	8.2 (0.6)	0.92
Creatinine, Serum	0.73 (0.10)	0.73 (0.11)	0.68

Values are either mean (SD), median [IQR], or number (%)

On Treatment, Indicators of Antiviral Efficacy Were Comparable

Week 48 (ITT-Completer)

	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	114	119	-
HIV RNA, Plasma (No. (%) ≤ 50 c/mL)	103 (91.2%)	109 (91.6%)	1.00
CD4+ T-cells (/μL)	396.6 (158.0)	396.5 (153.4)	1.00
CD8+ T-cells (/μL)	789.4 (368.0)	760.5 (360.8)	0.54
100% Adherence in Past 4 Days	113 (99.1%)	119 (100%)	0.49

Week 96 (ITT-Completer)

	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	112	118	-
HIV RNA, Plasma (No. (%) ≤ 50 c/mL)	104 (92.0%)	112 (95.7%)	0.28
CD4+ T-cells (/mm^3)	447.2 (179.3)	483.8 (183.8)	0.13
CD8+ T-cells (/mm^3)	811.3 (322.4)	850.6 (408.7)	0.42
100% Adherence in Past 4 Days	112 (100%)	116 (100%)	1.00

Values are either mean (SD), median [IQR], or number (%)

EFV-TDF-3TC Was Associated with Greater Decline After 96 Weeks
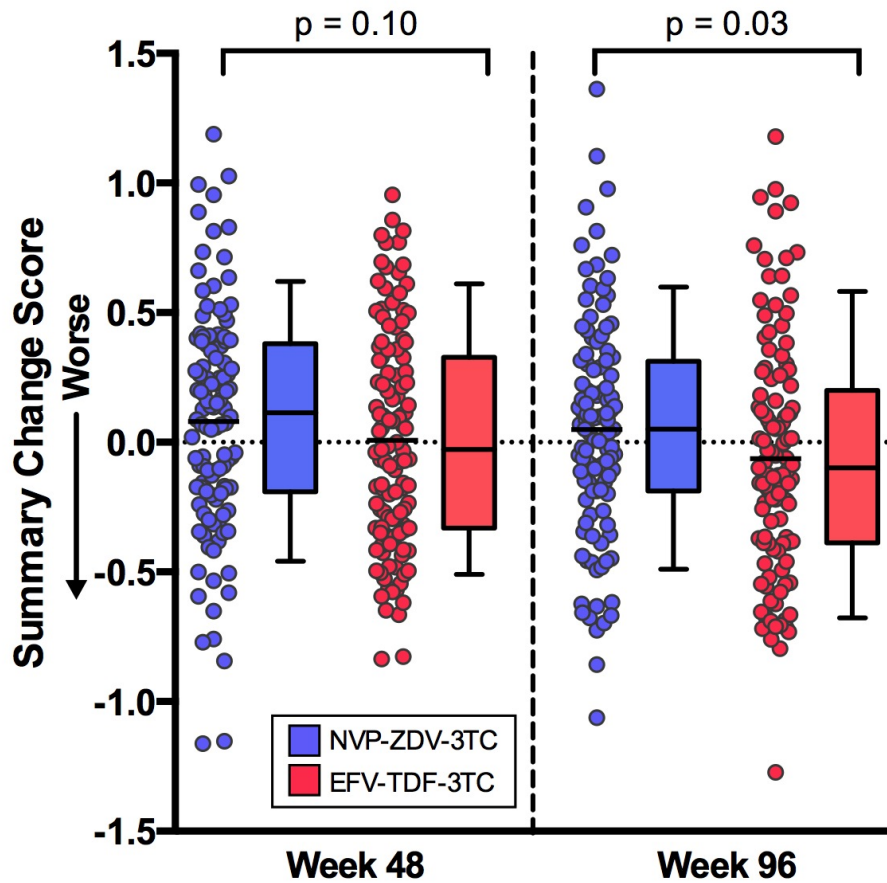
ITT-C Analysis, N = 233

As Treated Analysis, N = 187

Zhang et al, CROI 2015, Abstract 56

EFV-TDF-3TC Was Associated with Shorter Time-to-Impairment

Zhang et al, CROI 2015, Abstract 56
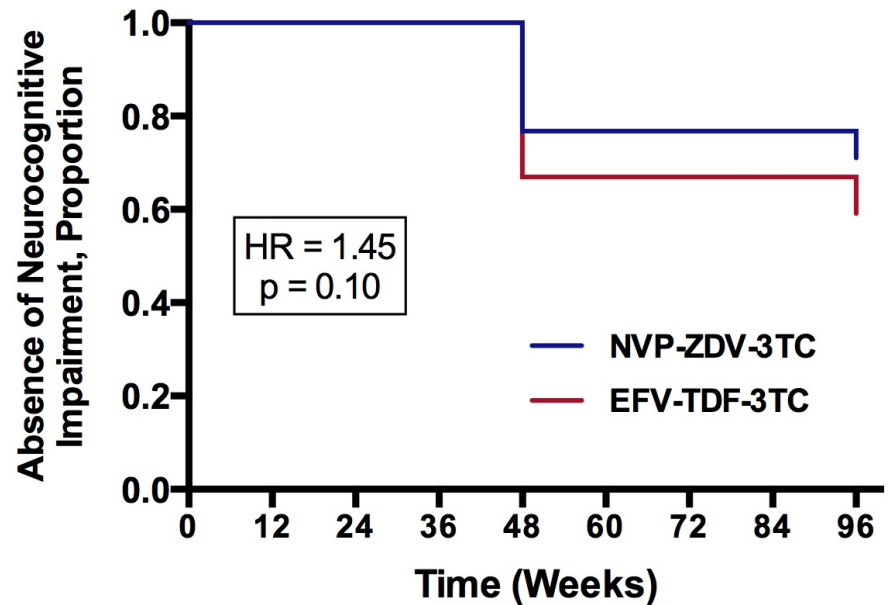
107 Subjects Had at Least One Adverse Event

	NVP-ZDV-3TC	EFV-TDF-3TC	P value
Subjects with at least 1 Adverse Event*			**< 0.001**
	66 (57.9%)	41 (34.4%)	
Most Severe Adverse Event Grade*			**0.006**
- Grade 1	19 (16.7%)	25 (21.0%)	
- Grade 2	15 (13.2%)	8 (6.7%)	
- Grade 3	**18 (15.8%)**	5 (4.2%)	
- Grade 4	**14 (12.3%)**	3 (2.5%)	
Adverse Event-Related Discontinuations*			**< 0.001**
	41 (32%)	1 (0.8%)	

- **All Adverse Event-Related Discontinuations Occurred before 28 Weeks**

*Denominator is Number of Subjects in the ITT-C Analysis

Liver toxicity, Hypersensitivity, and Bone Marrow Suppression Were More Common with NVP-ZDV-3TC

	NVP-ZDV-3TC	EFV-TDF-3TC	P value
Elevated ALT or AST	**40 (35.1%)**	23 (19.3%)	**0.008**
Rash	**24 (21.0%)**	3 (2.5%)	**< 0.001**
Neutropenia/Leukopenia	**20 (17.5%)**	5 (4.2%)	**0.001**
Fever	**13 (11.4%)**	1 (0.8%)	**< 0.001**
Anemia	**9 (7.9%)**	0 (0%)	**0.001**
Thrombocytopenia	6 (5.3%)	5 (4.2%)	0.76
Hyponatremia/Hypokalemia	3 (2.6%)	9 (7.6%)	0.08

- **All adverse events were reversible**
- **14 (6.0%) hospitalizations occurred**
  - **8 were considered "Definitely Related" to study treatment**
- **No deaths occurred**

***Denominator is Number of Subjects in the ITT-C Analysis**

Adverse Events and Discontinuations Differed by Site

	Site 1	Site 2	P value
Sample Size	138	95	-
Subjects with ≥ 1 Adverse Event	69 (50%)	38 (40%)	0.14
Most Severe Adverse Event Grade*			**0.003**
- Grade 1	33 (47.8%)	11 (28.9%)	
- Grade 2	19 (27.5%)	4 (10.5%)	
- Grade 3	10 (14.5%)	**13 (34.2%)**	
- Grade 4	7 (10.1%)	**10 (26.3%)**	
Discontinuations Per Subject with Adverse Event(s)*			**< 0.001**
	19/69 (27.5%)	**23/38 (60.5%)**	

- **Data Safety Monitoring Board recommended early termination of enrollment at Site 2**

***Denominator is Number of Subjects with Adverse Events at each Site**

Sites Differed in Other Characteristics

	Site 1	Site 2	P Value
Sample Size	138	95	-
Demographic Characteristics			
Age (Years)	33.3 (8.6)	**31.4 (7.2)**	**0.07**
Education (Years)	9 [9-12]	**14 [9-16]**	**< 0.001**
Sex (Number (%) Men)	134 (97.8%)	94 (98.9%)	0.65
Ethnicity (Number (%) Han)	133 (96.4%)	89 (93.7%)	0.72
HIV Disease Characteristics			
AIDS Diagnosis	**51 (21.9%)**	27 (28.4%)	0.15
HIV RNA, Plasma ($\log_{10}$ c/mL)	4.2 (0.9)	4.2 (0.8)	0.57
CD4+ T-cells (/mm^3)	225.8 (78.9)	227.4 (85.0)	0.89
Other Lab Characteristics			
Hemoglobin	14.5 (11.2)	**15.0 (11.0)**	**< 0.001**
Aspartate Transaminase, Serum	25.0 (8.1)	**22.8 (11.2)**	**< 0.001**
Total Protein, Serum	8.0 (5.3)	**8.3 (4.9)**	**< 0.001**

Values are either mean (SD), median [IQR], or number (%)

EFV-TDF-3TC Was Associated with Shorter Time-to-Impairment at Site 1
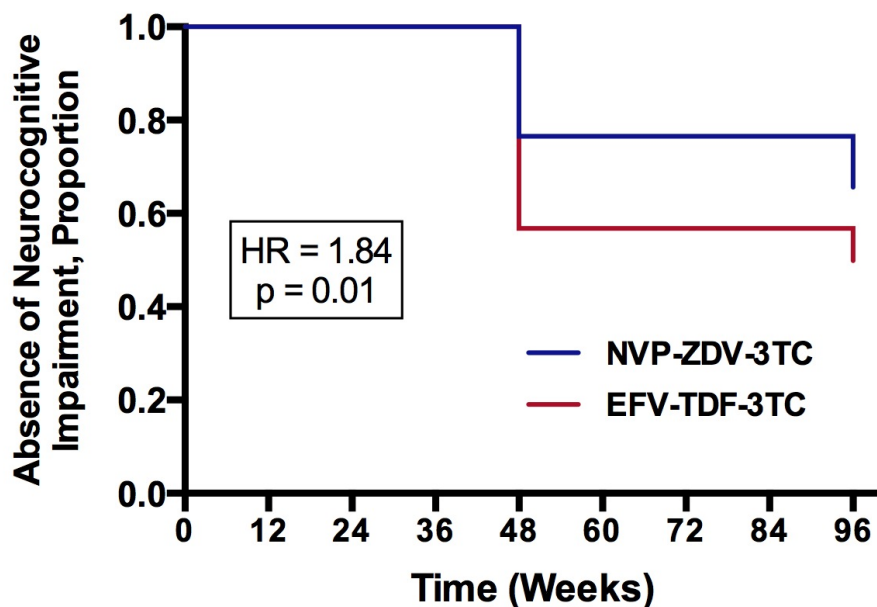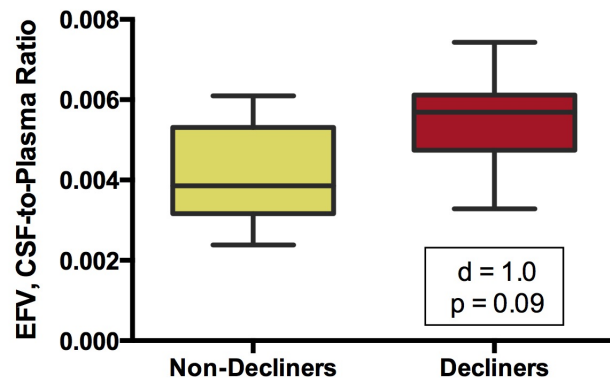

ITT-C Analysis, N = 138
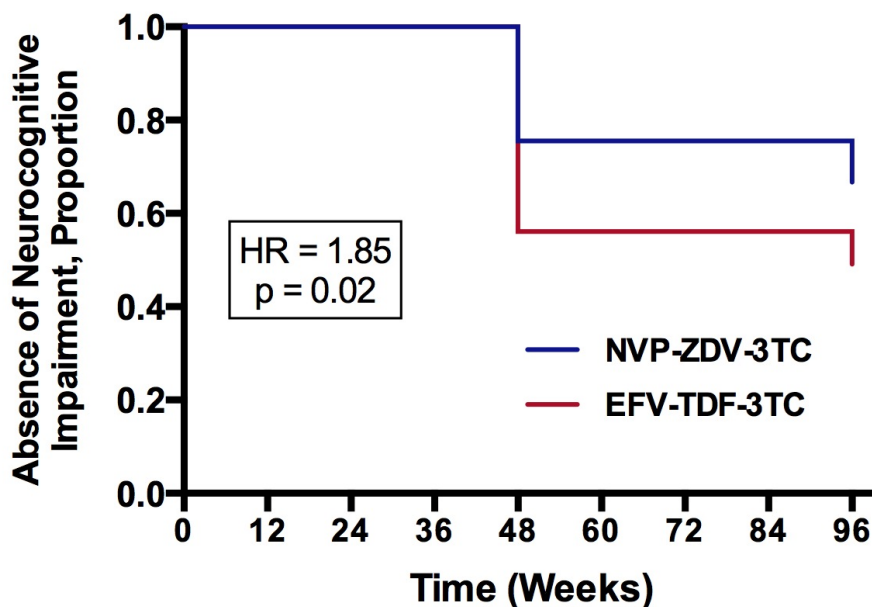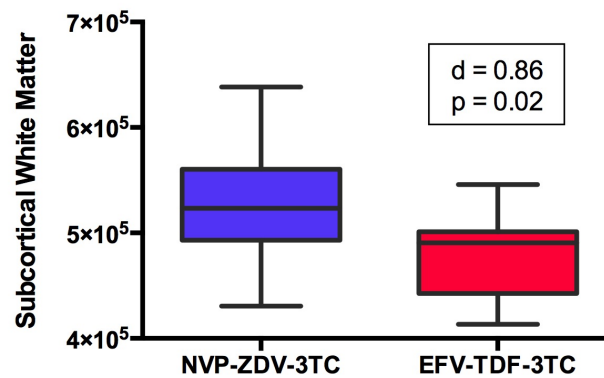
As Treated Analysis, N = 118
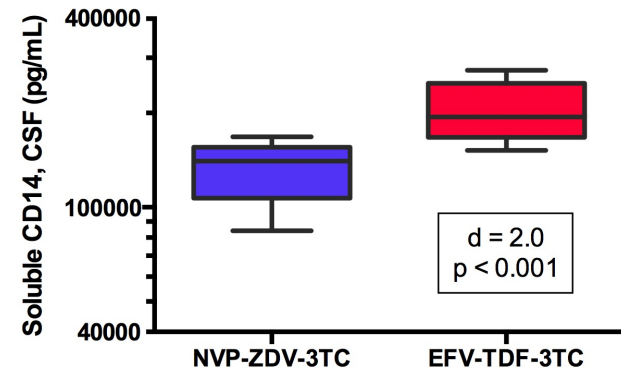
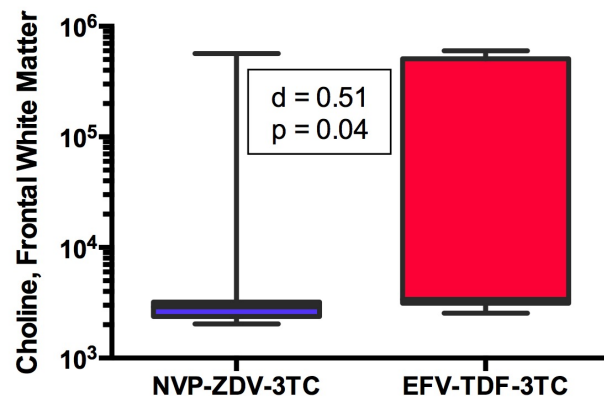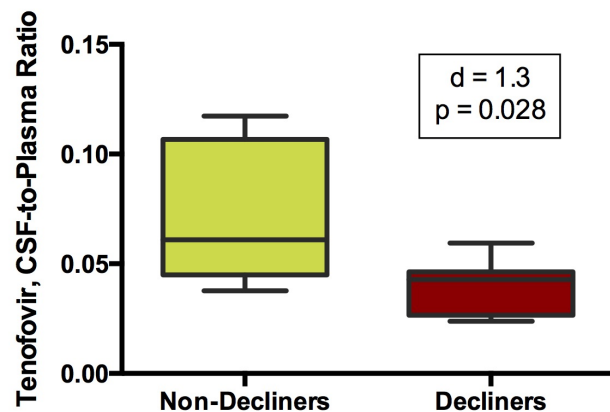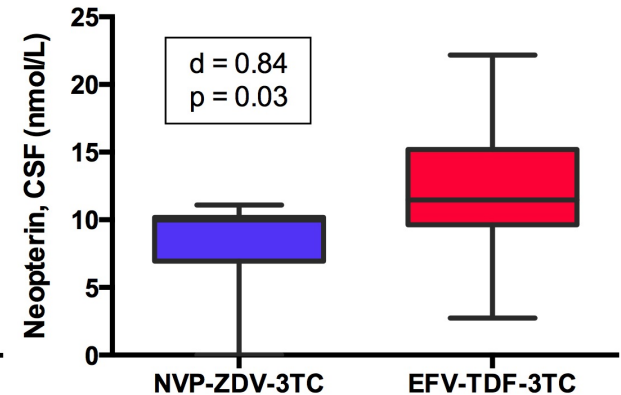# Nested Case-Control Study of 15 Decliners and 15 Matched Non-Decliners

Antiretroviral Drug Concentrations

Magnetic Resonance Imaging/Spectroscopy

CSF Biomarkers
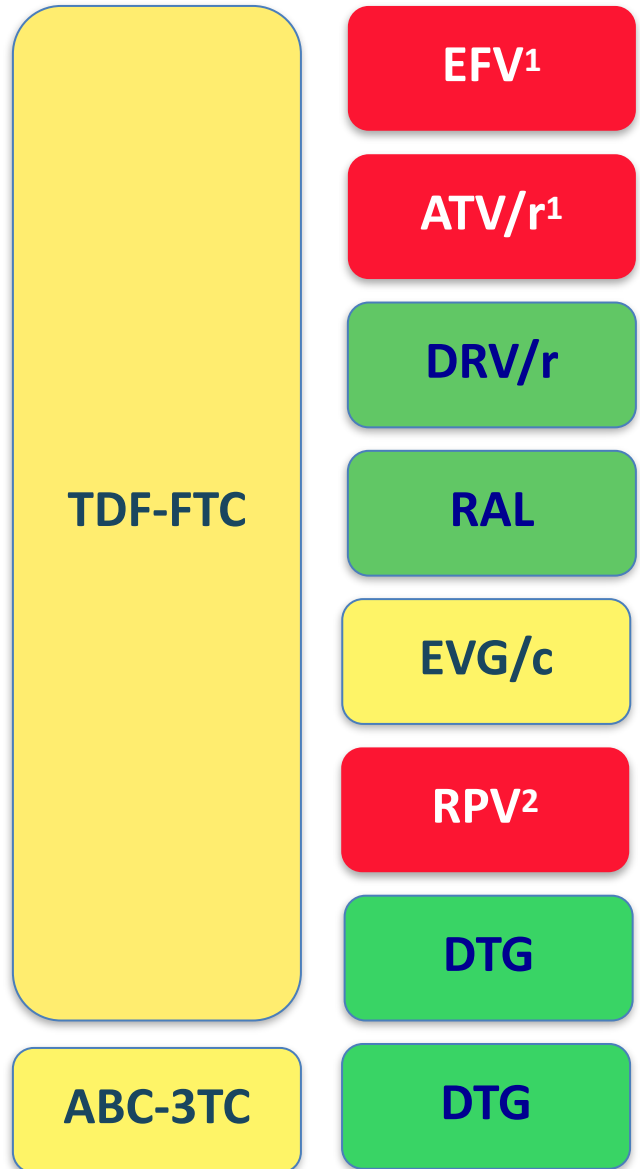
Ma et al, CROI 2015, Abstract 444

DHHS Preferred Regimens (ART Naive)

TDF-FTC

EFV[1]
- Short- and long-term neurotoxicity

ATV/r[1]
- CSF concentrations do not consistently exceed inhibitory concentrations
- Associated with CSF viral escape

DRV/r
- CSF concentrations exceed 50% inhibitory concentrations in all

RAL
- CSF concentrations exceed 50% inhibitory concentrations in all

EVG/c
- No CSF pharmacokinetic data

RPV[2]
- CSF concentrations do not consistently exceed inhibitory concentrations

DTG
- CSF concentrations exceed 50% inhibitory concentrations in all
- Fewer CNS side effects than EFV

ABC-3TC

DTG
- No CSF ABC pharmacokinetic data on daily dosing

[1]May be combined with ABC-3TC when HIV RNA < 100,000 copies/mL; [2]In patients with HIV RNA < 100,000 copies/mL; Last updated 1 May 2014; Available at http://www.aidsinfo.nih.gov/guidelines

US DHHS Preferred Regimens (ART Naive)

TDF-FTC

ABC-3TC

DRV/r
- CSF concentrations exceed 50% inhibitory concentrations in all

RAL
- CSF concentrations exceed 50% inhibitory concentrations in all

EVG/c
- No CSF pharmacokinetic data

DTG
- CSF concentrations exceed 50% inhibitory concentrations in all
- Fewer CNS side effects than EFV
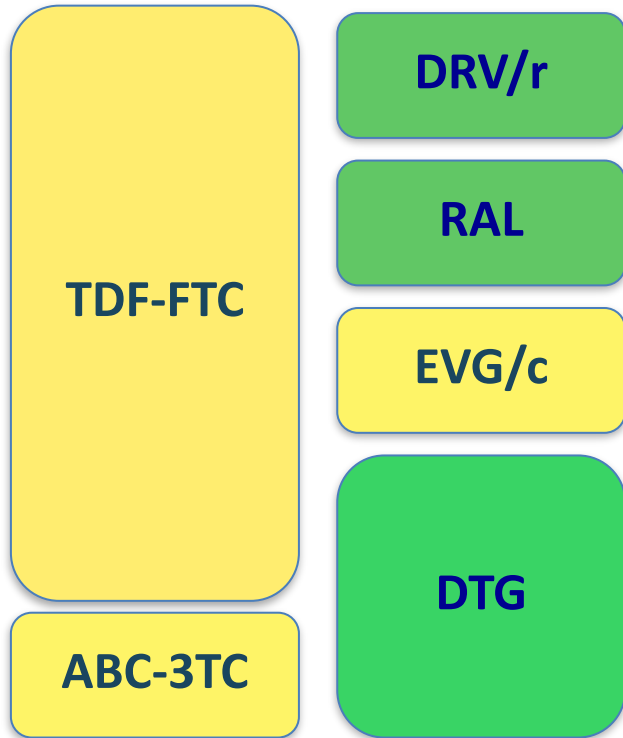- No CSF ABC pharmacokinetic data on daily dosing

Removed

EFV
- Short- and long-term neurotoxicity

ATV/r
- CSF concentrations do not consistently exceed inhibitory concentrations
- Associated with CSF viral escape

RPV
- CSF concentrations do not consistently exceed inhibitory concentrations

Last updated 8 April 2015; Available at http://www.aidsinfo.nih.gov/guidelines

Women May Have Different Exposure of Some ART Drugs Than Men

- Reviews of ART pharmacokinetics indicate that women can have higher drug exposure

- Difference exists for:
  - Zidovudine
  - Lamivudine
  - Ritonavir-Boosted PIs

- Mixed data for non-nucleoside RTIs

- Body weight and composition, blood and organ volumes (e.g. bone mass)
- Absorption, intestinal motility and secretions
- Transport and distribution
- Protein binding and tissue affinity
- Metabolism: phase I (hydrolysis, reduction, oxidation, cyclization, decyclization)
- Metabolism: phase II (conjugation)
- Excretion (glomerular filtration rate, renal clearance)
- Intracellular metabolism
- Activity of drug transporters
- Differential (hormone-mediated) gene expression

Effect modifiers:
- Adherence
- Diet and nutritional factors
- Nutritional status
- Concomitant treatments
- Hormonal environment
- Reproductive status
- Smoking

Floridia et al, Pharmacological Research 2008, 58:173–182
Ofotokun et al, Gender Medicine, 4(2):106-

HCV may not be as clear a risk factor for HAND as once thought

Absence of neurocognitive impairment in a large Chinese sample of HCV-infected injection drug users receiving methadone treatment

Saurabh Gupta[a,e], Jennifer E. Iudicello[a], Chuan Shi[c], Scott Letendre[a], Adam Knight[a], Jianhua Li[f], Patricia K. Riggs[a], Donald R. Franklin Jr[a], Nichole Duarte[a,e], Hua Jin[a,b], J. Hampton Atkinson[b,a], Xin Yu[c], Zunyou Wu[d], Igor Grant[a], Robert K. Heaton[a,*], HNRC China Collaboration Group[a]

Absence of neurocognitive effect of hepatitis C infection in HIV-coinfected people

HCV Co-Infection May Alter the Relation-ship Between ART Drugs & the CNS
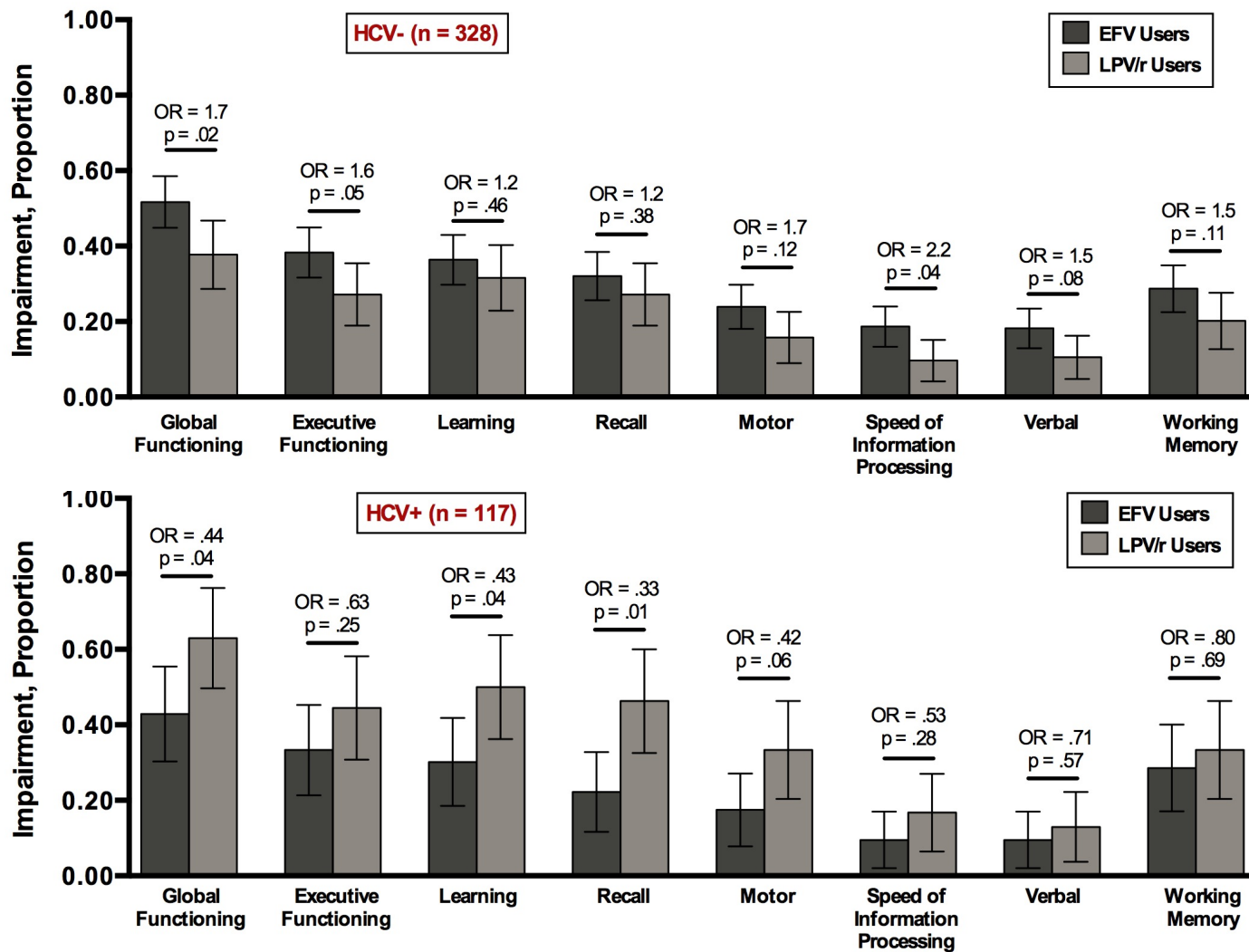
ART Drugs May Alter the Relationship Between HCV Co-Infection & the CNS
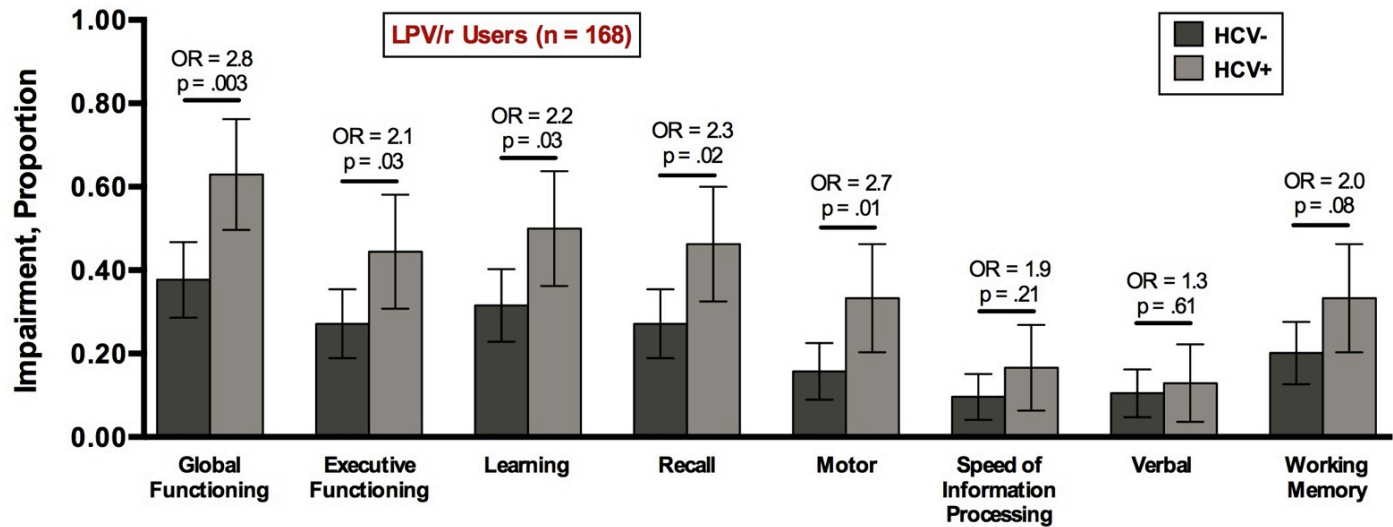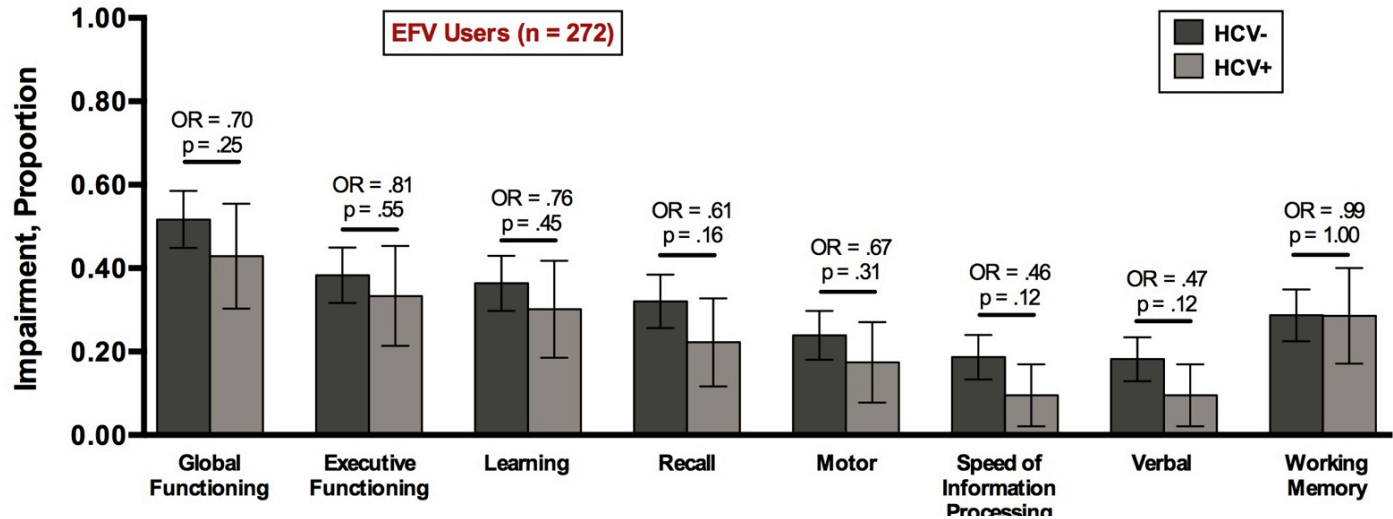
Protease Inhibitor Use is Associated with Cerebral Small Vessel Disease
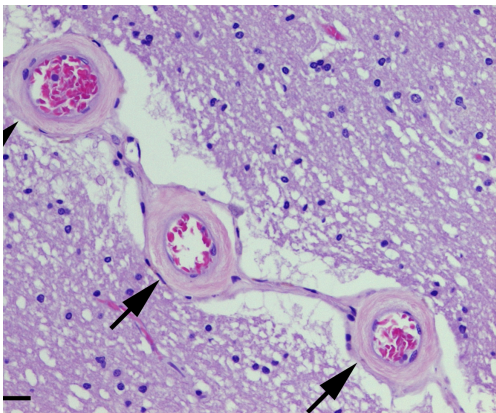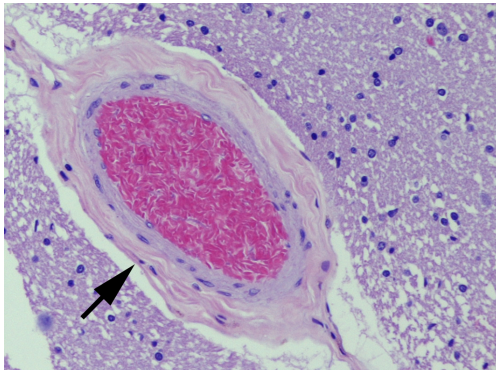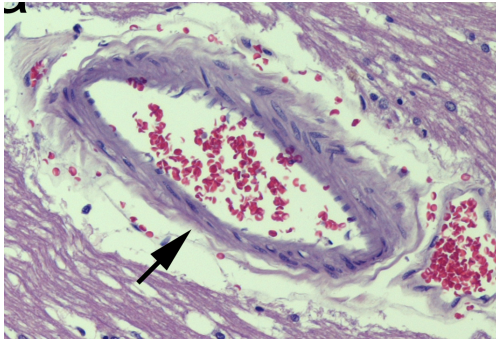
- **144 adults with HIV/AIDS who died between 1999 and 2011 and had been evaluated prior to death in the California NeuroAIDS Tissue Network**

- **Protease inhibitor use was associated with cerebral small vessel disease**
  - Mild: OR 2.8 (95% CI 1.03–7.9)
  - Moderate-severe: 2.6 (95% CI 1.03–6.7)

- **Mild CSVD was associated with HAND**
  - OR 4.8 (95% CI 1.1–21.2)

Soontornniyomkij et al, AIDS 2014, 28:1297–1306

ART Drug Concentrations in Brain: Regional Variation, CSF Comparability

	n	Overall Mean	WM mean (ng/mL)	GP mean (ng/mL)	CGM mean (ng/mL)	CSF (ng/mL)
Concentrations Similar to Historical CSF Concentration						
Atazanavir (ATV)	2	< 25	< 25	< 25	< 25	10.3[1]
Efavirenz (EFV)	2	38.6	45.2	34.8	35.9	15.6[2]
Emtricitabine (FTC)	4	181.3	230.4	173.2	140.3	109.0[3]
Lamivudine (3TC)	3	196.9	205.5	209.8	175.4	107.8[4]
Concentrations in White Matter Higher than Historical CSF Concentration						
Lopinavir (LPV)	4	153.3	410.6	< 25	< 25	16.8[5]
Concentrations Higher than Historical CSF Concentration						
Tenofovir (TDF)	6	206.0	220.0	212.1	185.8	5.5[6]

WM = White Matter; GP = Globus Pallidus (Deep Gray Matter); CGM = Cortical Gray Matter

Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test)

Summary

- **More HIV+ adults may have symptomatic HAND than previously appreciated**
- **Aging and perhaps sex appear to alter the presentation of HAND**
- **In China, EFV-TDF-3TC was associated with earlier neurocognitive decline**
  - Primarily at one of the two sites
- **Treatment guidelines have tended to move toward ART drugs that are less neurotoxic**
  - Maraviroc intensification may have promise
  - Protease inhibitors may accentuate CNS damage from HCV

UCSanDiego

6TH INTERNATIONAL WORKSHOP ON

HIV&AGING

WASHINGTON, DC, USA • 5 - 6 OCTOBER 2015

WHO SHOULD ATTEND?

Internal Medicine specialists (clinicians working in cardiovascular, renal, endocrine, and metabolic complications of HIV areas), infectious disease specialists, (virologists, immunologists, pharmacologists), geriatricians, neurologists, epidemiologists, geneticists and other clinical researchers.

WHY SHOULD YOU ATTEND?

- This workshop is the premier international meeting on HIV and aging.

- This workshop is intended as a compact, focused meeting to encourage **crossdisciplinary scientific dialogue** and **in-depth discussions** among all attendees, including presenters.

- This meeting is a **stepping stone for young medical professionals** to present their research in an informal and encouraging setting. We encourage their participation by offering them a complimentary registration (for more information see meeting website).

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ABSTRACT SUBMISSION

We invite you to submit your abstracts in the following categories:

- Neurology
- Pharmacology
- Immunology
- Metabolic/ cardiovascular complications
- Effect of aging on organ systems (renal, musculoskeletal, hepatic and endocrine)
- Malignancy
- Geriatrics and Clinical care

Abstract submission deadline: 31 July 2015

virology education

Registration and information: www.virology-education.com

Acknowledgements & Conflicts
Study Volunteers

Barcelona

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Ana Curiel

Ruth Boza

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- Ben Gouaux
- Jennifer Marquie
- Donald Franklin

U.S. National Institutes of Health

Industry

- Abbvie
- Cipla
- Gilead Sciences
- Janssen
- Merck, Inc.
- ViiV Healthcare

Laboratory Measures of Activities of Daily Living

- Finances (budget, pay bills, manage checkbook)
- Shopping (from memory and with list)
- Meal Planning and Preparation
- Restaurant Scenario
- Medication Management
- Standardized Work Samples
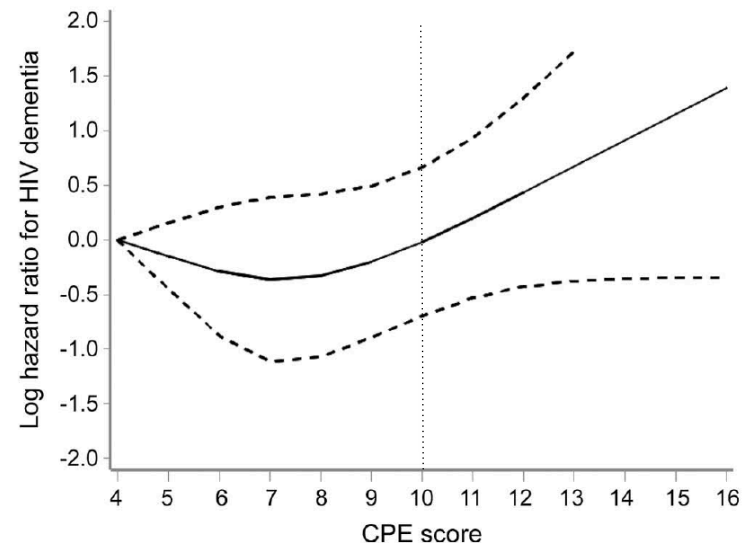
The relationship of CPE to HIV dementia

Slain by an ugly fact?

Design

- Data from 61,938 patients combined from 9 independent HIV cohorts from Europe and the U.S.
- Patients were evaluated prior to ART initiation between 1998 and 2013
- "Intent-to-treat" analysis
- CPE transformed into 3 categories
  - "Low": ≤ 7
  - "Medium": 8-9
  - "High": ≥ 10

Findings

- 235 "HAD" events in 259,858 person-years of follow-up
  - 1 per 1106 person-years
- "High" CPE group had a 74% increased hazard ratio of "HAD"

Log hazard ratio for HIV dementia (y-axis: -2.0 to 2.0) vs CPE score (x-axis: 4 to 16)

Caniglia et al, Neurology 2014;83:1–8; Berger & Clifford, Neurology 2014;83:1–2

The relationship of CPE to HIV dementia

Slain by an ugly fact?

- **Did not use standardized assessments for diagnosing "HAD"**
  - "…diagnostic procedures that reflect standard clinical practice"
- **The categorical transformation of CPE is unusual**
  - Only 8.8% were in the "high CPE" group
  - No statistically significant association was found with CPE when analyzed continuously or as a 4-category variable
- **The between-group difference in absolute risk is not clinically meaningful:** 1 "HAD" case per > 4,500 person-years of follow-up
- **Does not account for factors that were associated with:**
  - <u>Changes in ART over time</u>: **68% changed their initial regimen during observation**
  - <u>"High" CPE regimens</u>: more than 3 antiretroviral drugs, initiation of ART prior to 2004
  - <u>Non-HIV causes of neurocognitive disease</u>: psychiatric disease, substance use, co-infections

Caniglia et al, Neurology 2014;83:1–8; Berger & Clifford, Neurology 2014;83:1–2

Reasons for Greater Risk for Cognitive & Mood Disorders in HIV+ Women

- Social, financial and healthcare disadvantage
- Stress due to sexual violence and food insecurity
- Comorbid conditions, e.g., metabolic syndrome, drug use, depression
- Co-infections, e.g., CMV, HPV, STIs

- Differences in immune responses, inflammation, and oxidative stress
- Impact of sex hormones: Pregnancy and Menopause
- Differences in pharmacology and toxicity of ART and other drugs