SNC e Infección VIH

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University of California, San Diego

Disclosures

Research awards were paid to UC San Diego on behalf of Dr. Letendre:

- National Institutes of Health
- Gilead Sciences

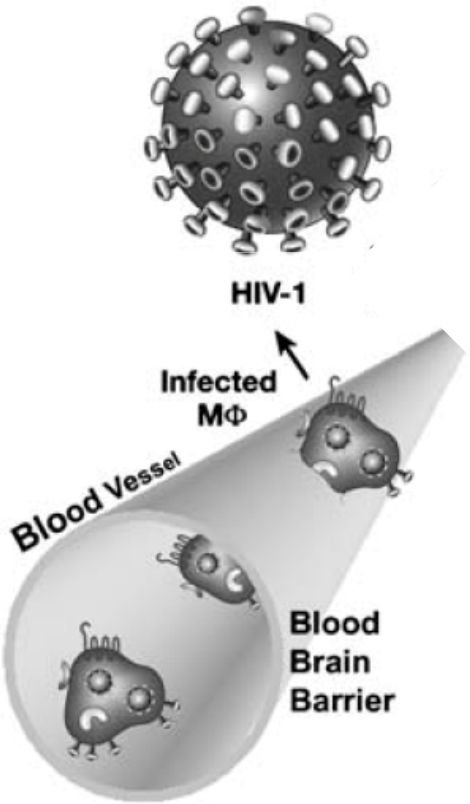
Dr. Letendre was paid as an advisor:

- Merck & Co., Inc.
- ViiV Healthcare

Dr. Letendre was paid as a lecturer:

- Janssen
- Gilead Sciences

HIV Pathogenesis in the CNS



Kaul & Lipton, J Neuroimmune Pharmacol (2006) 1: 138–151

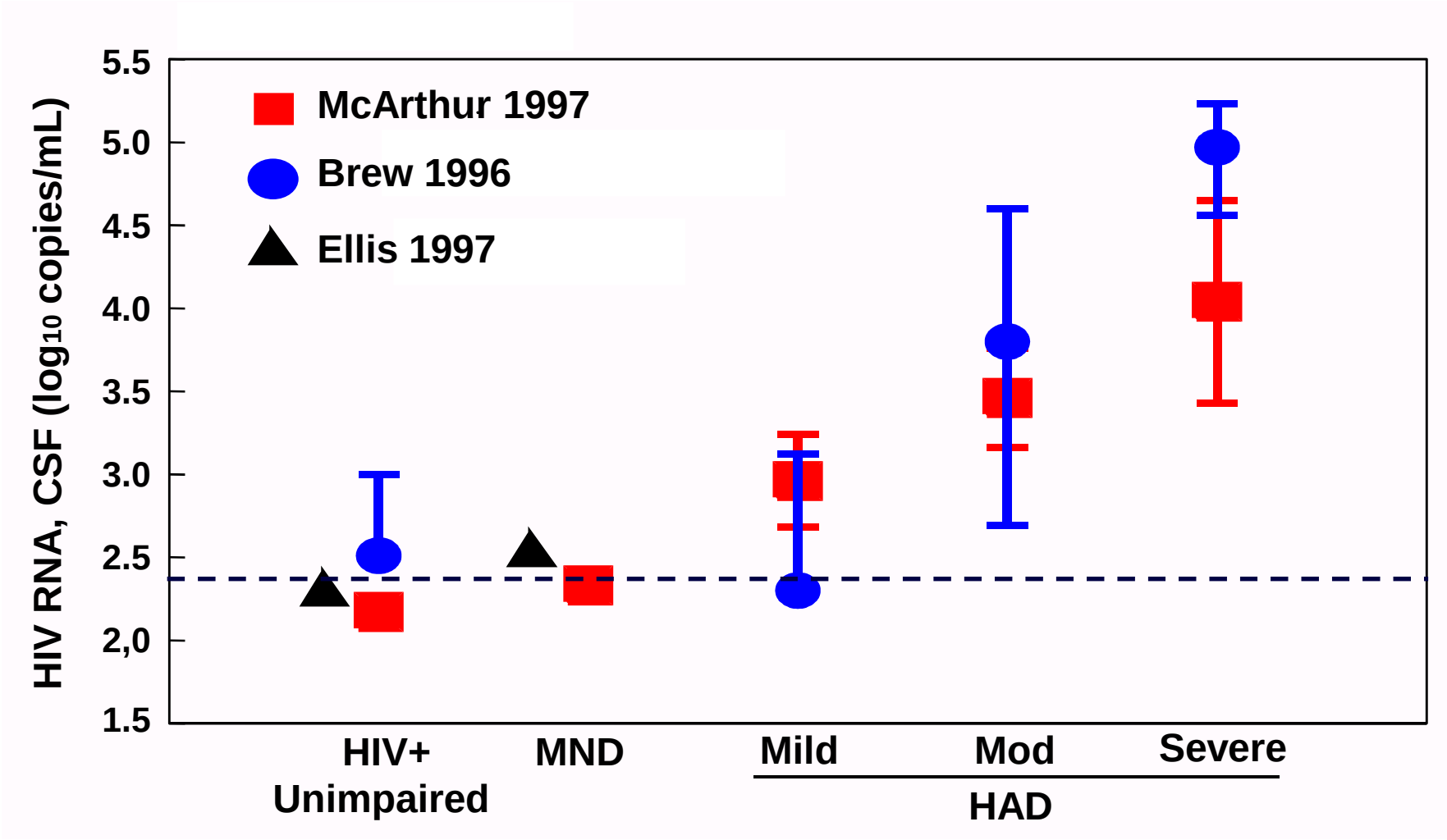
Severity and Daily Functioning Differentiate HAND Syndromes

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

UC San Diego

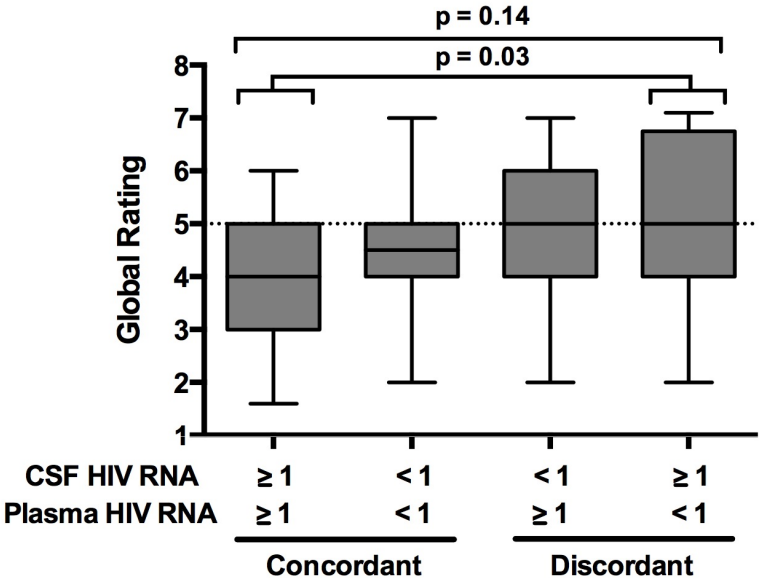
Antinori et al, Neurology 2007, 69: 1789-99

HIV RNA in CSF was Linked to HAND in the Mid-1990s

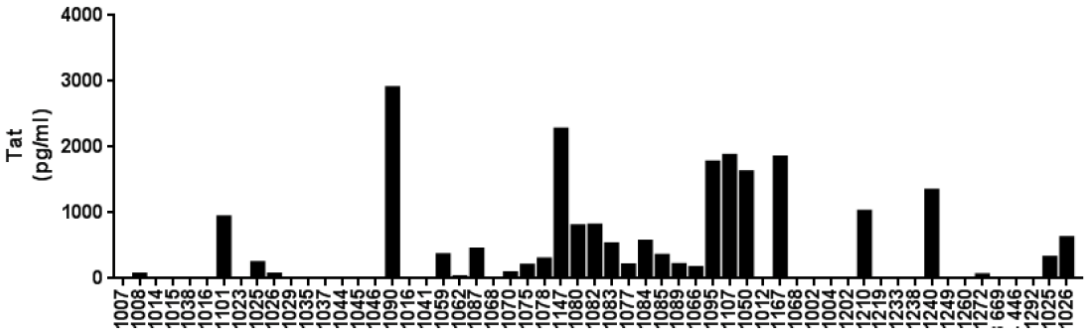


Slide Courtesy Justin McArthur

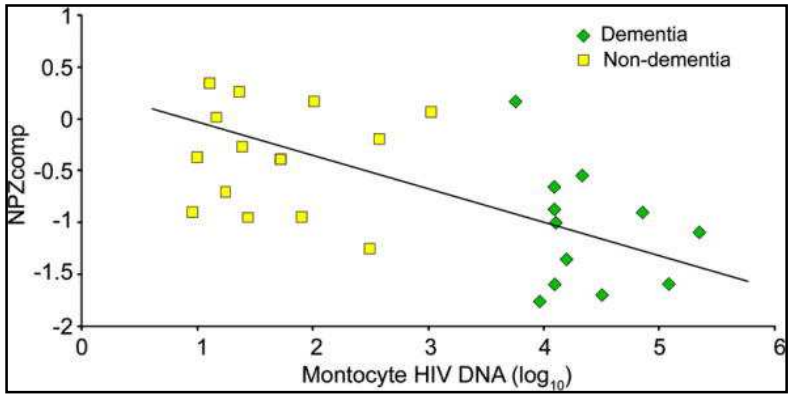
When HIV RNA is Suppressed, Other Viral Biomarkers Are Needed



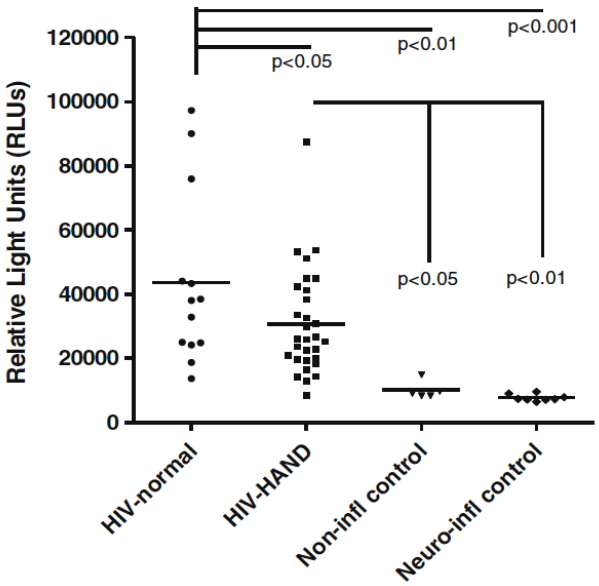
Anderson et al, J Infect Dis 2016, In Press



von Geldern et al, CROI 2015, Abstract 456

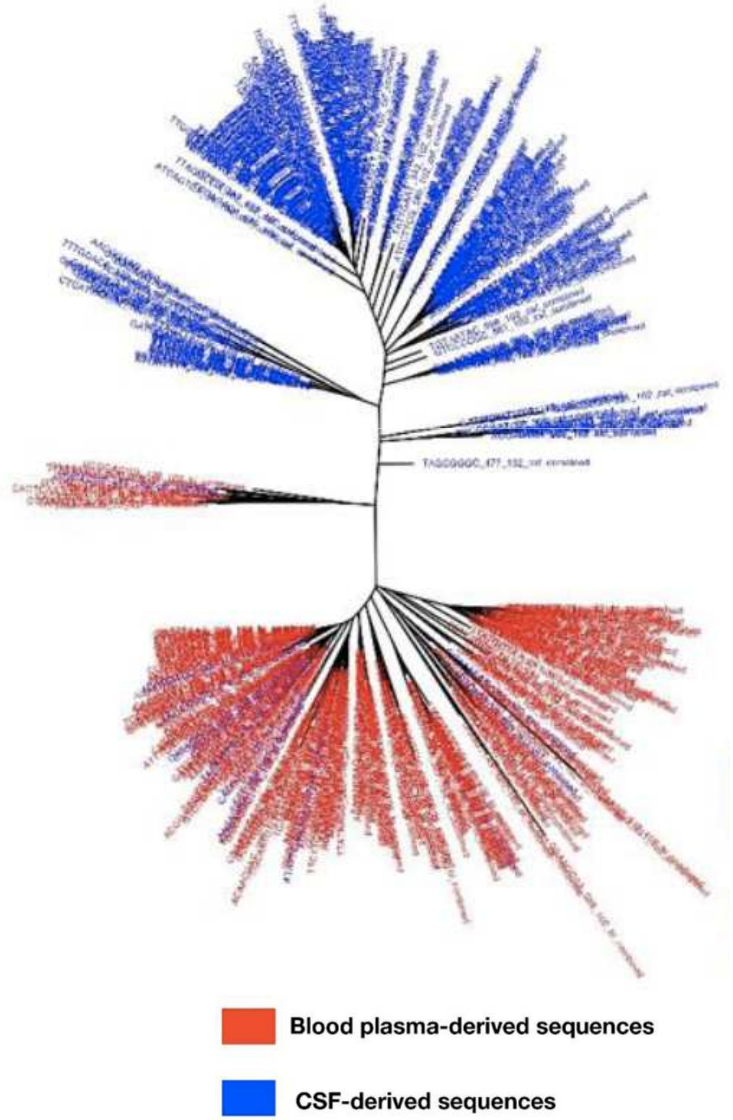


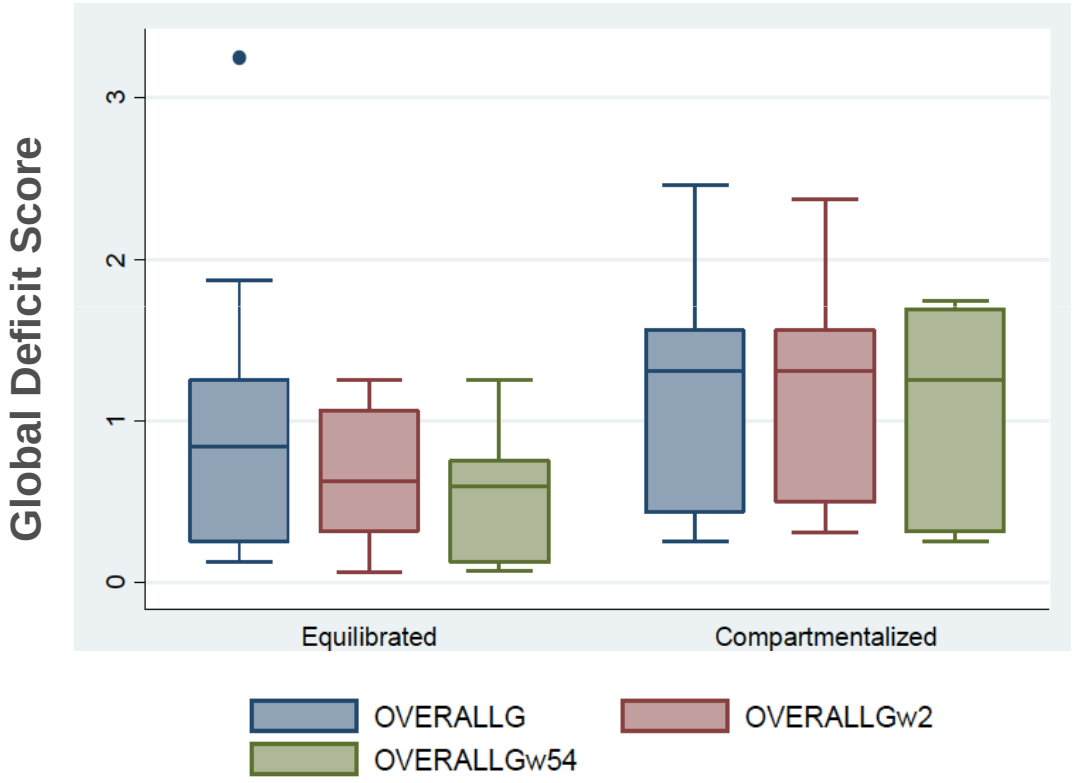
Valcour et al, Neurology, 2009. 72(11):992-8



Bachani et al, J. Neurovirol. (2013) 19:82–88

HIV Compartmentalization in the CNS Is Associated With HAND

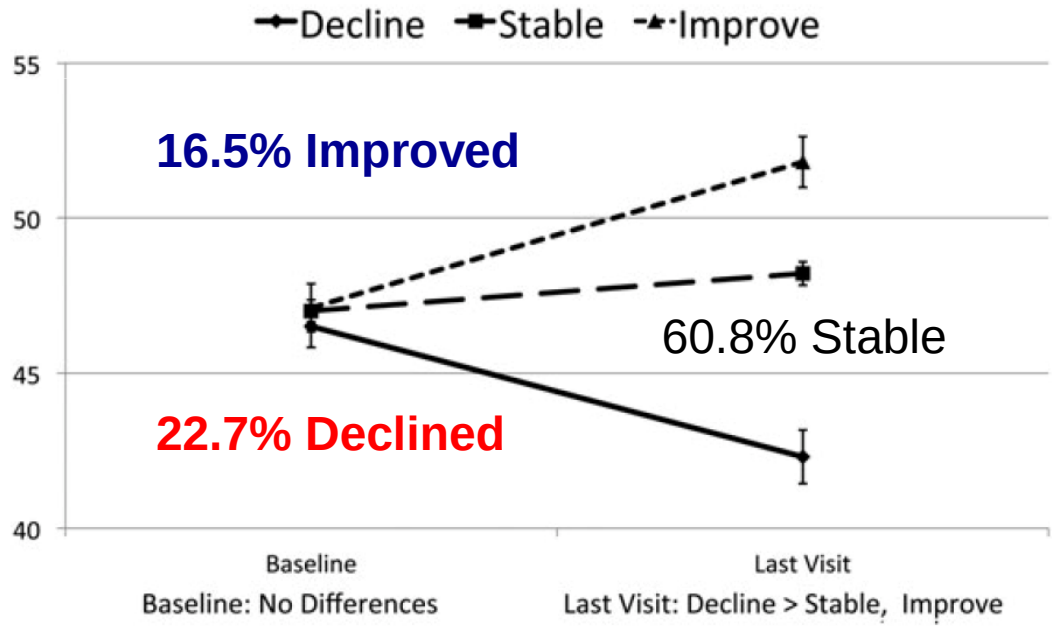




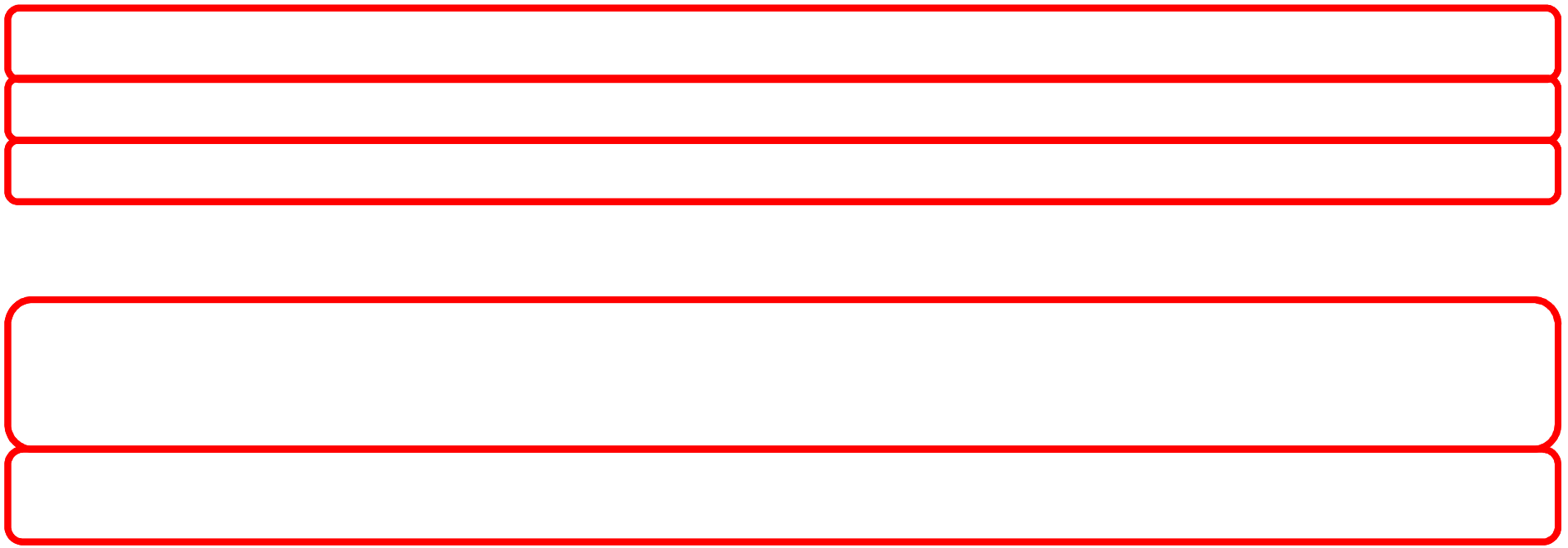
Bowman et al, CROI 2016, Abstract 401

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

- Analyzed incidence and predictors of neurocognitive change in 436 HIV+ adults who were assessed every 6 months over about 3 years on average (mean 35 months)



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

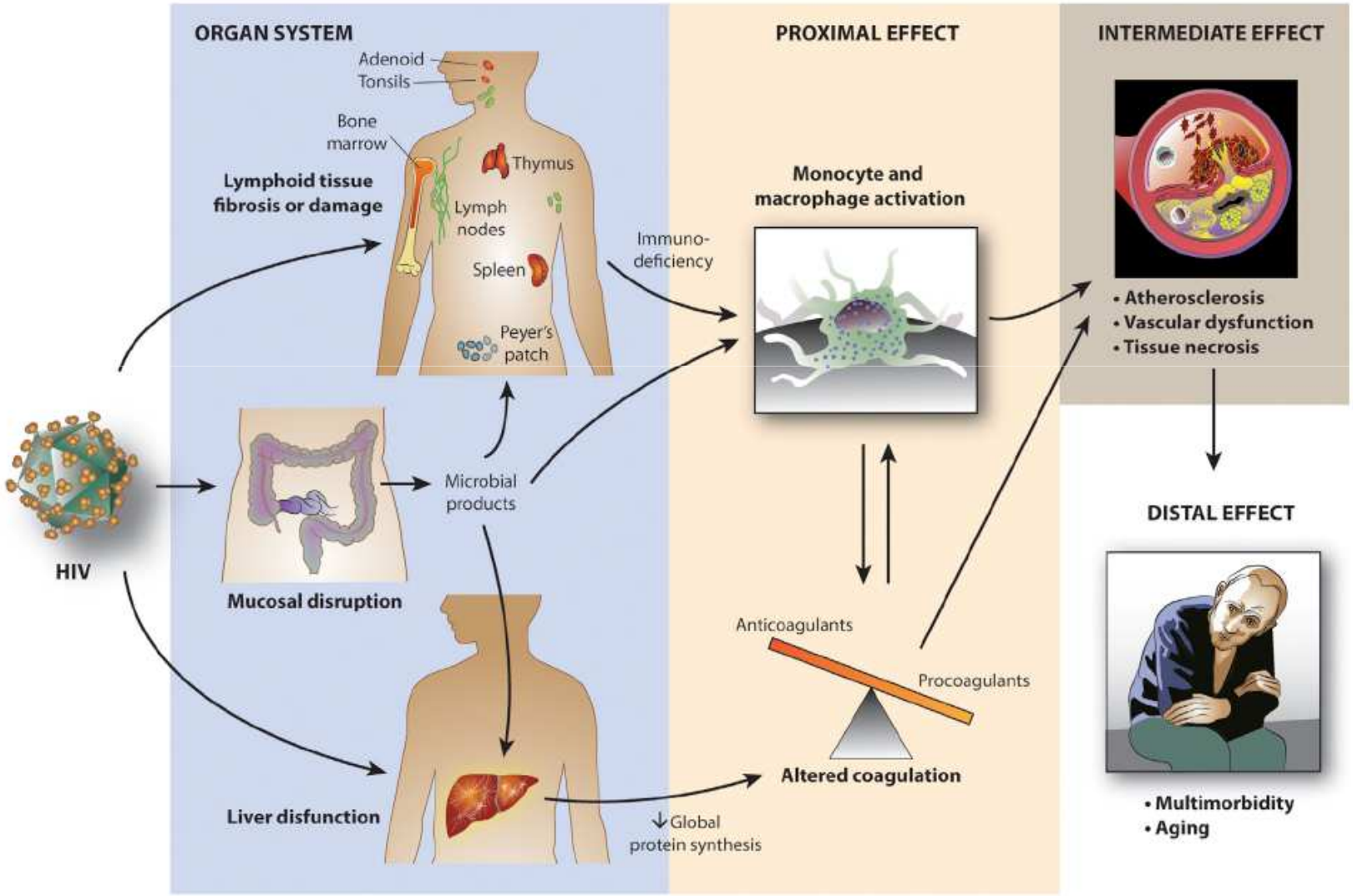


**p < 0.05, **p < 0.01, ***p < 0.0001*

[†]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 multivarable model (in red)

Inflammation Plays a Central Role in Unsuccessful Aging of HIV+ Adults



Deeks, Tracy, & Douek, Immunity 2013, 39: 633-45

Vascular and Metabolic Disease Increase Risk for Neurocognitive Impairment

- **292 HIV+ adults in the START study**
- **Prior CVD was associated with NCI**

Wright et al. Neurology 2010; 75: 864

	Risk	OR	p
Prior CVD	Yes	6.2	0.01
Total cholesterol	Higher	1.1	0.06
AIDS	No	0.41	0.08
Race	Black	2.2	0.08

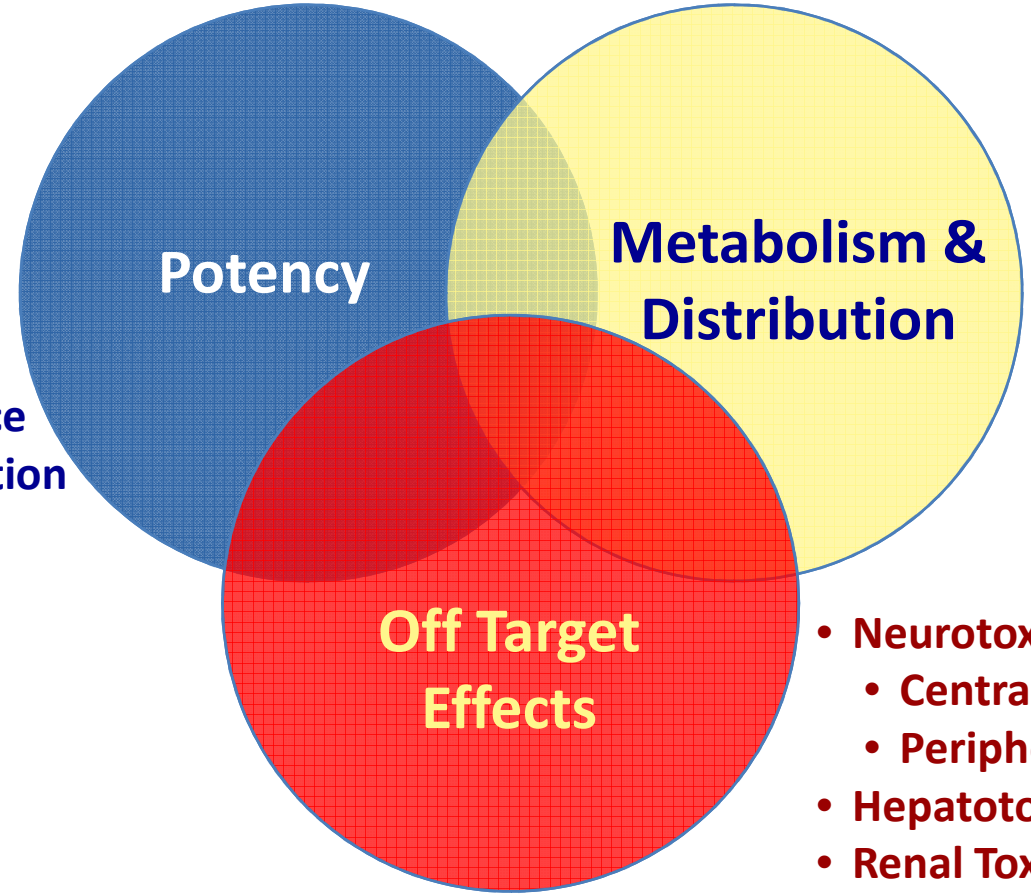
- **130 HIV+ adults in the CHARTER study**
- **Diabetes and waist circumference were associated with NCI**

McCutchan et al. Neurology 2012. 78: 485

	Risk	OR	p
AIDS	Yes	49.6	0.01
Diabetes	Yes	17.6	0.07
Waist circumference	Larger	1.3	0.001
Triglycerides	Lower	0.32	0.09
BMI	Smaller	0.69	0.04

Several ART Drug Characteristics Can Influence ART Efficacy in the CNS

- **Suppression of HIV Replication**
  - Lymphocytes
  - Monocytes & Macrophages
- **Barrier to Resistance**
- **Viral Protein Inhibition**
- **Immune Recovery**



- **Long Half-Life**
- **Protein Binding**
- **Lipophilicity**
- **Molecular Weight**
- **Molecular Transporters**

- **Neurotoxicity**
  - **Central NS**
  - **Peripheral NS**
- **Hepatotoxicity**
- **Renal Toxicity**
- **Metabolic & Vascular Disorders**

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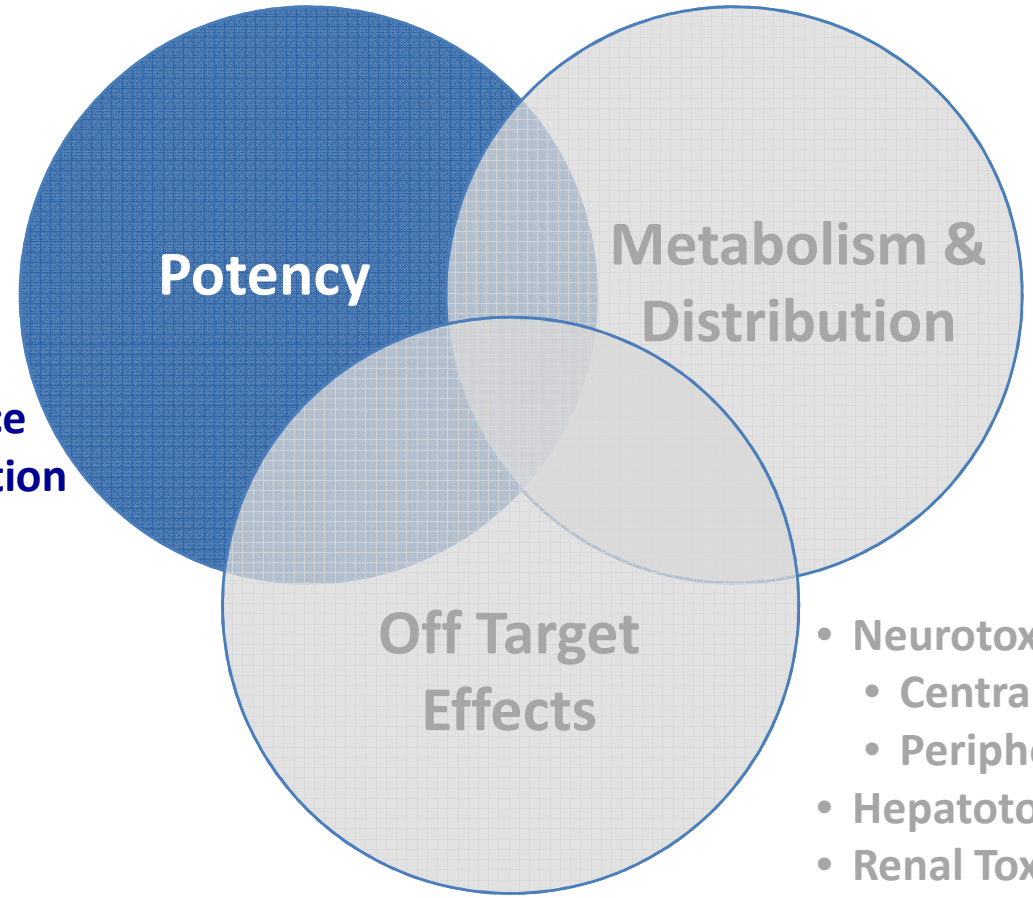

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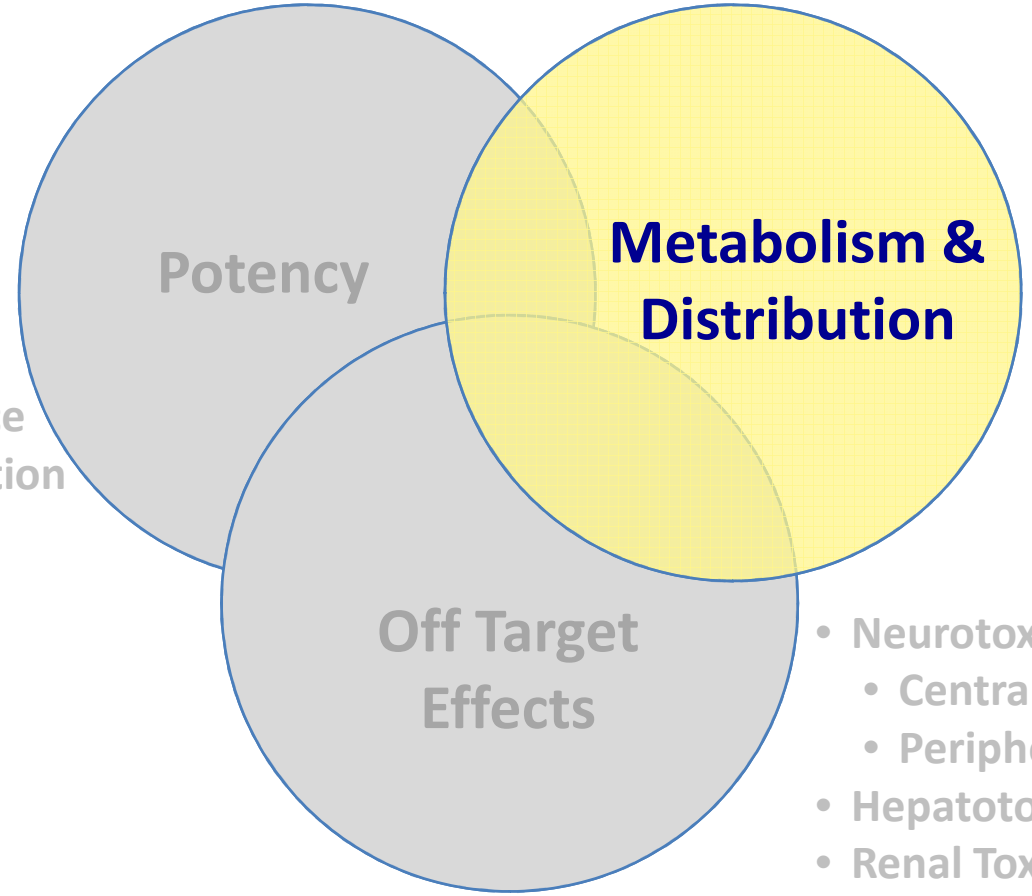

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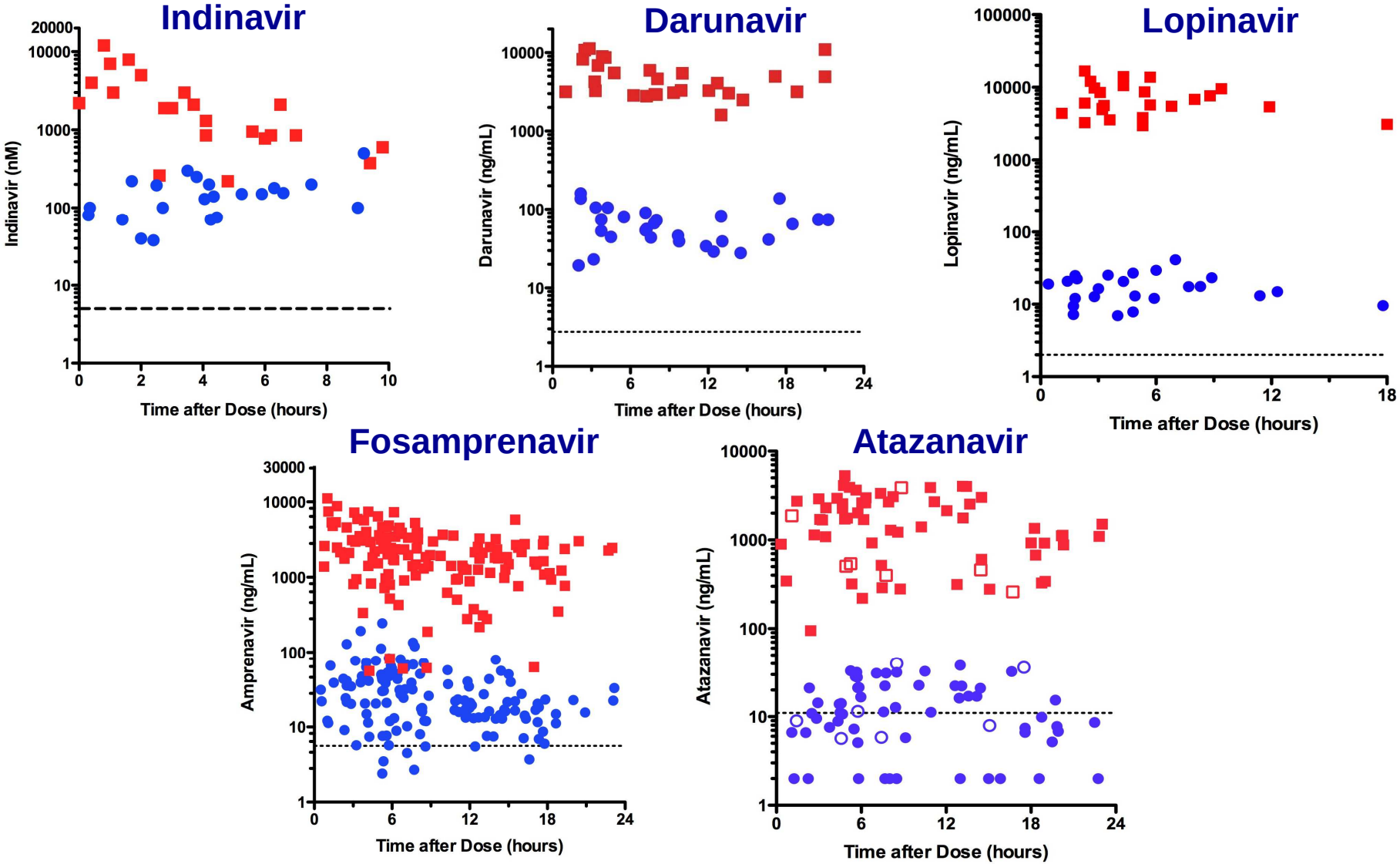
ART Pharmacokinetics in CSF and Blood



Best et al, AIDS 2009; 23: 83-87; Capparelli et al, AIDS 2005; 19:949–952; Letendre et al, 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2009; Letendre et al, 9th Intl Workshop on Clinical Pharmacology of HIV Therapy, 2009; Letendre et al, Antimicrobial Agents and Chemotherapy 2000, 44: 2173

CNS Penetration Effectiveness Estimates

	Much Above Average	Above Average	Average	Below Average
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine *Rilpivirine*	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
InSTIs	*Dolutegravir*	Raltegravir	*Elvitegravir*	
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide

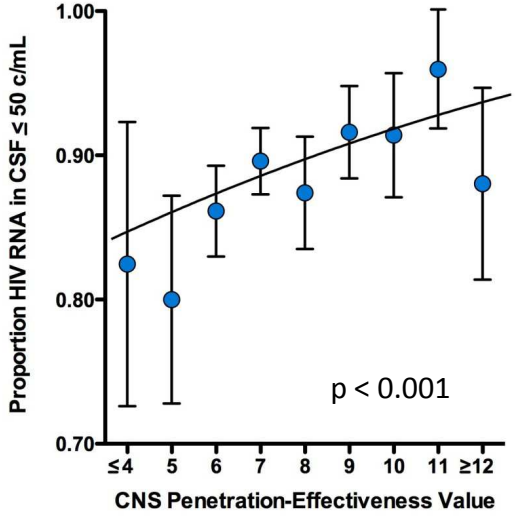
Letendre SL, et al. Topics in Antiviral Medicine 2011, 19(4):137-42

CNS Penetration Effectiveness Estimates

	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz	*Rilpivirine*	
PIs	Indinavir-r	Darunavir-r	Atazanavir	Nelfinavir
		Fosamprenavir-r	Atazanavir-r	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir-r		Saquinavir-r
				Tipranavir-r
InSTIs	*Dolutegravir*	Raltegravir	*Elvitegravir*	
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide

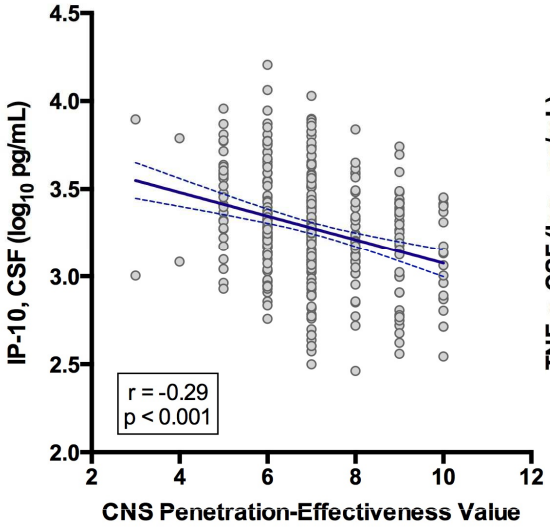
Letendre SL, et al. Topics in Antiviral Medicine 2011, 19(4):137-42

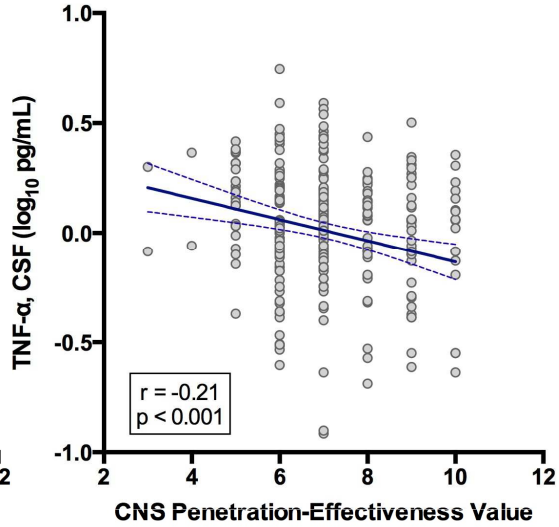
2,207 CSF Viral Loads in 413 Volunteers Over 30 months



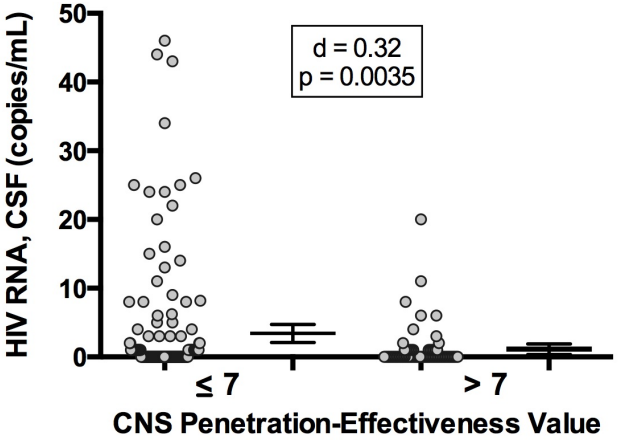
Letendre et al, 19th CROI, 2012, Abstract 473

CSF Inflammation Biomarkers in 394 Volunteers Taking Suppressive ART

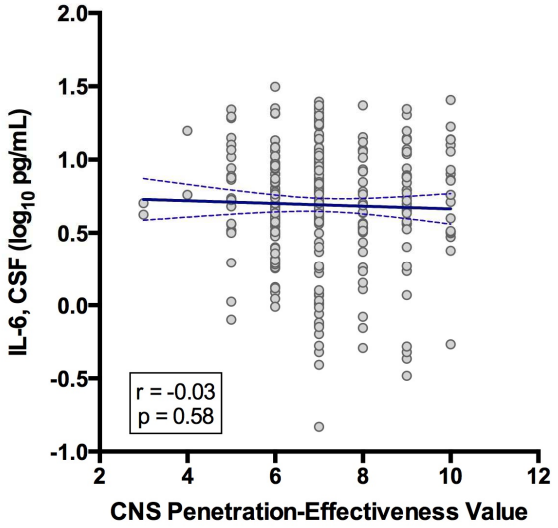




Single-Copy Assays in CSF in 283 Volunteers Taking Suppressive ART



Letendre et al, J Infect Dis 2016 In Press



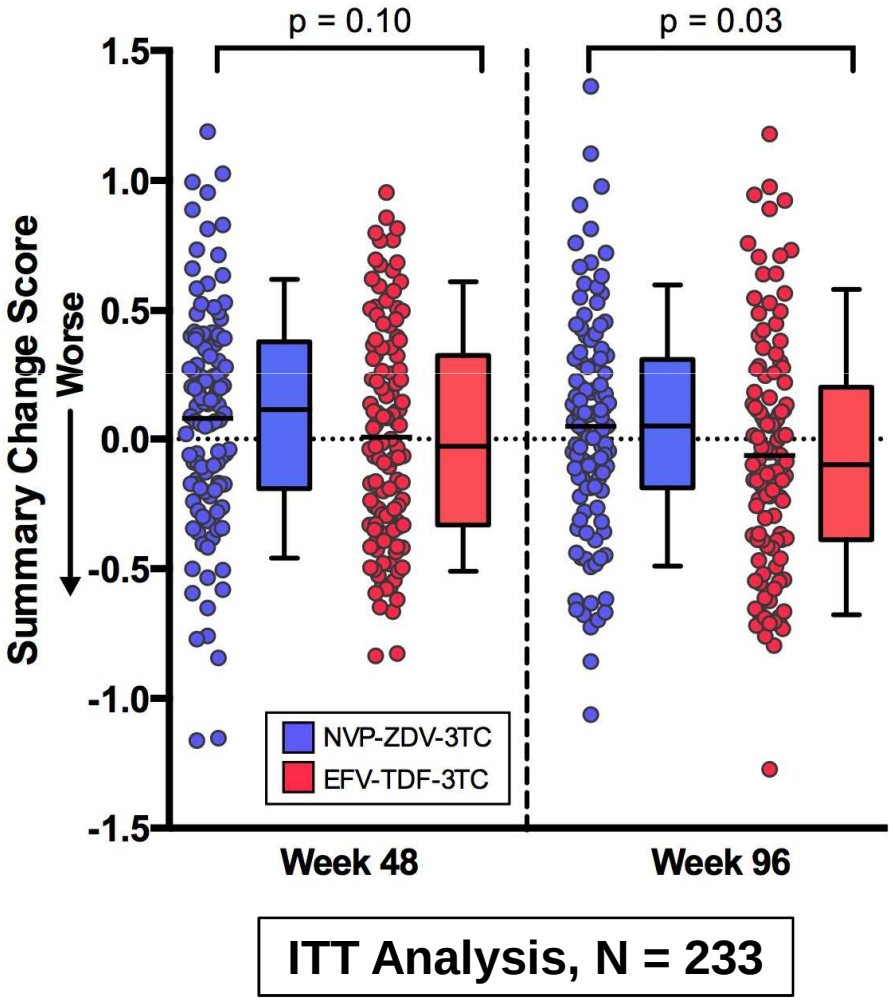
Letendre et al, CROI 2016, Abstract 412

		N	NP	Duration	Principal Finding	Notes
Ciccarelli[1]	C-S	101	C	-	**Beneficial**	2010 version stronger than 2008 version
Fabbiani[2]	C-S	215	C	-	**Beneficial**	Adjusted CPE using GSS
Casado[3]	C-S	69	B	-	**Beneficial**	Beneficial if nadir CD4 < 200
Vassallo[4]	L	96	C	22 months	**Beneficial**	~25% were not virologically suppressed
Cross[5]	L	69	C	1 year	**No association**	Binary transformation only
Ghate[6]	L	92	C	1 year	**Beneficial**	Benefit on working memory
Carvalhal[7]	C-S	417	C	-	**Beneficial**	Benefit with 3-drug regimens
Smurzynski[8]	L	2,636	B	4.7 years	**Beneficial***	Benefit with > 3 ART drugs
Ellis[9]	RCT	49	C	16 weeks	**No association**	Benefit when HIV RNA < 50
Wilson[10]	C-S	118	B	-	**Detrimental on 2 tests**	Binary transformation only Substance users only
Kahouadji[11]	C-S	93	B	-	**Detrimental on 1 test**	Methodological flaws
Caniglia[12]	L	61,938	N	~3 years	**Detrimental (no tests)**	Absolute risk 1.1% vs. 0.9%

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

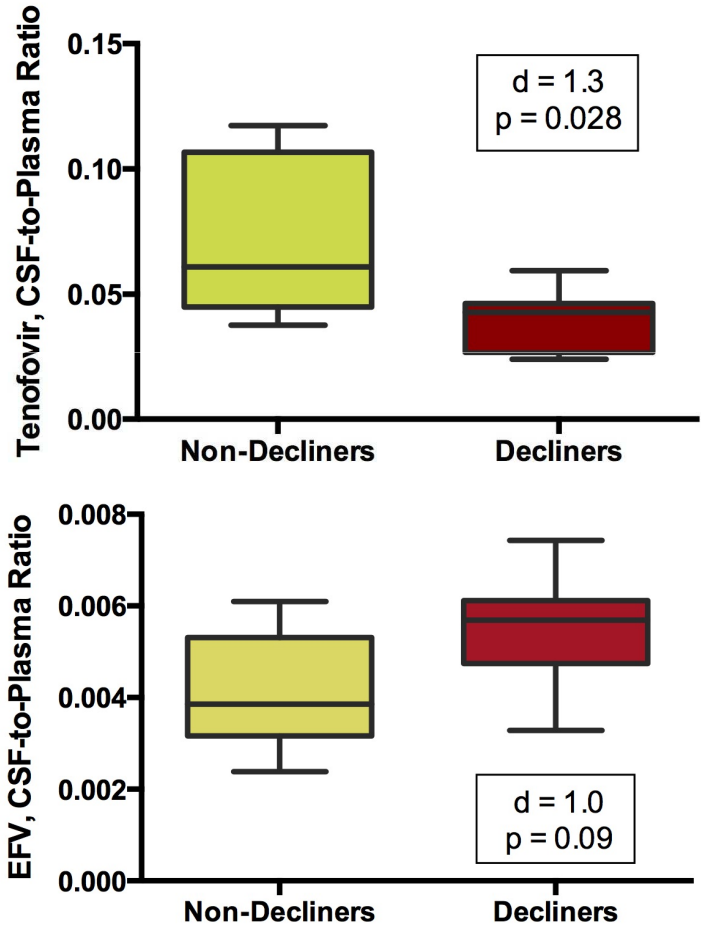
[1]Ciccarelli et al, Antiviral Therapy 2013, 18: 153-160; [2]Fabbiani et al, Antiviral Therapy 2014, PMID: 25516553; [3]Casado et al, J Neurovirol 2014, 20: 54-61; [4]Vassallo et al, AIDS 2014, 28(4):493-501; [5]Cross et al, S Afr Med J 2013;103(10):758-762; [6]Ghate et al, J Neurovirol 2015, PMID: 25750072; [7]Carvalhal et al, J Neurovirol 2015; [8]Ellis et al, Clin Infect Dis. 2014;58(7):1015-22; [9]Ellis et al, Clin Infect Dis. 2014;58(7):1015-22; [10]Wilson et al, J Clin Experim Neuropsych 2013, 35:915-25, [11]Kahouadji et al, HIV Medicine 2013, 14: 311-5; [12]Caniglia et al, Neurology 2014;83:1

Cognitive Decline May Be Linked to Drug Distribution into CSF



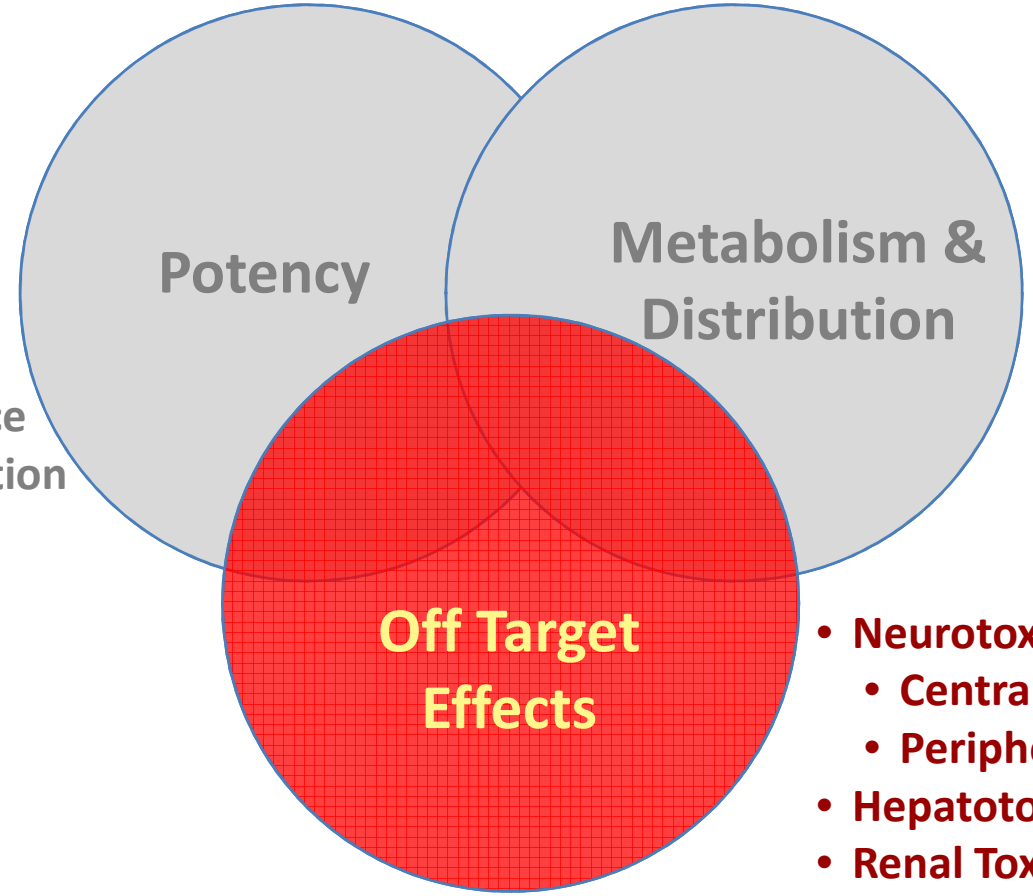
ITT Analysis, N = 233

Zhang, et al, CROI 2015, Abstract 56



Ma et al, CROI 2015, Abstract 444

Several ART Drug Characteristics Can Influence ART Efficacy in the CNS



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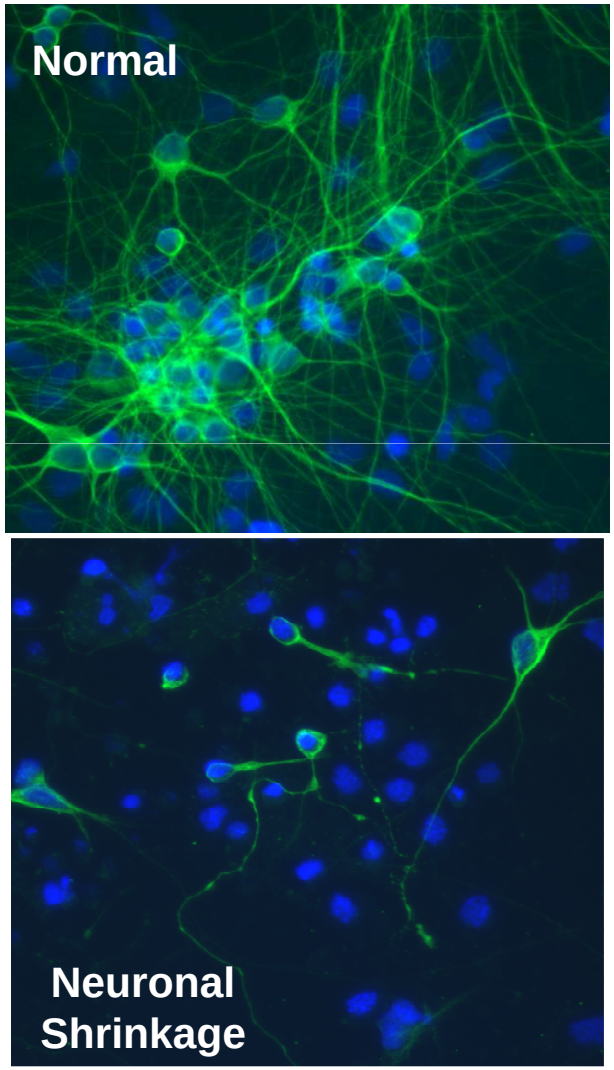
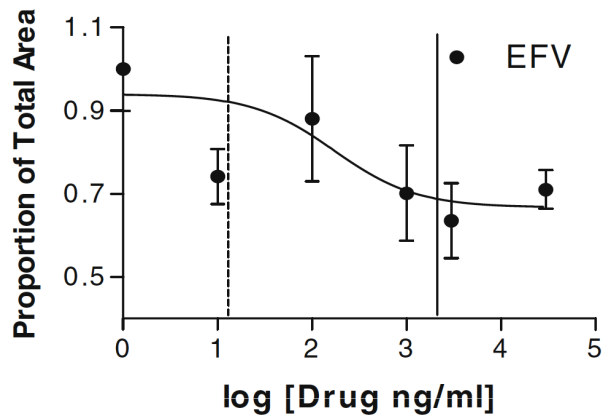
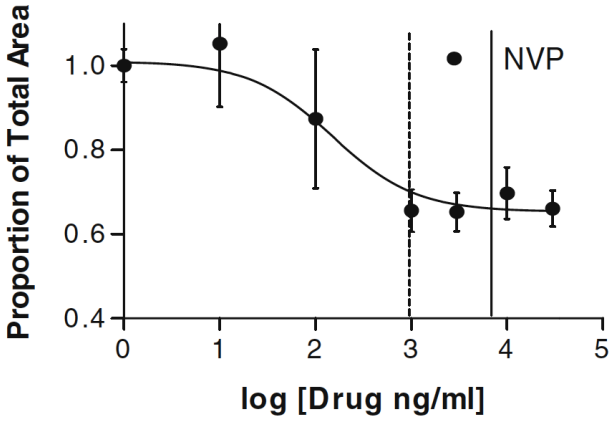
Neurotoxicity in Cortical Neuronal Cell Culture System

- Exposed cell cultures to increasing drug concentrations
- At least mild neuronal injury was seen with all drugs

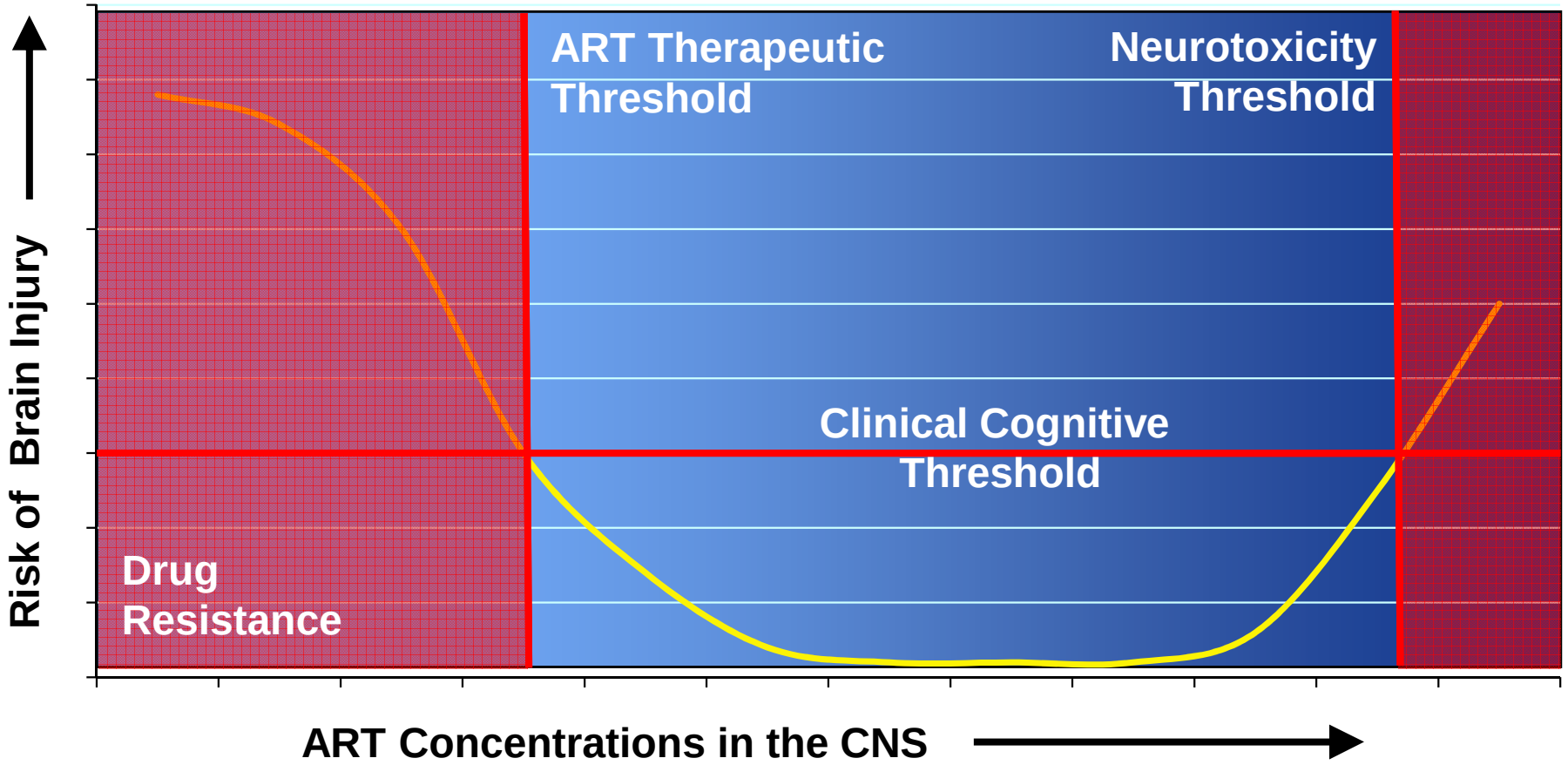






Robertson et al, J Neurovirol 2012, 18: 388-299

CNS Therapeutic Window



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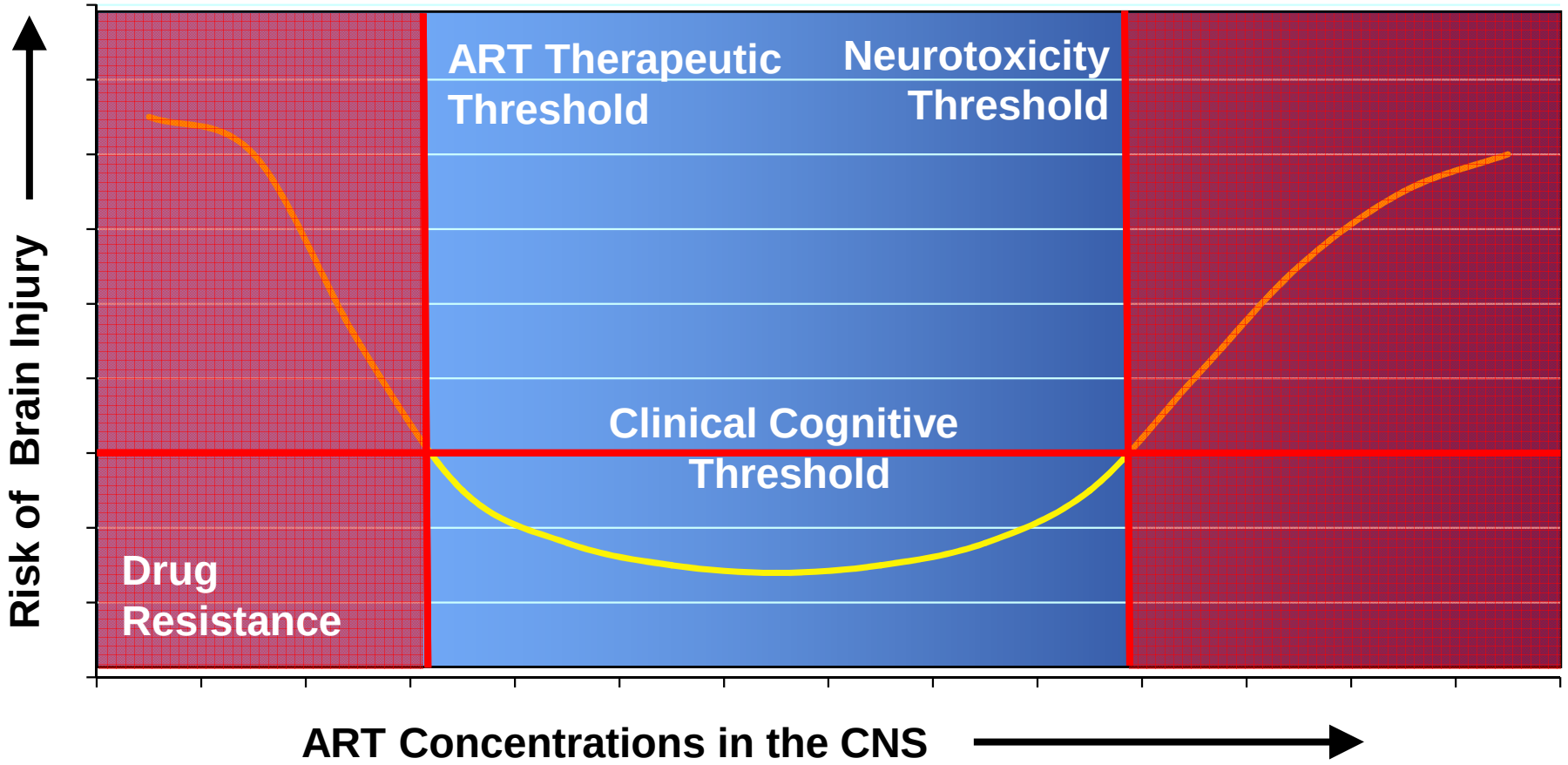

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Acknowledgements & Conflicts

Study Volunteers

UC San Diego

- Igor Grant
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- Jennifer Marquie
- Eliezer Masliah
- Debra Rosario
- Mariana Cherner
- Steven P. Woods

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- Justin McArthur
- Ned Sacktor
- Ann Collier
- David Clifford
- Christina Marra
- Susan Morgello
- David Simpson
- Ben Gelman
- Donald Franklin

National Institutes of Health

- …Mental Health
- …Drug Abuse
- …Allergy and Infectious Diseases

Industry

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

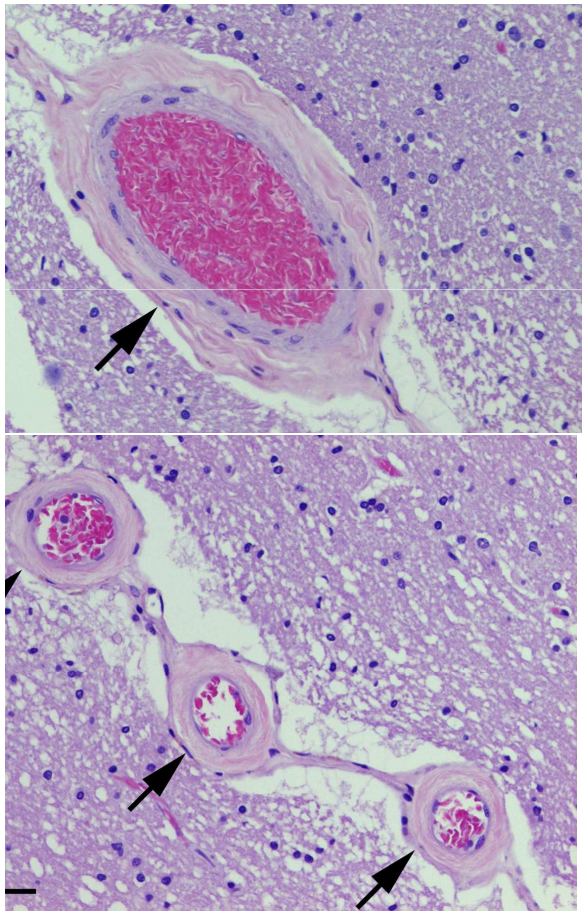
Other Signs of ART Neurotoxicity Have Been Accumulating

Efavirenz is Associated with HAND

Risk Factor	Odds Ratio	P Value
Age (per 10 years)	0.83	0.29
Education (per 1 year)	0.85	0.002
Non-Italian Born	3.5	0.056
Efavirenz use	**4.0**	**0.008**

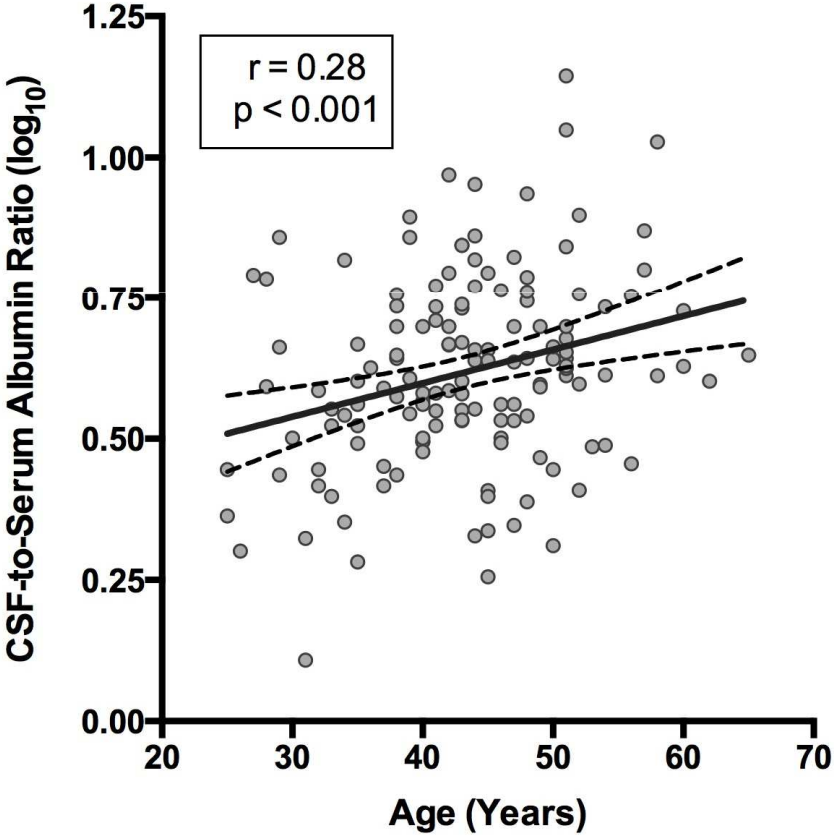
Ciccarelli et al, Neurology 2011, 76: 1403

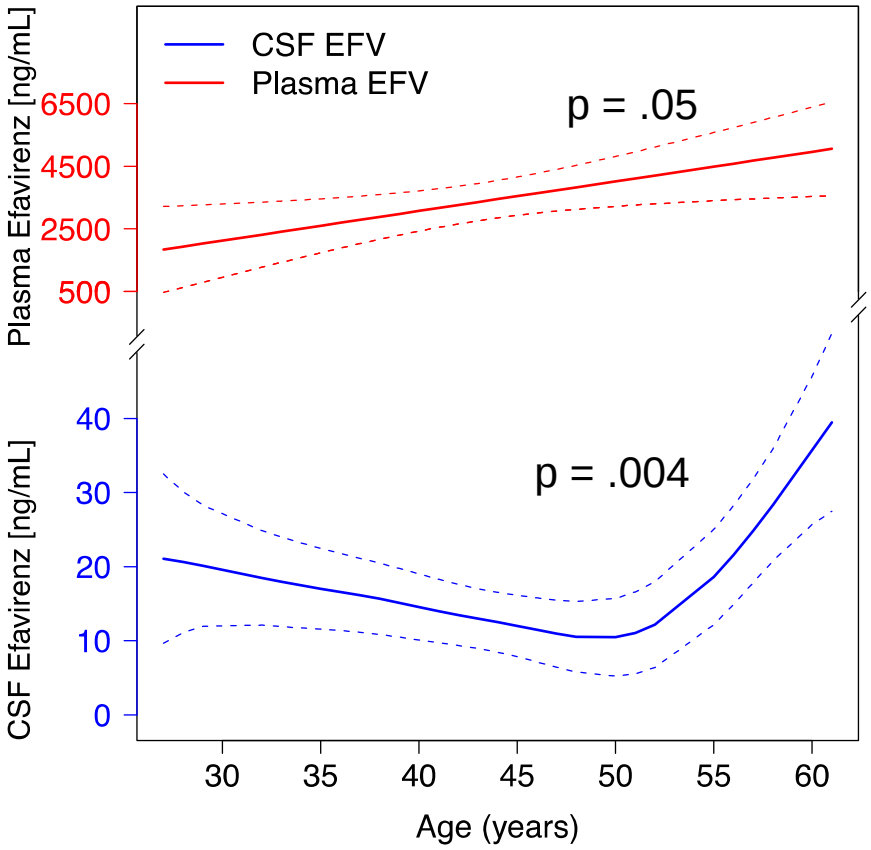
Protease Inhibitors are Associated Cerebral Small Vessel Disease



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

Blood-Brain Barrier Permeability Increases with Age and may Increase Drug Distribution into the CNS



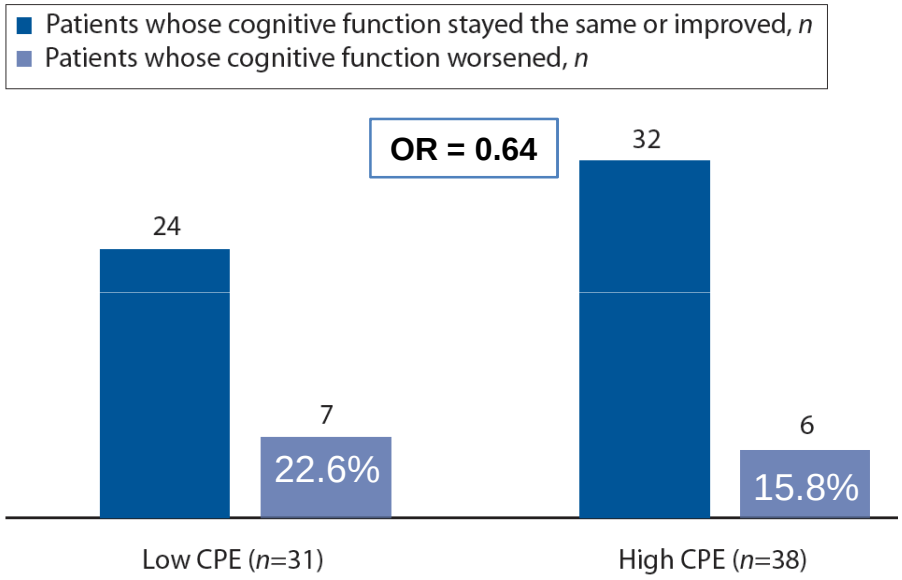


Letendre et al, 18th CROI, 2011, Abstract 408

Croteau et al, 19th CROI, 2012, Abstract 592

Similar Effect Sizes in 2 Observational Studies but Different Conclusions

South Africa

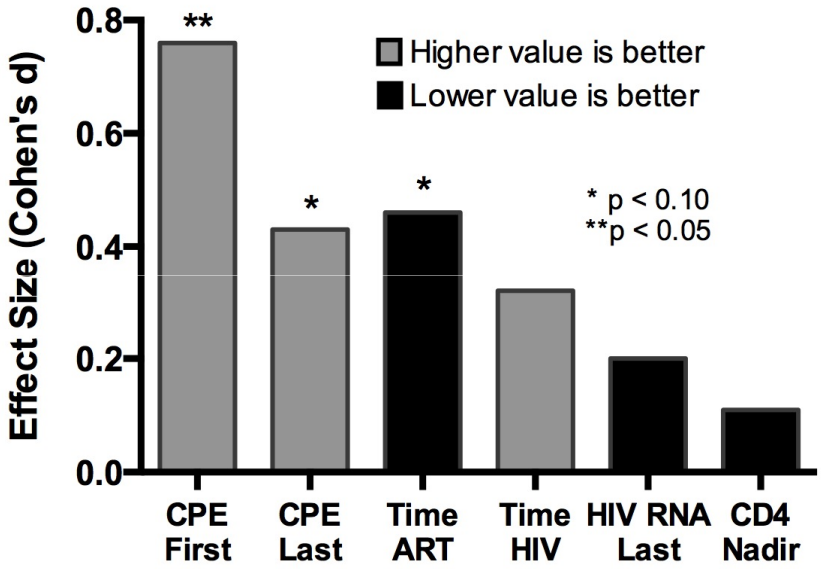


Cross et al, S Afr Med J 2013;103(10):758-762

Odds ratio is calculated from data in the manuscript

N = 69

France



Vassallo et al, AIDS 2014, 28(4):493-501

Graph is adapted from Table 2

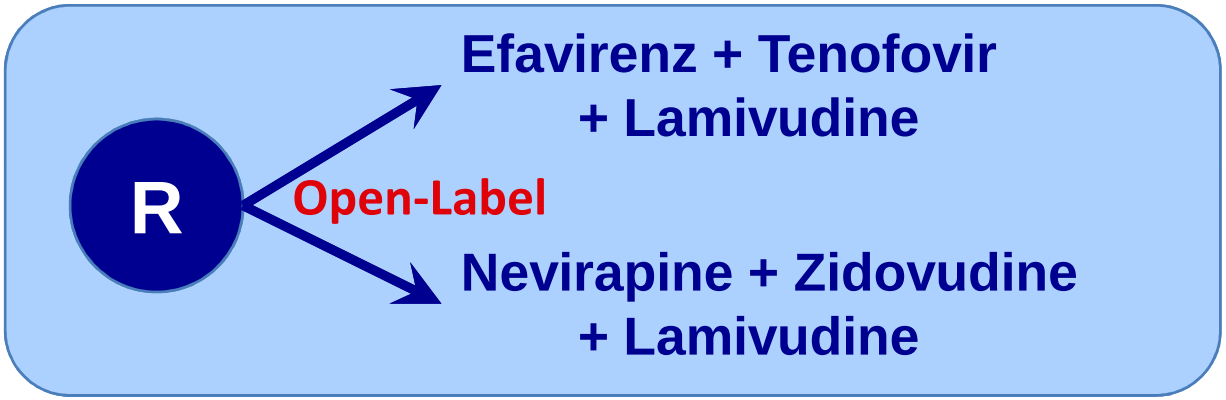
Odds ratios from multivariable regression:

- Initial (first) CPE: 0.54
- End-of-follow-up (last) CPE: 0.65

N = 96

Randomized Clinical Trial of CNS Penetrating ART to Prevent HAND

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

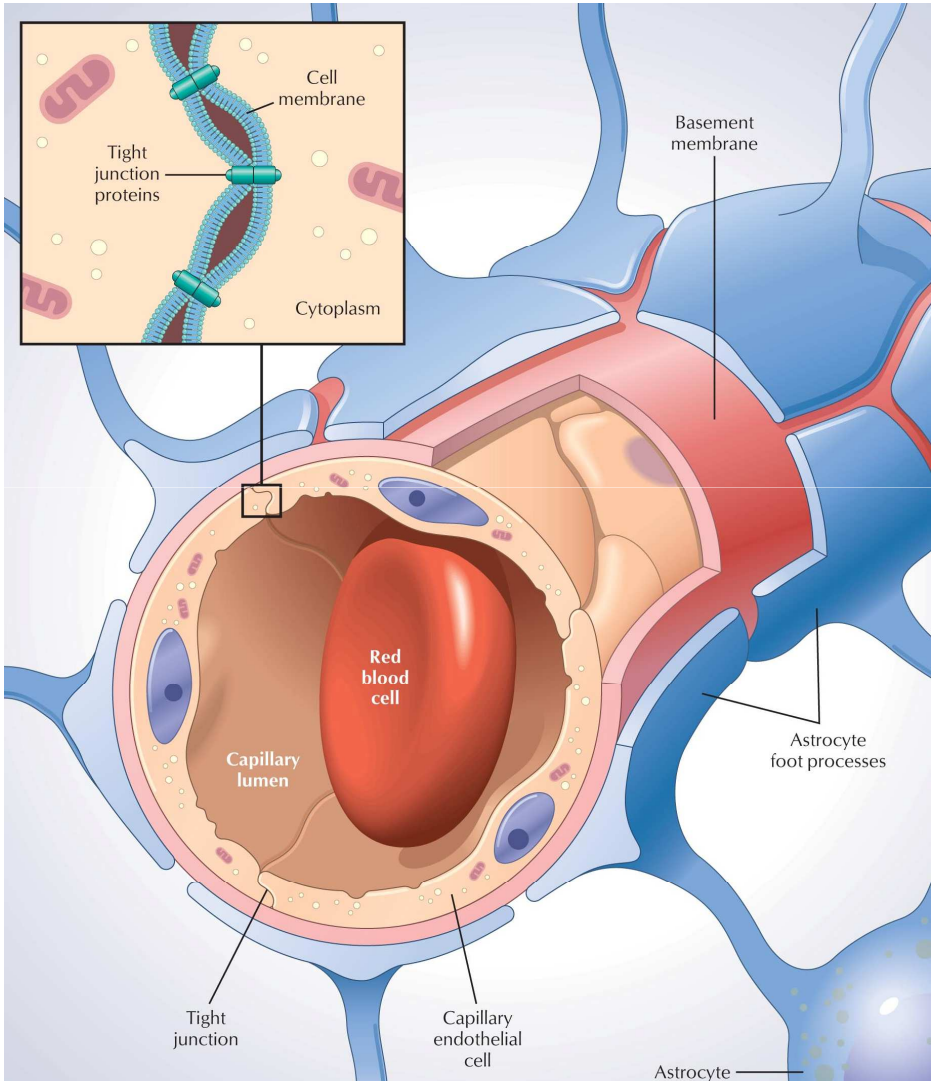


Blinded to Treatment Arm: Investigators from US, China CDC, and Beijing University Mental Health Institute

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

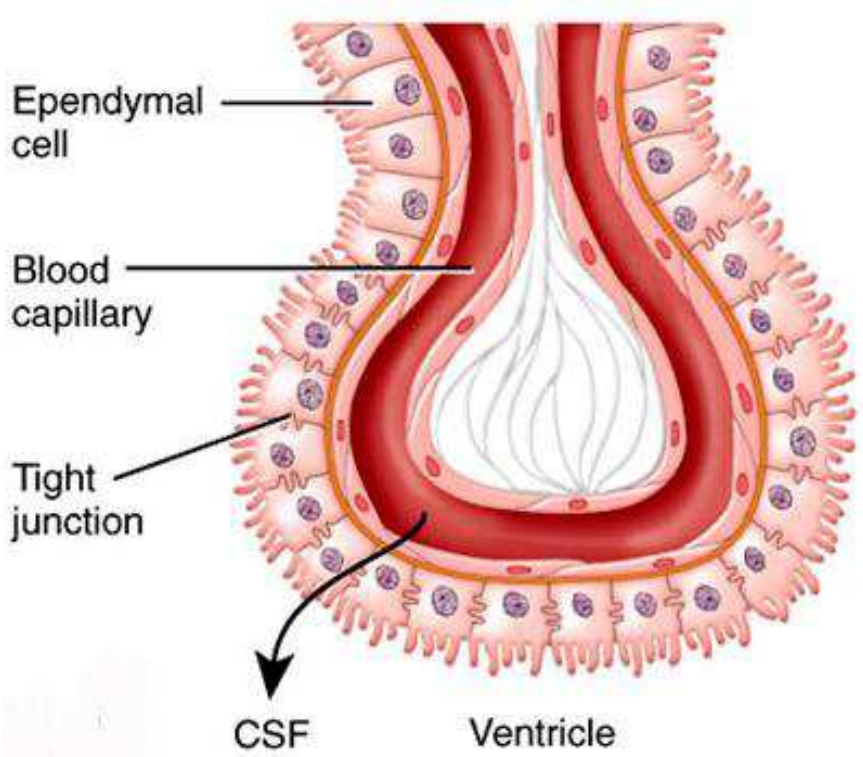
Zhang et al, CROI 2015, Abstract 56

Blood-Brain Barrier



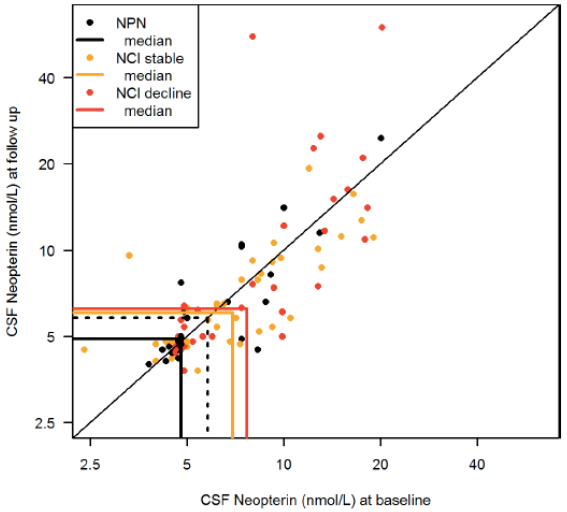
Graphic Licensed from NetterImages

Blood-CSF Barrier

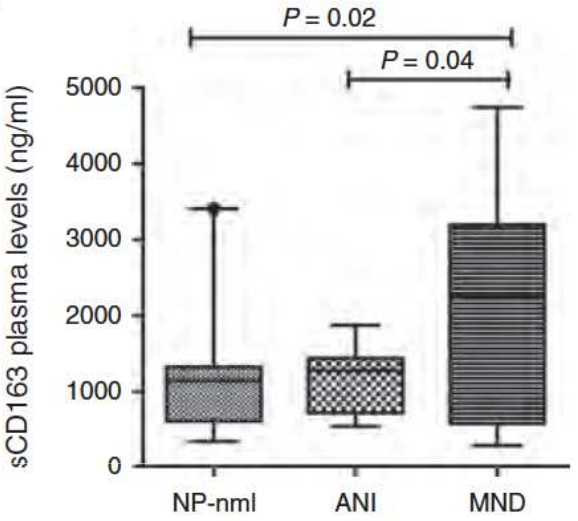


Choroid Plexus

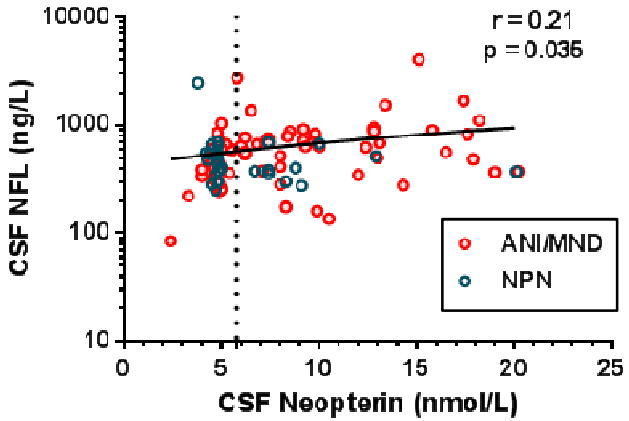
Macrophage Activation during ART is Another Contributor to HAND



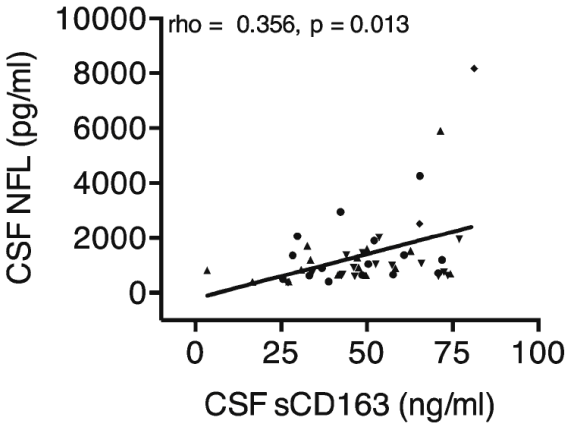
Edén et al, PLoS One 2016, DOI:10.1371/journal.pone.0157160



Burdo et al, AIDS 2013, 27:1387–1395

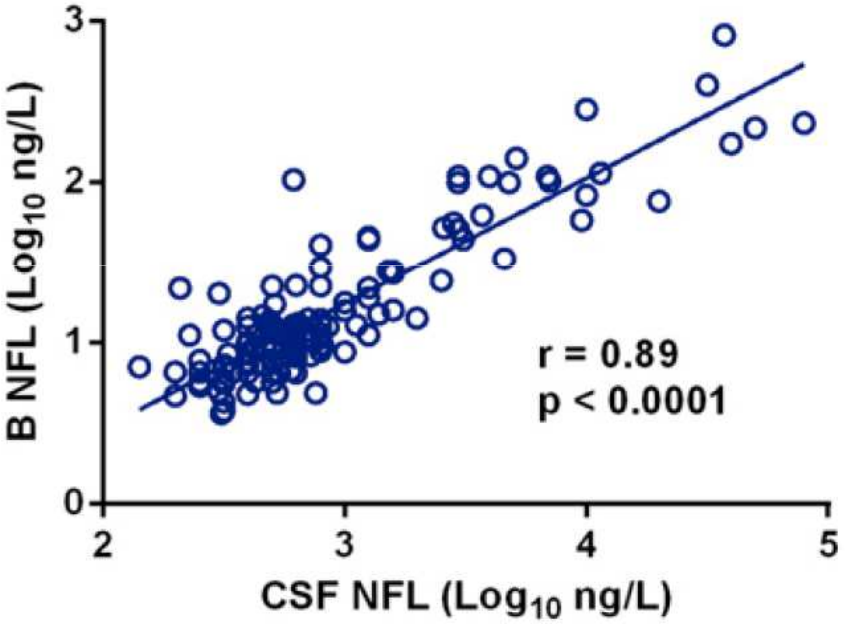


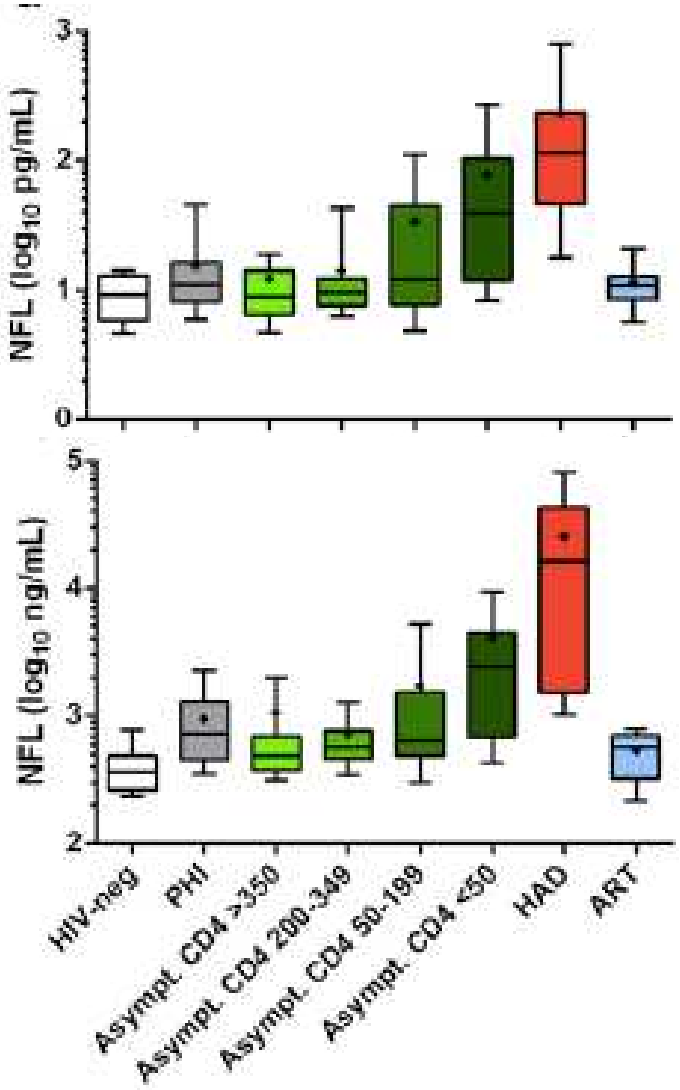
Edén, et al, PLoS One. 2016; 11(6):e0157160



McGuire et al, J Neurovirol 2015, DOI 10.1007/s13365-015-0333-3

Neurofilament-Light Can Now Be Measured in Blood





Gisslen et al, EBioMedicine 3 (2016) 135–140

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	✔	✔

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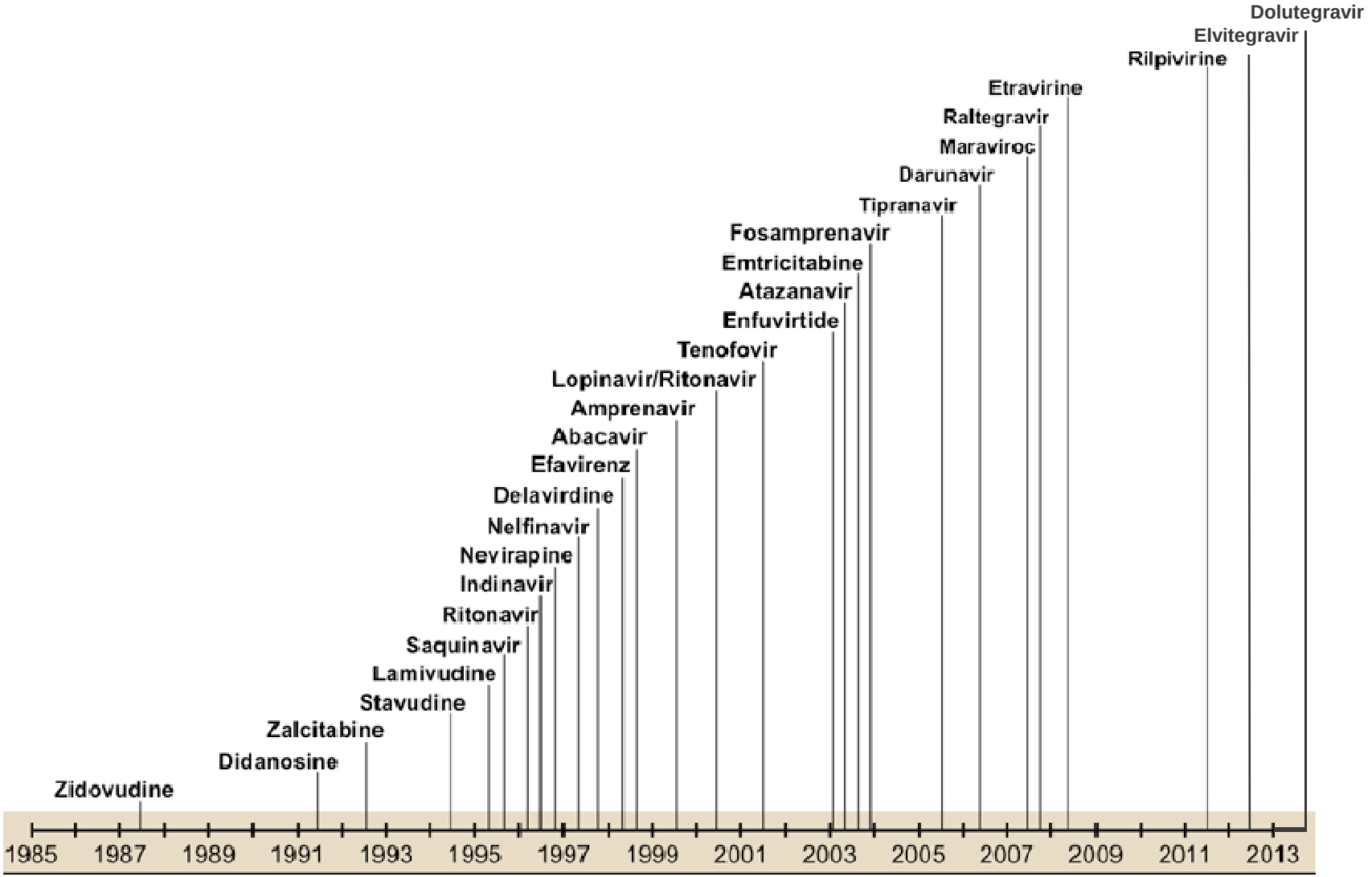
Antinori et al, Neurology 2007, 69: 1789-99

Rapid Development of Antiretroviral Drugs Since the Mid-1990s



http://depts.washington.edu/hivaids/images/arvrx/arvrx_c2_d03.png

Controversies in HIV-associated neurocognitive disorders

Sam Nightingale, Alan Winston, Scott Letendre, Benedict D Michael, Justin C McArthur, Saye Khoo, Tom Solomon

Lancet Neurol 2014; 13: 1139–51

Some ART drugs are more effective in the CNS than others

For

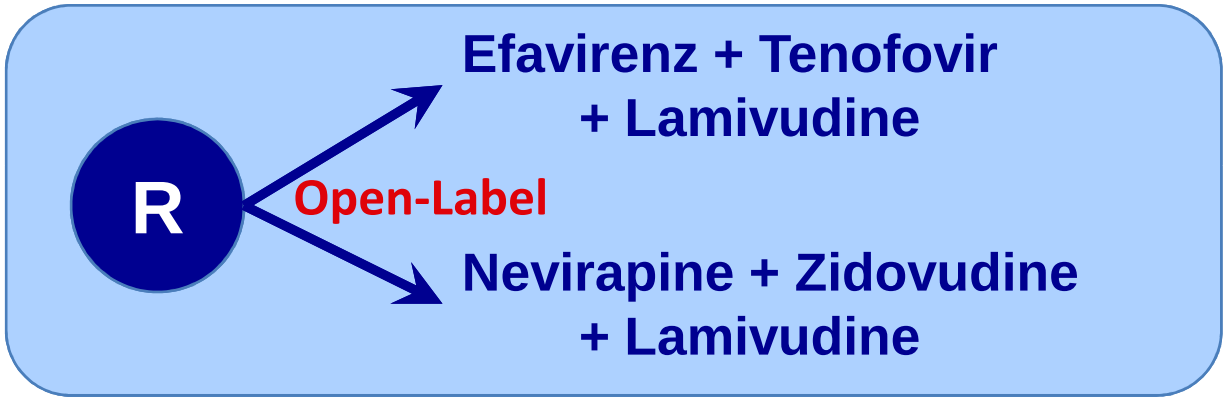
- ART drugs differ in the extent to which their CSF concentrations exceed HIV inhibitory concentrations
- Drugs with better CPE values are associated with undetectable HIV RNA in CSF
- Drugs with better CPE values are associated with better cognitive function in some studies
- CSF viral escape has been linked to regimens with worse CPE values

Against

- CPE values are largely based on pharmacokinetics in CSF, which might not accurately reflect pharmacokinetics in brain
- Drugs with better CPE values are associated with no benefit or worse cognitive function in some studies
- In vitro studies have shown that some ART drugs are neurotoxic
- CSF viral escape is uncommon

Randomized Clinical Trial of ART to Prevent HAND

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



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

Hypothesis: Neurocognitive decline will be greater in the EFV-TDF-3TC arm

Zhang et al, CROI 2015, Abstract 56

Arms were Comparable at Baseline

	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 (%)*

Zhang et al, CROI 2015, Abstract 56

On Treatment, Indicators of Antiviral Efficacy Were Comparable

Week 48 (ITT-Completer)

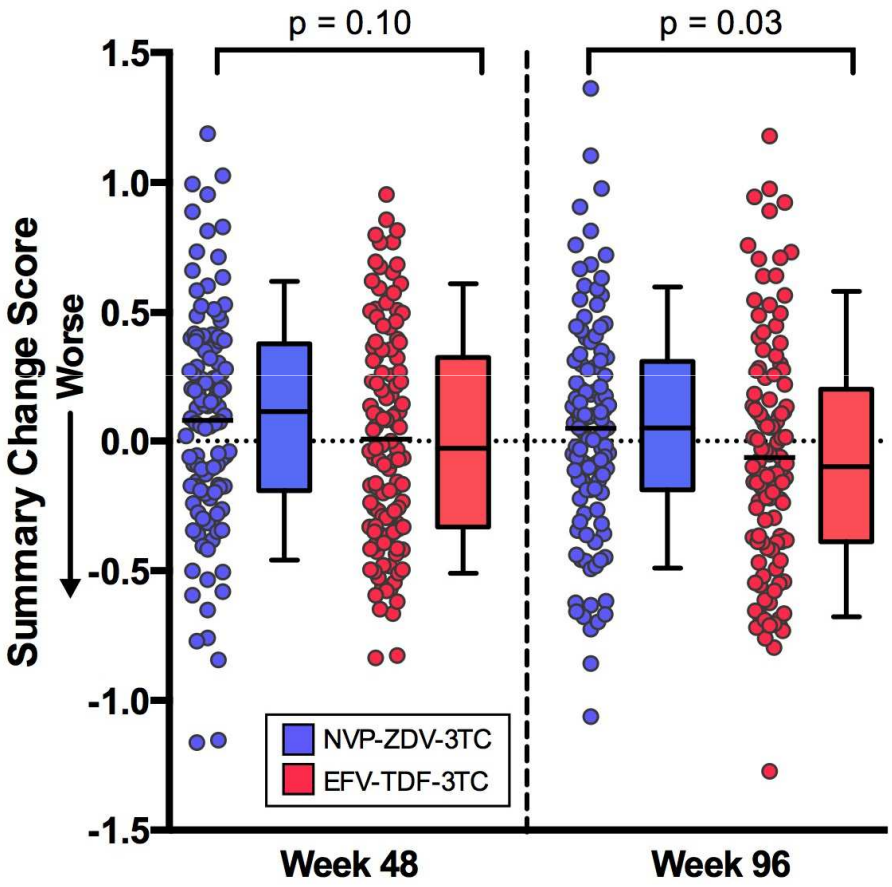
	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	114	119	-
HIV RNA, Plasma (No. (%) ≤ 50 c/mL)	103 (91.2%)	109 (91.6%)	1.00
CD4+ T-cells (/µL)	396.6 (158.0)	396.5 (153.4)	1.00
CD8+ T-cells (/µL)	789.4 (368.0)	760.5 (360.8)	0.54
100% Adherence in Past 4 Days	113 (99.1%)	119 (100%)	0.49

Week 96 (ITT-Completer)

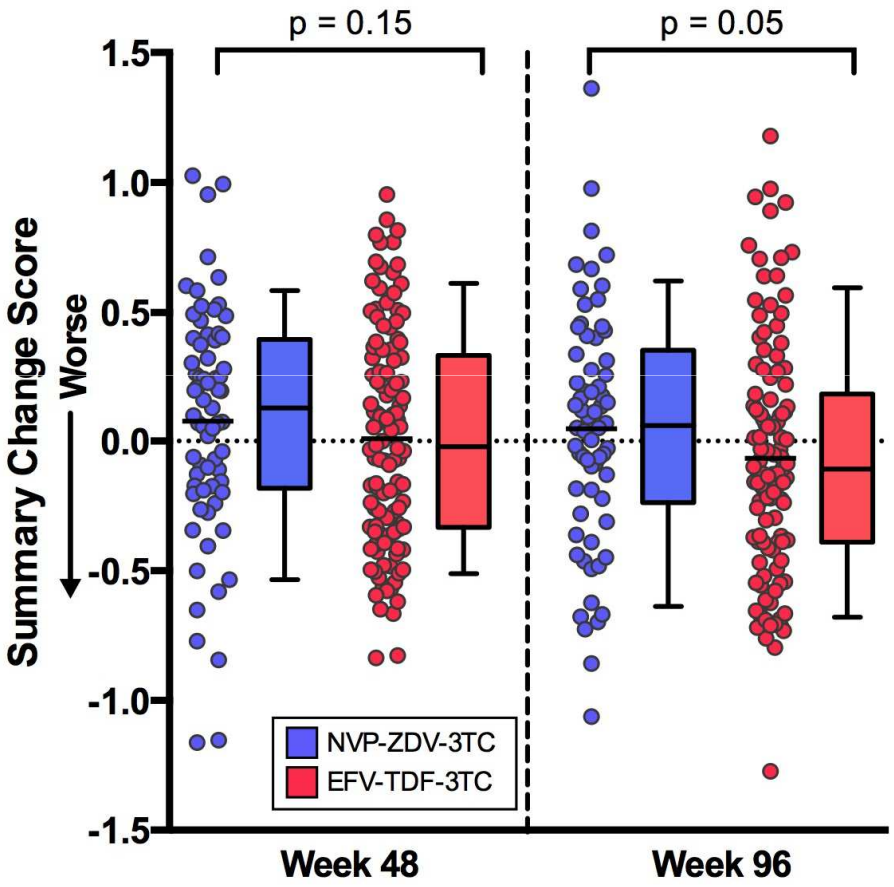
	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	112	118	-
HIV RNA, Plasma (No. (%) ≤ 50 c/mL)	104 (92.0%)	112 (95.7%)	0.28
CD4+ T-cells (/µL)	447.2 (179.3)	483.8 (183.8)	0.13
CD8+ T-cells (/µL)	811.3 (322.4)	850.6 (408.7)	0.42
100% Adherence in Past 4 Days	112 (100%)	116 (100%)	1.00

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

EFV-TDF-3TC Was Associated with Greater Decline After 96 Weeks



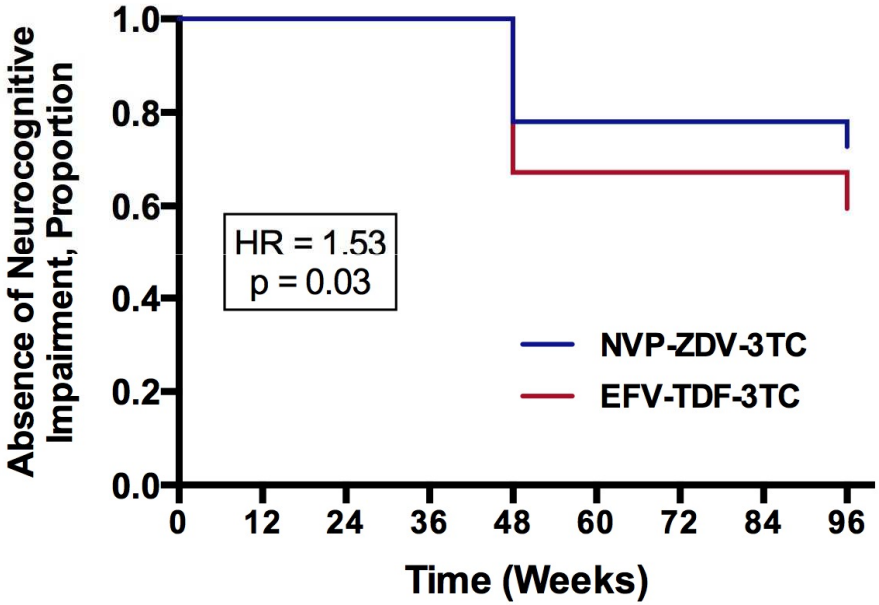
ITT-C Analysis, N = 233



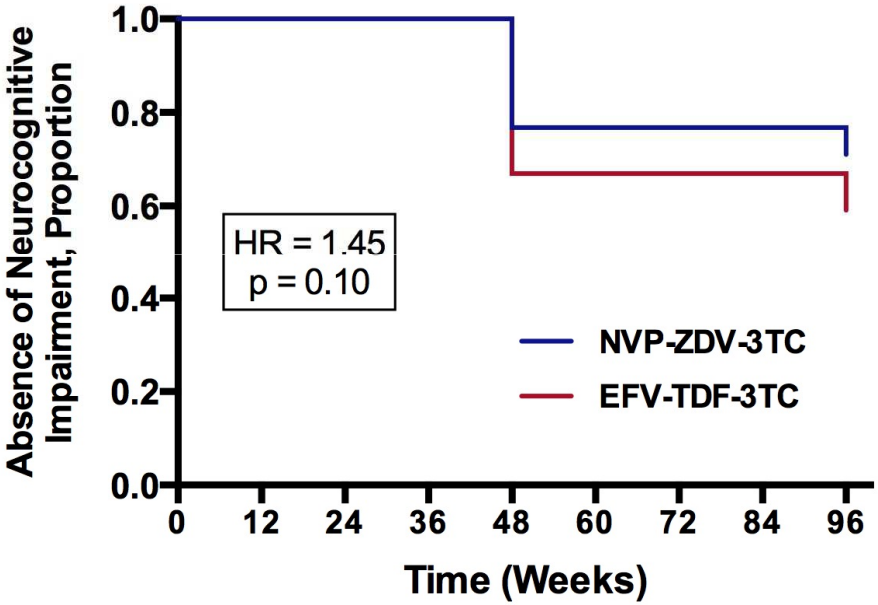
As Treated Analysis, N = 187

Zhang et al, CROI 2015, Abstract 56

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



ITT-C Analysis, N = 233

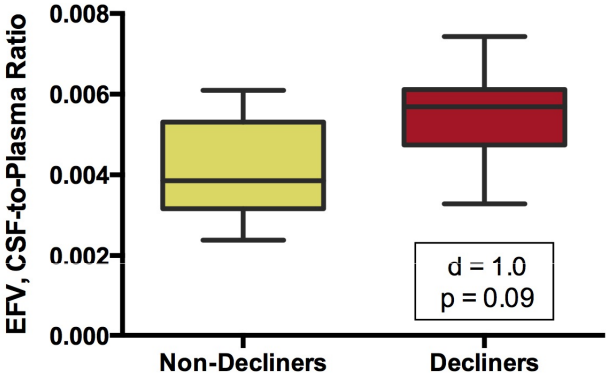


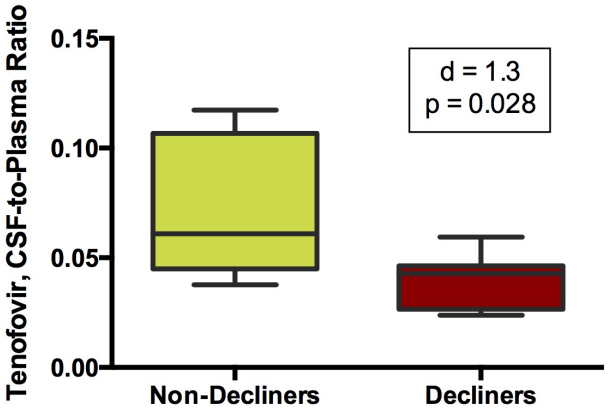
As Treated Analysis, N = 187

Zhang et al, CROI 2015, Abstract 56

Nested Case-Control Study of 15 Decliners and 15 Non-Decliners

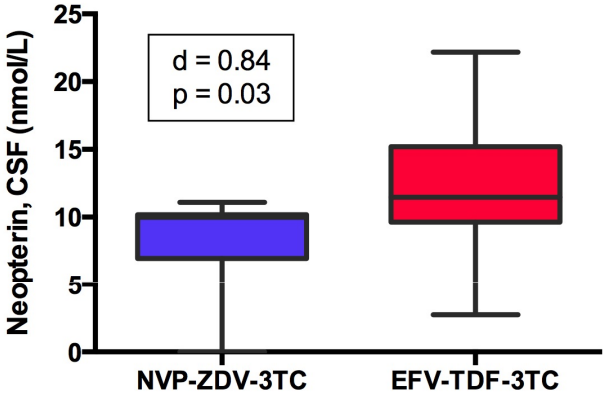
Antiretroviral Drug Concentrations

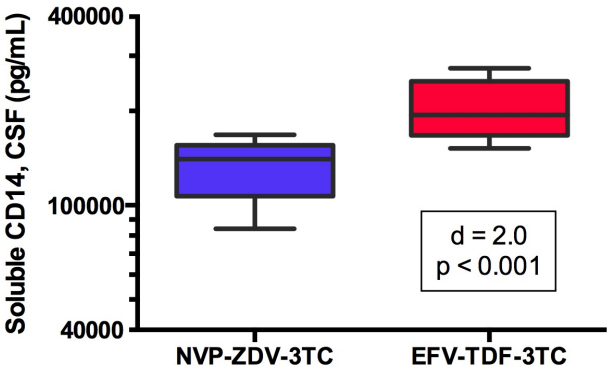




Ma et al, CROI 2015, Abstract 444

CSF Biomarkers

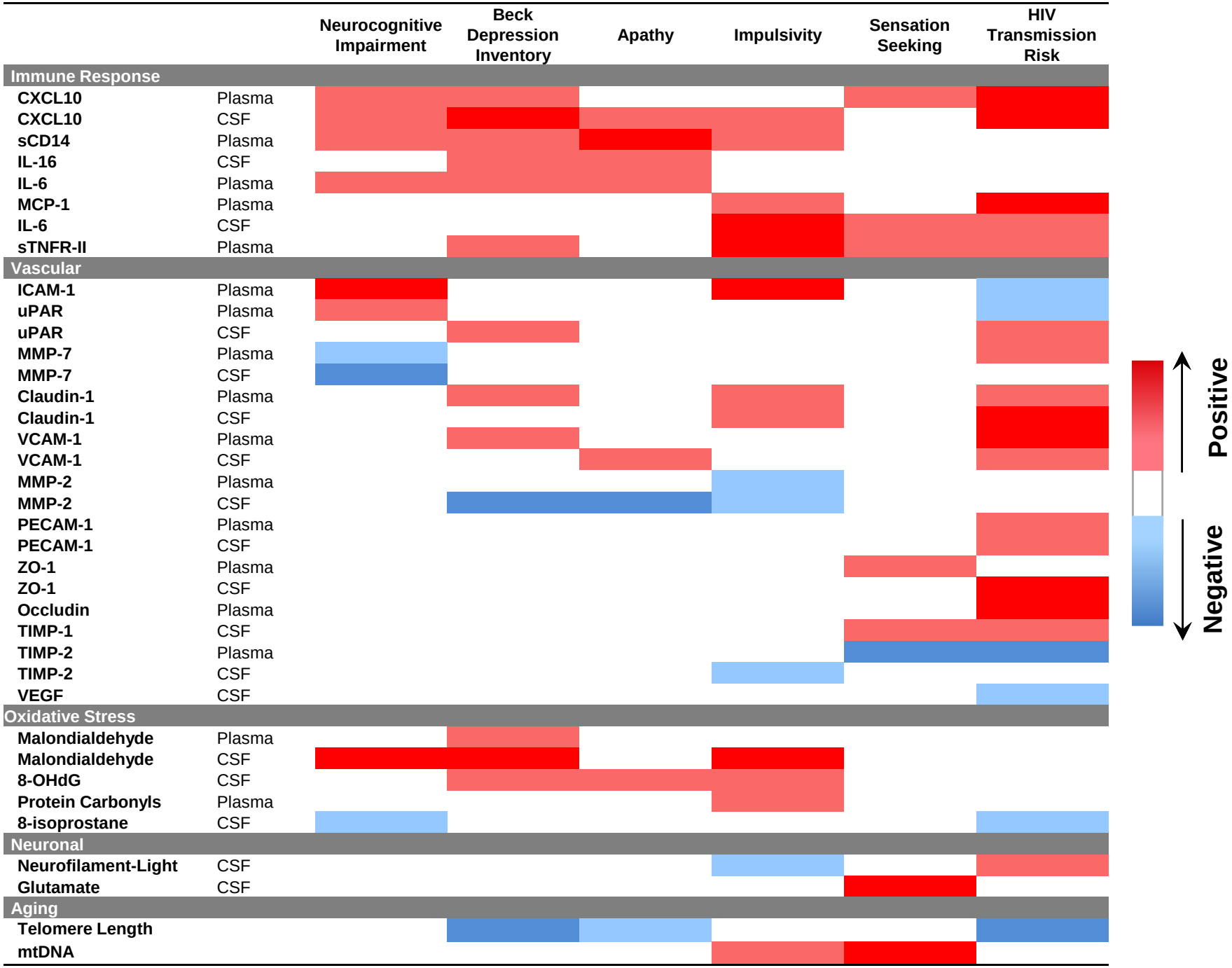




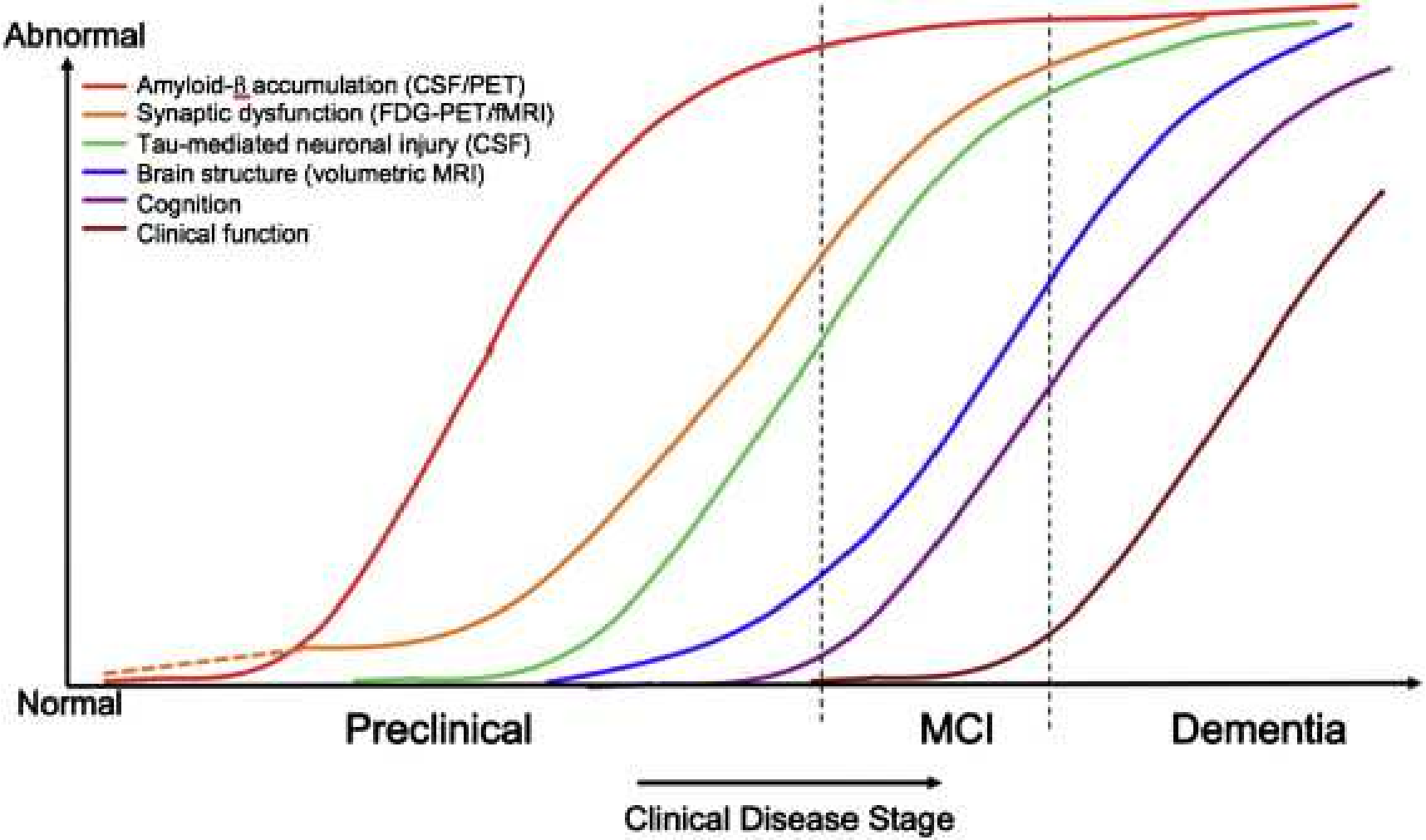
Zhang et al, CROI 2015, Abstract 56

Baseline Characteristics

	Decline	Stable	Improve	
Number of visits	6.2 (1.1)	6.1 (1.2)	6.2 (1.2)	
Age (Years)	42.7 (8.4)	44.2 (8.7)	43.8 (7.5)	
Education (Years)	12.6 (2.6)	12.9 (2.4)	13.3 (2.4)	
Ethnicity (% White)	37%	44%	50%	
Sex (% Male)	72%	81%	86%	D < I
Neuropsychiatric Comorbidity (% Contributing)	20%	8%	11%	D > S
Baseline Neurocognitive Impairment (%)	51%	45%	42%	
AIDS (%)	55%	62%	61%	
Current CD4+ Count (/μL)	433	467	432	
ART Use	68%	70%	72%	
HCV Seropositive (%)	30%	24%	25%	
HIV RNA, Plasma (% ≤ 50 c/mL on ART)	50%	56%	69%	I > D
HIV RNA, CSF (% ≤ 50 c/mL on ART)	70%	76%	92%	I > D,S


Neurocognitive Impairment
Beck Depression Inventory
Apathy
Impulsivity
Sensation Seeking
HIV Transmission Risk
Immune Response
CXCL10 Plasma
CXCL10 CSF
sCD14 Plasma
IL-16 CSF
IL-6 Plasma
MCP-1 Plasma
IL-6 CSF
sTNFR-II Plasma
Vascular
ICAM-1 Plasma
uPAR Plasma
uPAR CSF
MMP-7 Plasma
MMP-7 CSF
Claudin-1 Plasma
Claudin-1 CSF
VCAM-1 Plasma
VCAM-1 CSF
MMP-2 Plasma
MMP-2 CSF
PECAM-1 Plasma
PECAM-1 CSF
ZO-1 Plasma
ZO-1 CSF
Occludin Plasma
TIMP-1 CSF
TIMP-2 Plasma
TIMP-2 CSF
VEGF CSF
Oxidative Stress
Malondialdehyde Plasma
Malondialdehyde CSF
8-OHdG CSF
Protein Carbonyls Plasma
8-isoprostane CSF
Neuronal
Neurofilament-Light CSF
Glutamate CSF
Aging
Telomere Length
mtDNA
Positive
Negative

Biomarkers Identify a Preclinical Stage in Alzheimer's Disease



Sperling et al, Alzheimer's & Dementia 7 (2011) 280–292

Biological Classification of HAND?

	Higher HIV DNA	Higher sCD163	Higher Neurofilament Light	Higher Neopterin	Alternative Diagnosis on Imaging
	Blood	Blood	Plasma	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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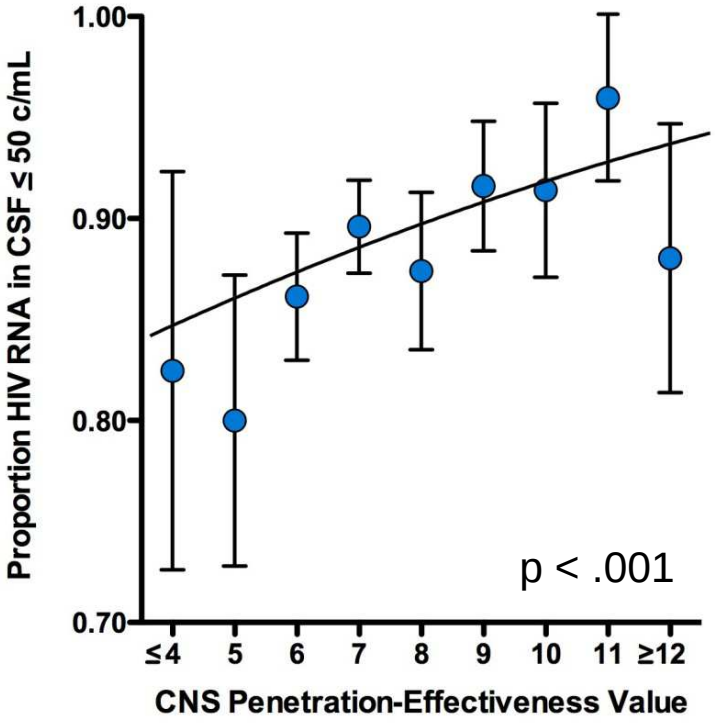
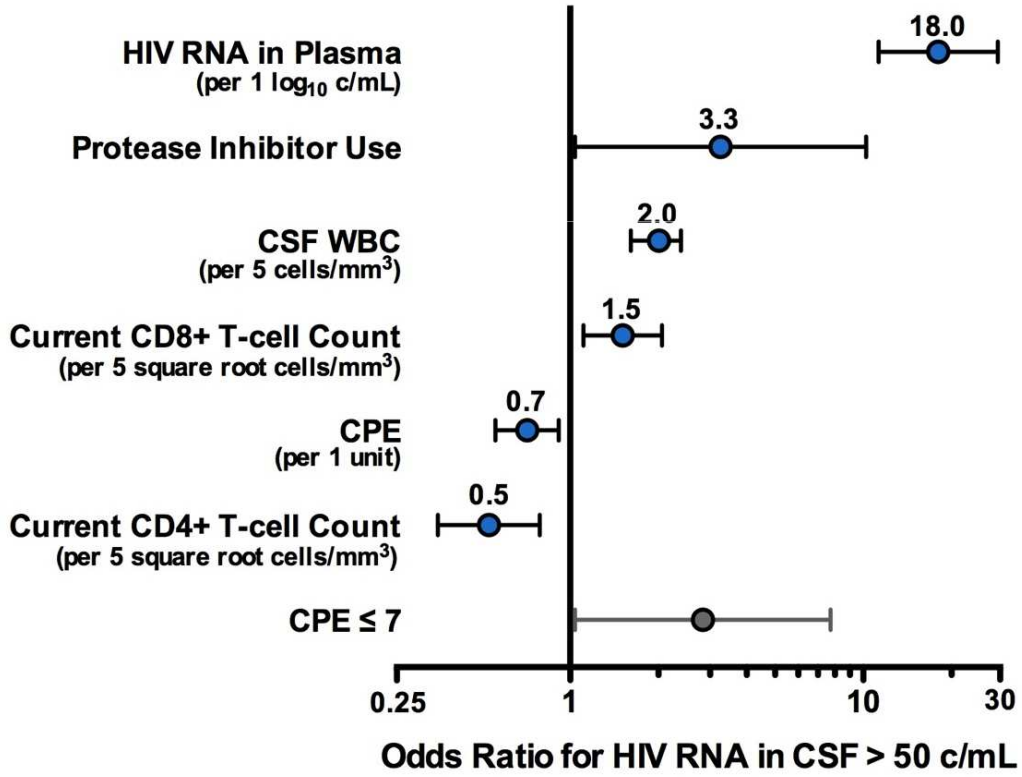
Higher CPE Values Correlate with Undetectable HIV RNA in CSF Over Time

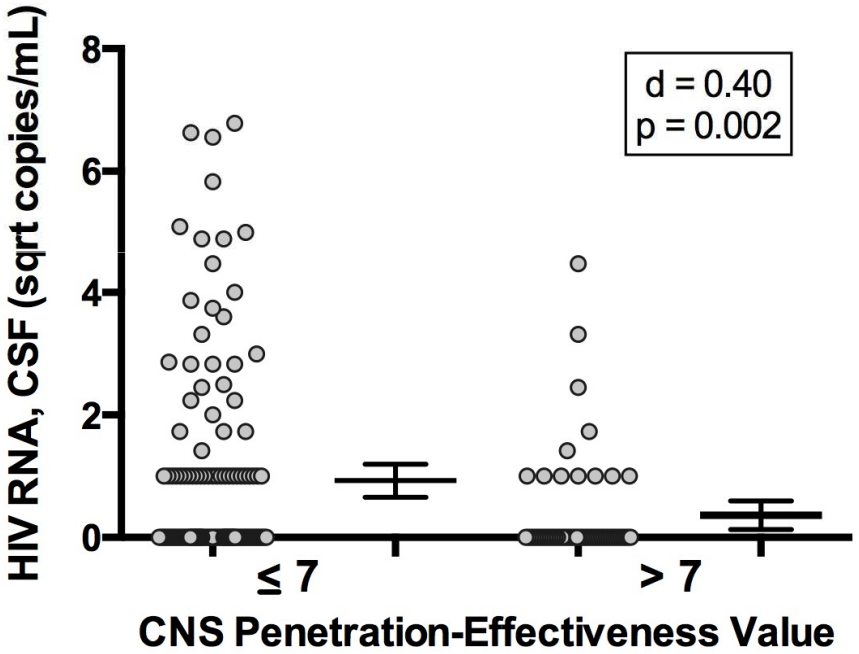
2,207 CSF Viral Loads in 413 Volunteers in CHARTER

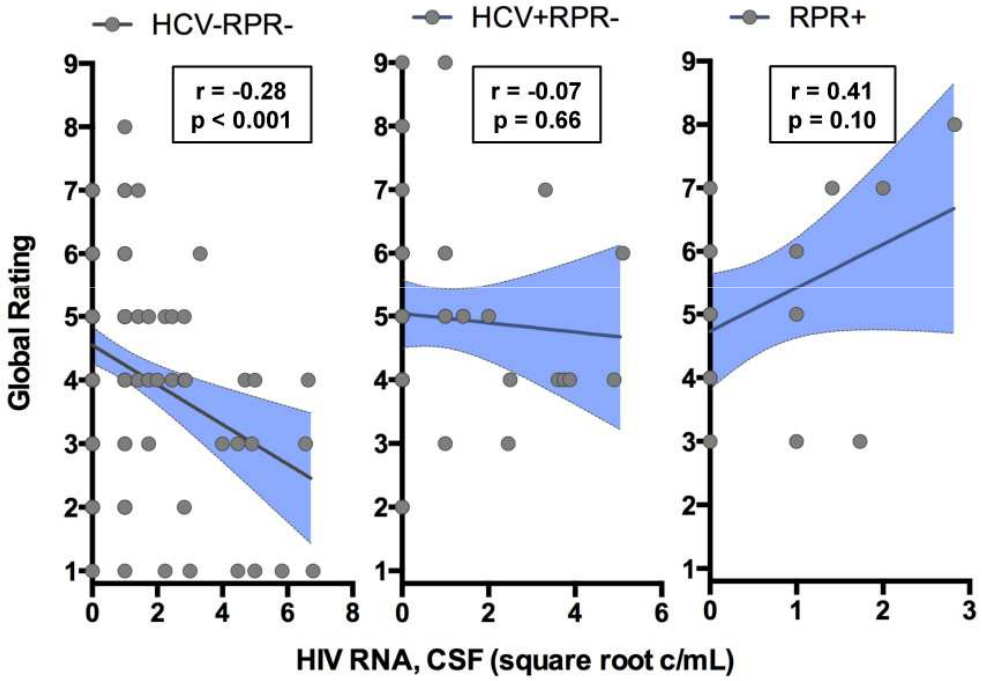




Letendre et al, 19th CROI, 2012, Abstract 473

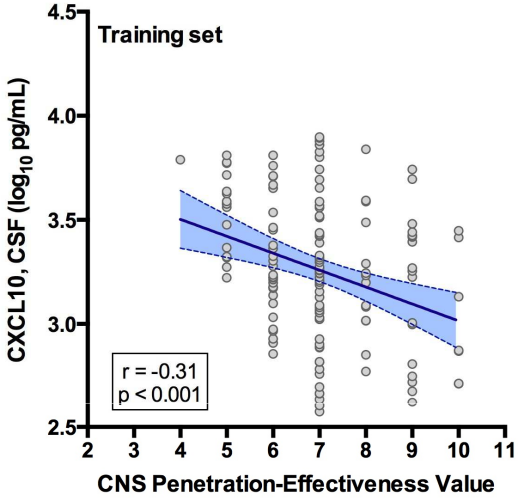
Low-Level HIV RNA in CSF is Associated with Lower CPE Values

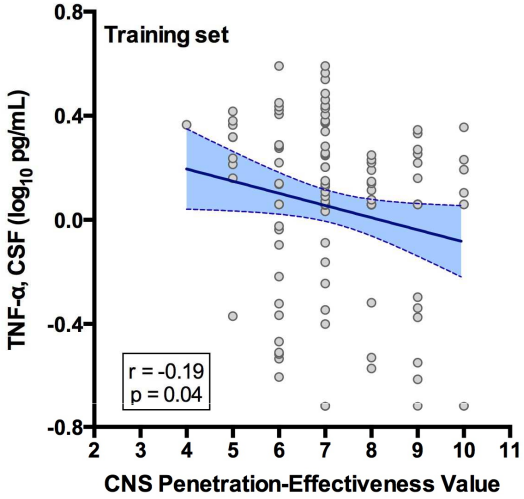


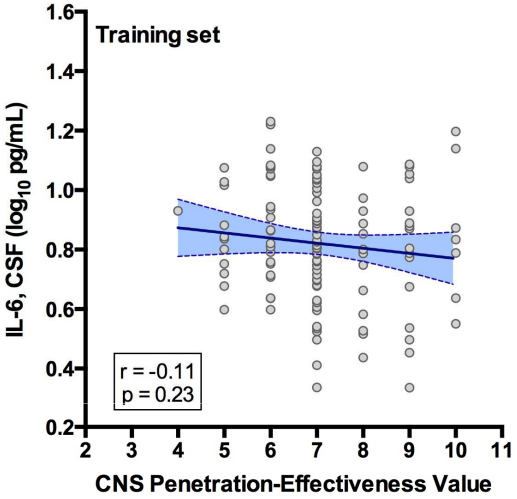


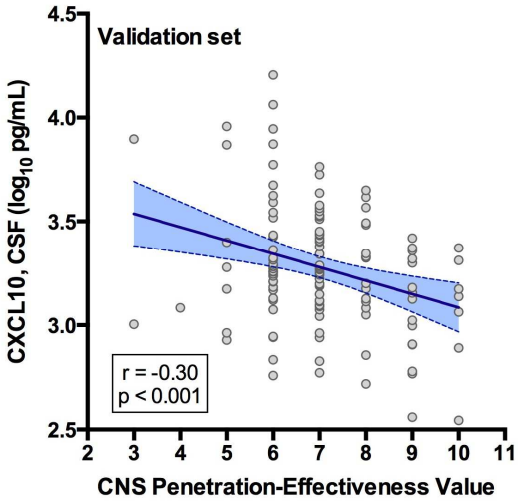
Anderson, et al, J Infect Dis 2016, In Press

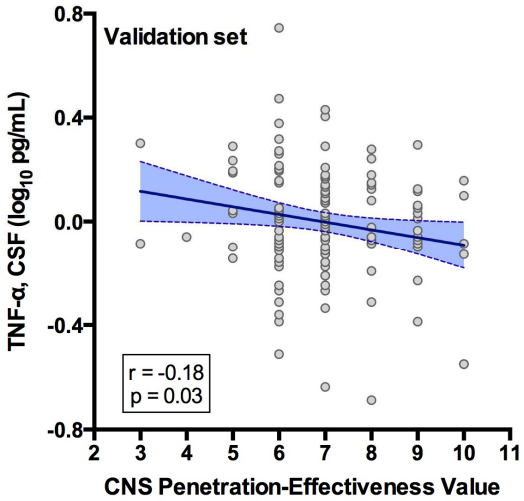
Higher CPE Values Associated with Lower Levels of Some Biomarkers

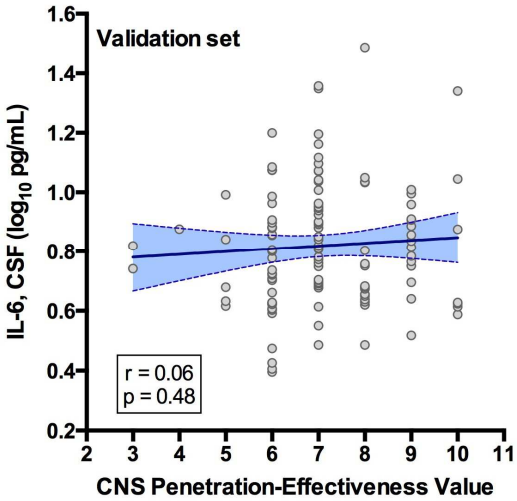








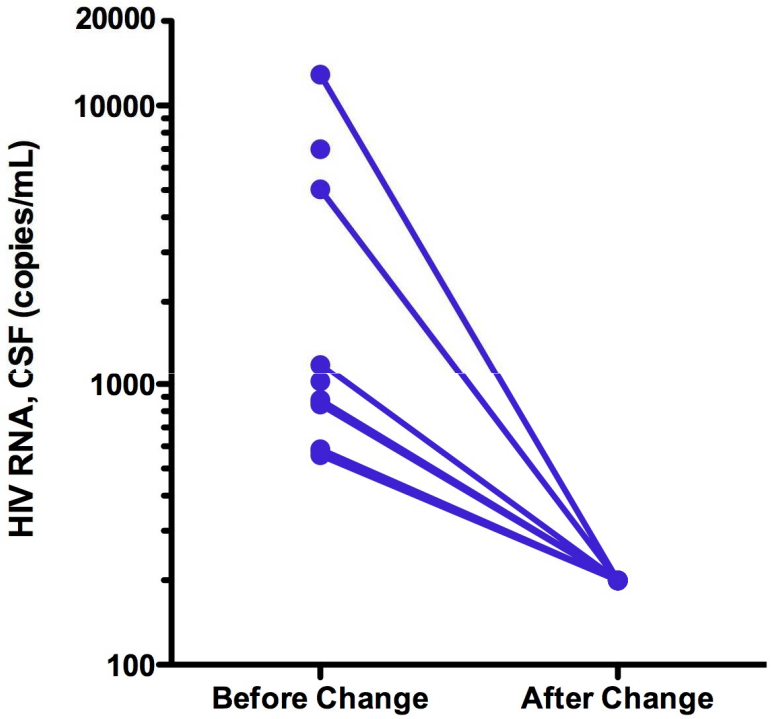




Anderson, et al, CROI 2016, Abstract 412

Case Series from Paris Raised Concerns About CSF Viral Escape

- 11 patients with new neurological symptoms and CSF viral escape* during ART
- **Drug resistance mutations in CSF in 7 of 8**
- ART was modified
  - Drug resistance testing and estimated drug CNS distribution
- All patients clinically improved with reduction of HIV RNA in CSF



* Defined as CSF RNA > 50 c/mL when plasma HIV RNA < 50 c/mL or CSF RNA > 1.0 $\log_{10}$ c/mL greater than plasma HIV RNA

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

ART Characteristics Are Associated with CSF Viral Escape

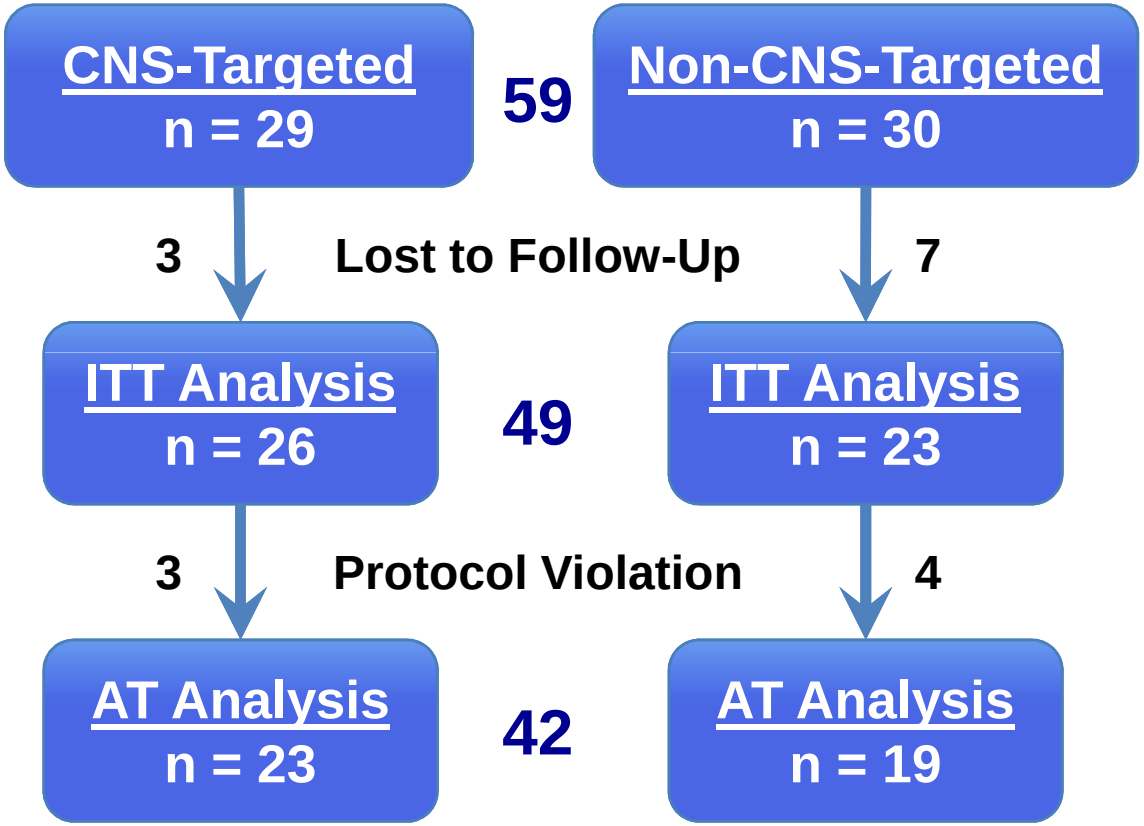
First Author	Sample Size	Percent with CSF VE	ART Correlates
Rawson[1]	142	**21%**	↓ CPE
Cusini[2]	60	**6.7%**	↓ CPE
Dravid[3]	1236	**1.0%**	↓ CPE
Edén[4]	69	**11.0%**	Not ZDV
Perez-Valero[5]	1,264	**4.4%**	PI/r Use ATV Use
Pinnetti[6]	303	**10.6%**	ATV/r Use ABC+3TC Use
Edén[7]	373	**10.0%**	Not Noted
Average		**9.2%**	

[1]Rawson et al, Journal of Infection (2012) 65, 239e245; [3]Cusini et al, J Acquir Immune Defic Syndr 2013, 62:28–35; [3]Dravid et al, EACS Conference, 2015; [4]Eden et al, J Infect Dis 2010, 2010; 202(12):1819–1825; [5]Perez-Valero et al, J Intl AIDS Soc 2012, 15(Suppl 4):18189; [6]Pinnetti et al, CROI 2014, Abstract 443; [7]Eden et al, CROI 2014, Abstract 445

Published case series/reports of CSF Viral Escape:

Canestri et al, CID 2010; Peluso et al, AIDS 2012; Khoury et al, J Neurovirol 2013

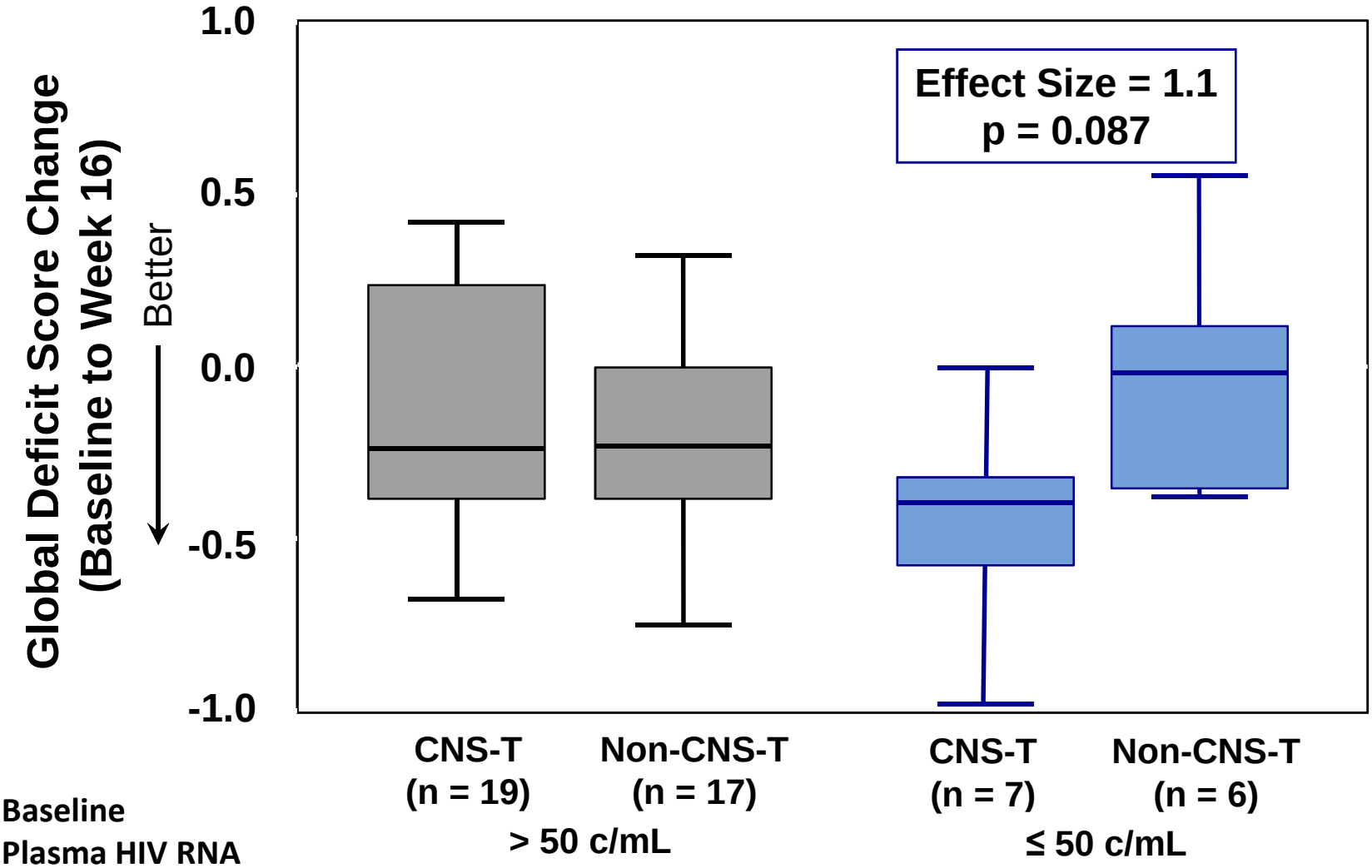
Cognitive Intervention Trial 2: Only Enrolled Half of Planned 120



ITT = Intent-to-treat
AT = As treated

Ellis et al, Clin Infect Dis. 2014; 58(7):1015-22

Possible Benefit in Those Who Changed ART with Viral Suppression



Ellis et al, Clin Infect Dis. 2014; 58(7):1015-22

The relationship of CPE to HIV dementia

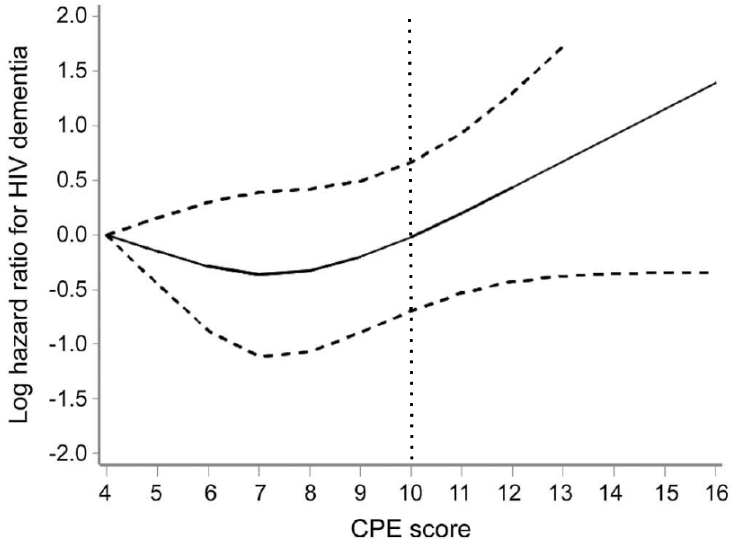
Slain by an ugly fact?

Design

- Data from 61,938 patients from 9 European and U.S. cohorts
- Evaluated prior to ART initiation between 1998 and 2013
- "Intent-to-treat"-like analysis based on initial regimen
- CPE transformed into 3 categories: ≤ 7, 8-9, ≥ 10

Major Findings

- 235 "HAD" events in 259,858 person-years of follow-up
  - 1 per 1,106 person-years
- "High" CPE group had a 74% increased hazard ratio of "HAD"



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?

- **Enriched for HAD by excluding 4 cohorts that had no HAD events**
- **Did not use standardized assessments for diagnosing "HAD"**
  - "…diagnostic procedures that reflect standard clinical practice"
- **Between-group difference in absolute risk is not clinically meaningful:** 1 "HAD" case per > 4,500 person-years of follow-up
- **Did not account for influential factors:**
  - **Changes in ART over time: 68% changed their initial regimen during observation**
  - Non-HIV causes of neurocognitive disease: psychiatric disease, substance use, co-infections
- **Categorical transformation of CPE is unusual**
  - Only 8.8% were in the "high CPE" group (≥ 10)
  - No statistically significant association was found when CPE was analyzed continuously or as a 4-category variable

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

Ideal **Characteristics of Analyses of CNS Effectiveness of ART**

- **Randomized and longitudinal**
- **Adequate power and follow-up duration**
- **Standardized and comprehensive assessments**
- **Similar drug potency and toxicity**
  - For those that focus on CPE, regimens should have the same number of drugs

Arms were Comparable at Baseline

	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 (%)*

Zhang et al, CROI 2015, Abstract 56

On Treatment, Indicators of Antiviral Efficacy Were Comparable

Week 48 (ITT-Completer)

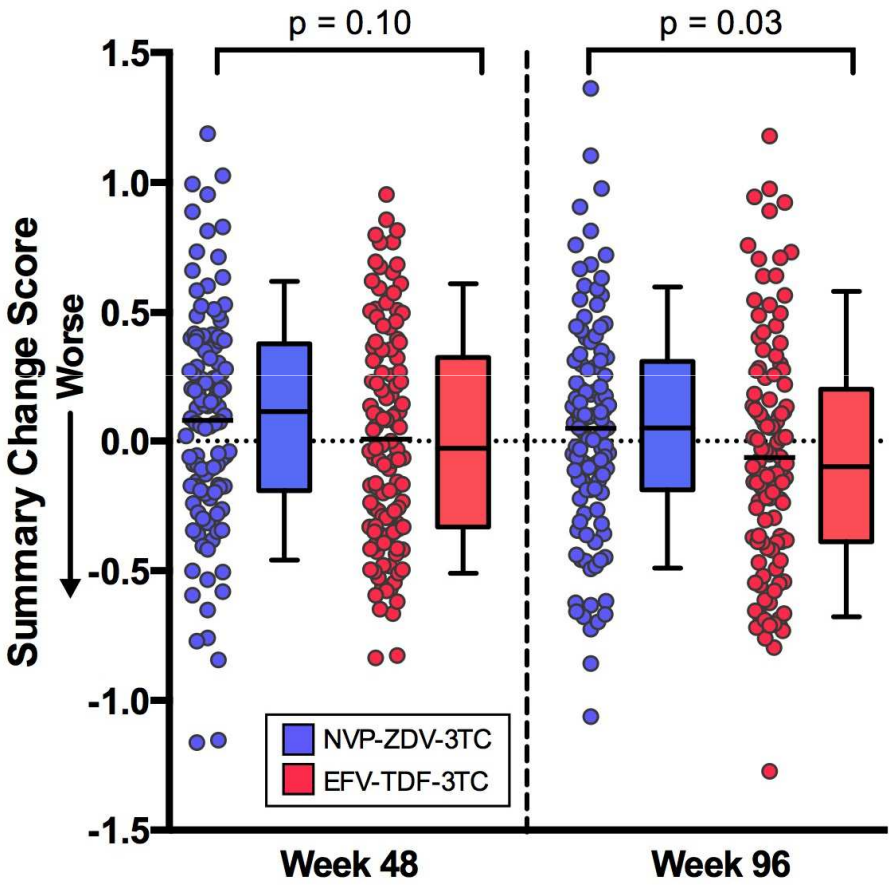
	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	114	119	-
HIV RNA, Plasma (No. (%) ≤ 50 c/mL)	103 (91.2%)	109 (91.6%)	1.00
CD4+ T-cells (/µL)	396.6 (158.0)	396.5 (153.4)	1.00
CD8+ T-cells (/µL)	789.4 (368.0)	760.5 (360.8)	0.54
100% Adherence in Past 4 Days	113 (99.1%)	119 (100%)	0.49

Week 96 (ITT-Completer)

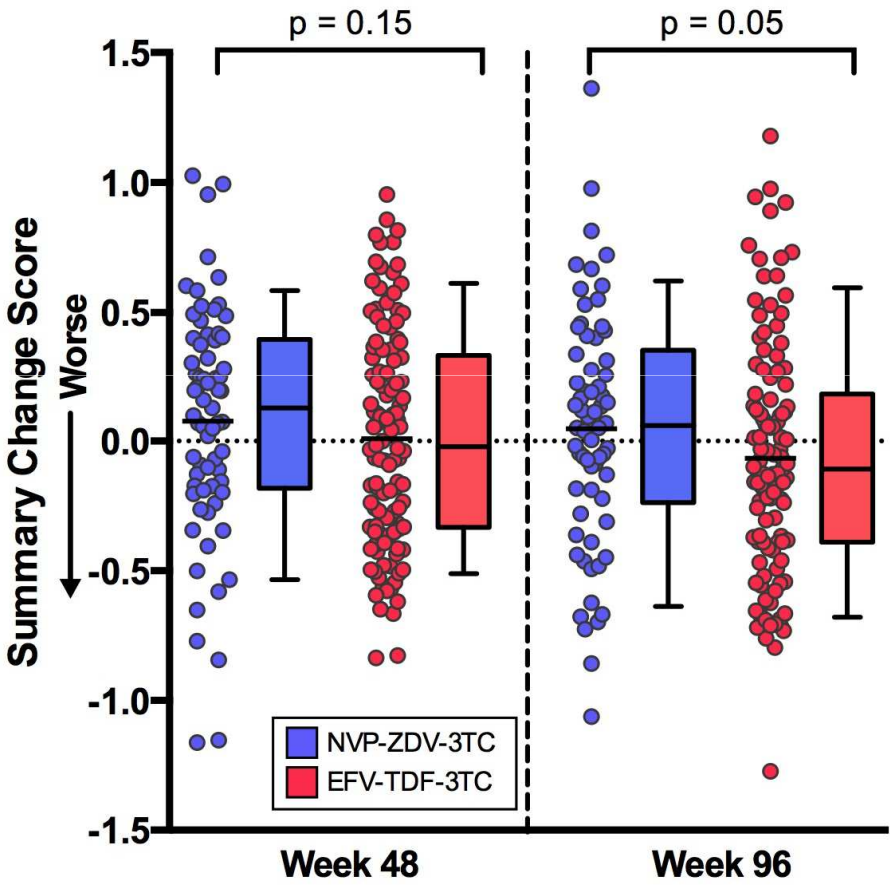
	NVP-ZDV-3TC	EFV-TDF-3TC	P Value
Sample Size	112	118	-
HIV RNA, Plasma (No. (%) ≤ 50 c/mL)	104 (92.0%)	112 (95.7%)	0.28
CD4+ T-cells (/mm^3)	447.2 (179.3)	483.8 (183.8)	0.13
CD8+ T-cells (/mm^3)	811.3 (322.4)	850.6 (408.7)	0.42
100% Adherence in Past 4 Days	112 (100%)	116 (100%)	1.00

**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

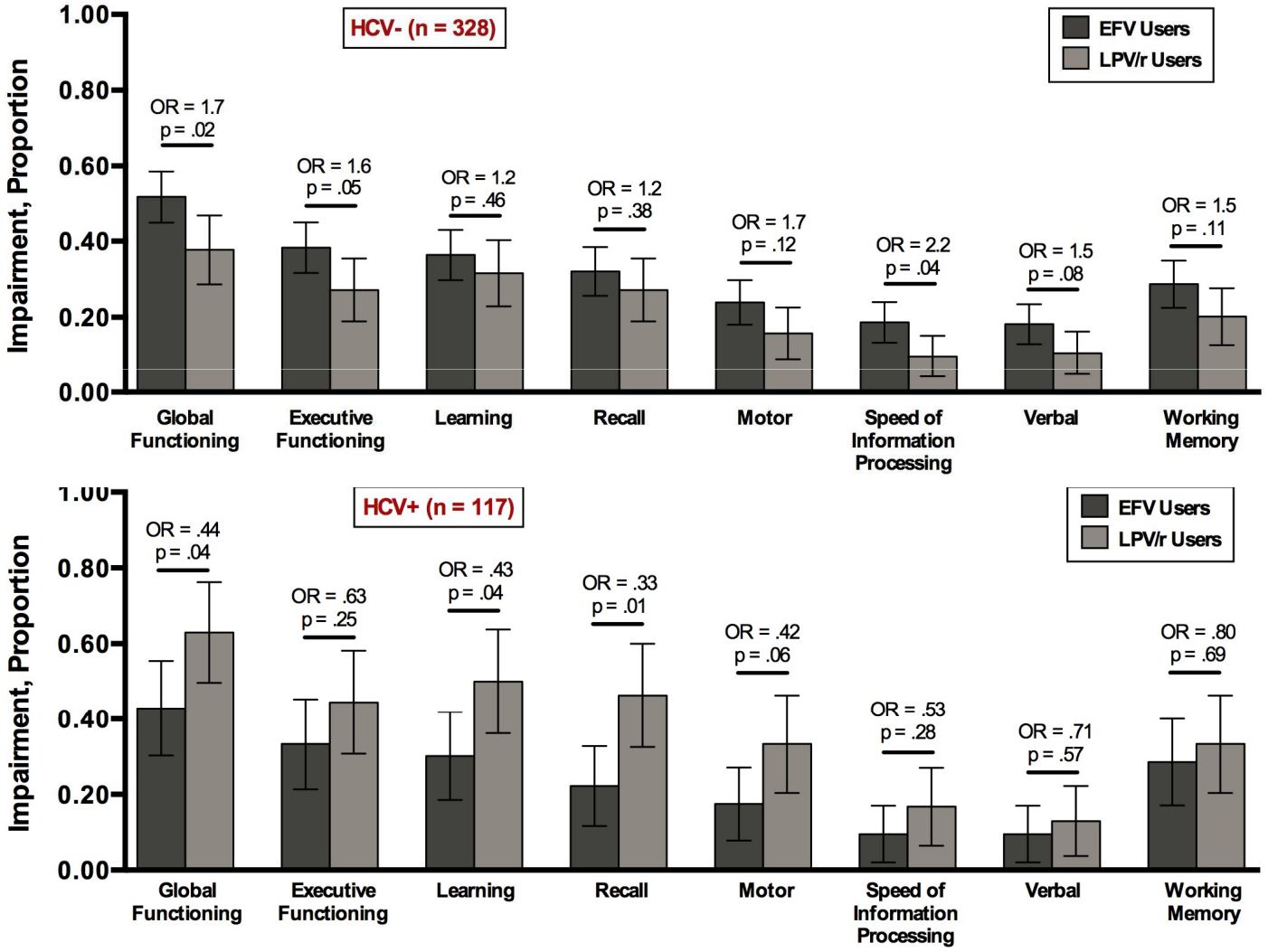
Zhang et al, CROI 2015, Abstract 56

Other Drug Characteristics May Influence the Effects of ART on the CNS

- **Distribution of ART drugs into the brain**
  - CSF may not be equivalent to brain
- **Timing of ART initiation**
  - ART initiated at higher CD4 counts may better prevent HAND
- **Toxicity**
  - Directly in the brain
  - Indirectly, e.g., vascular disease
- **Efficacy in different cell types**
  - Macrophages are the target cells in the brain
- **Host factors**
  - Aging changes in drug metabolism & distribution
  - Blood-brain barrier permeability

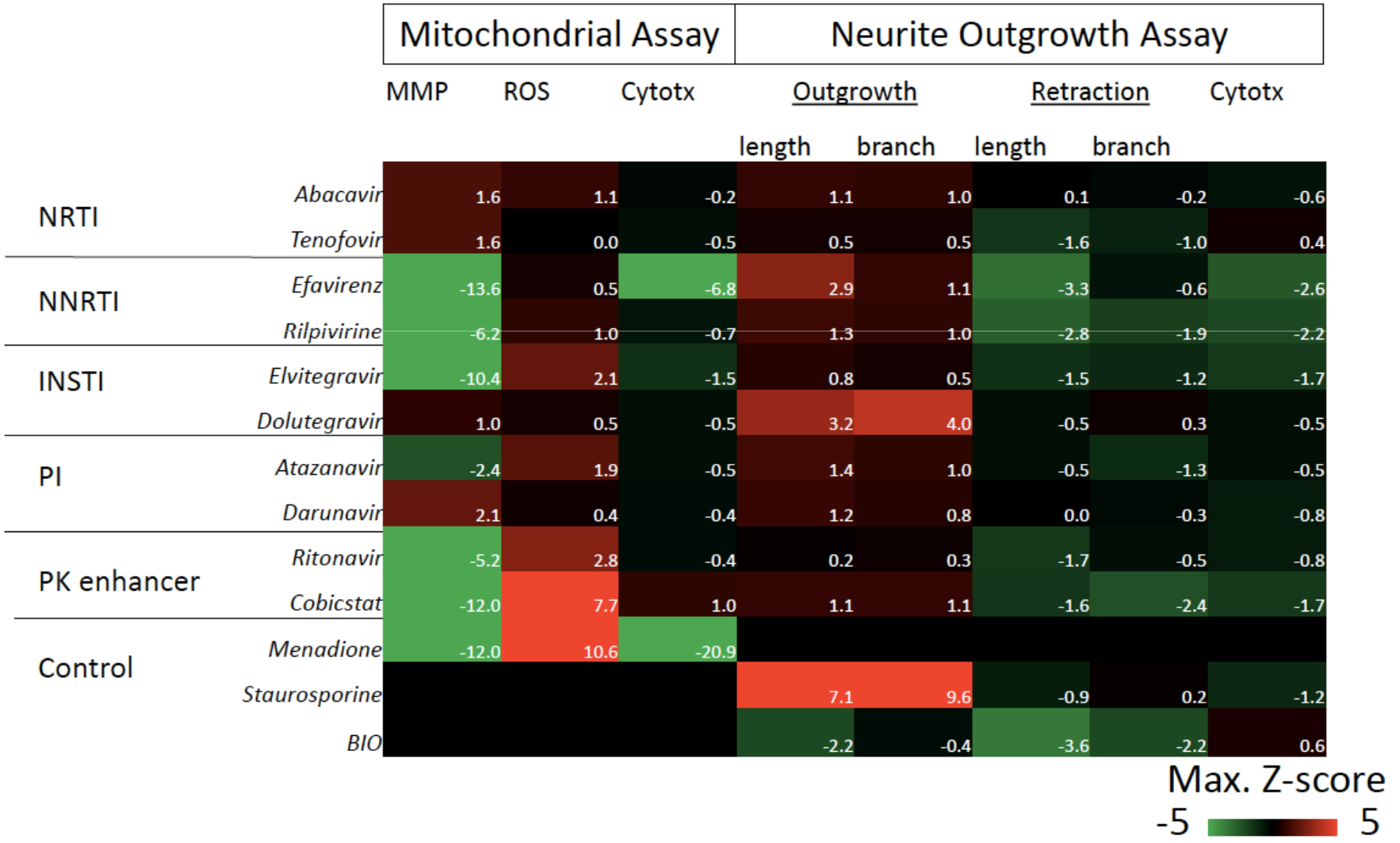
UCSanDiego

Protease Inhibitors May be More Neurotoxic with HCV Co-infection



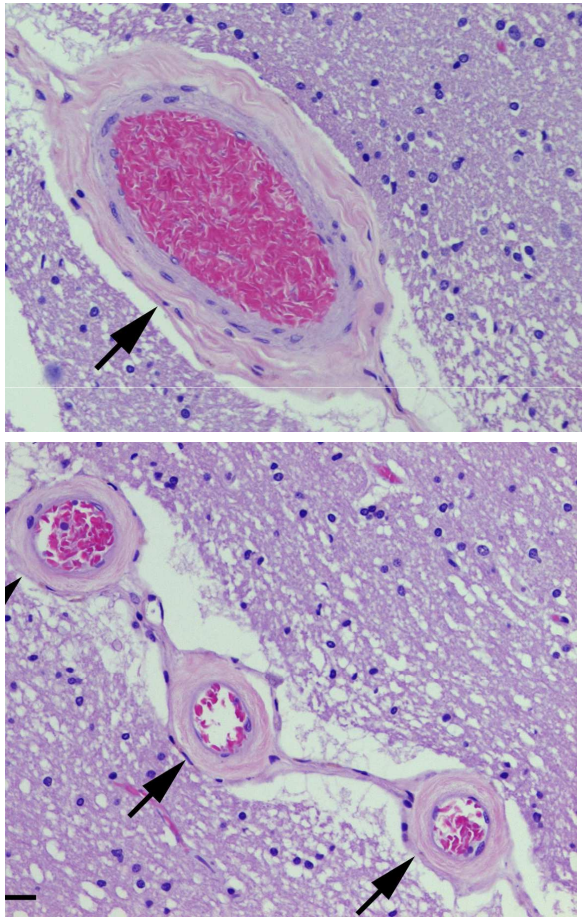
Ma et al, J. Neurovirol. (2016) 22:170–178

Neurotoxicity Screening of ART Drugs With Human Neurons



Hinckley et al, CROI 2016, Abstract 395

Protease Inhibitor Use is Associated with Cerebral Small Vessel Disease



- **Protease inhibitors were associated with cerebral small vessel disease at autopsy**
  - Mild: **OR 2.8** (95% CI 1.03–7.9)
  - Moderate-severe: **OR 2.6** (95% CI 1.03–6.7)
- **Mild cerebral small vessel disease was associated with neurocognitive impairment**
  - **OR 4.8** (95% CI 1.1–21.2)

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

Controversies in HIV-associated neurocognitive disorders

Sam Nightingale, Alan Winston, Scott Letendre, Benedict D Michael, Justin C McArthur, Saye Khoo, Tom Solomon

HAND is common in the era of effective ART

For

- **Well powered, observational studies have found prevalence of up to 60% in HIV+ adults with access to ART**
- **Most patients have asymptomatic disease**
- **Some studies that found high prevalence used a thorough neurocognitive evaluation and matched control data**
- **Prevalence of cognitive impairment is high in subpopulations with few neuropsychiatric comorbidities**

Against

- **Prevalence estimates depend on the use of appropriate norms**
  - Some studies did not have an appropriate normative population
- **Using current criteria, ~14% of those at the lower end of cognitive functioning in a normative population will be classified as impaired**
  - HIV-related neuropathology is not necessarily the cause
- **Some studies found patients taking long-term ART who do not have other conditions that affect cognitive function to be similar to HIV- adults**

Lancet Neurol 2014; 13: 1139–51

Severity and Daily Functioning Differentiate HAND Syndromes

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

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