Antiretroviral Therapy for Prevention and Management of HIV-Associated Neurocognitive Impairment: What is really changing?

Scott Letendre, M.D.

Associate Professor of Medicine

University of California, San Diego

To Understand Where We Are Going, We Must Understand Where We Have Been

-Multiple versions attributed to multiple authors

Portegies Group Publishes Review of CSF Pharmacology in Early HAART Era

Drug	% Protein binding	Oil/water partition coefficients	Molecular weight (Da)	IC_{50} (μmol/l)
Nucleoside analogues				
Zidovudine	34–38	1.1	267	0.01–0.05
Stavudine	Negligible	0.144	224	0.05–0.5
Zalcitabine	< 4		211	0.03–0.5
Didanosine	< 5	0.055	236	1.0–2.5
Lamivudine	< 36		229	0.003–0.09
Abacavir	49		404	0.26
Protease inhibitors				
Saquinavir	98	4.1 $\log_{10}$	767	0.002–0.007
Ritonavir	98–99		721	0.045
Indinavir	61	2.6 $\log_{10}$	712	0.025–0.1
Nelfinavir	> 99	5.7 $\log_{10}$	568	0.022
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine	60	1.8 $\log_{10}$	266	0.01–0.1
Efavirenz	46		316	0.03*
Delavirdine	98		516	0.066

Enting et al, AIDS 1998; 12: 1941-55

Early Evaluation of CSF/IC_{50} Ratios Suggested 3 Categories

	Molecular Weight	Protein Binding	ARV Concentrations Plasma Cmax	ARV Concentrations CSF	ViroLogic IC50	CSF / IC50 Low	CSF / IC50 High	CSF / IC50 Median
Nucleoside Analogue Reverse Transcriptase Inhibitors								
Zidovudine	267	34-38	4.49-6.74	0.12-0.41	0.01-0.04	3.0	41	22
Abacavir	404	49	5.2-10.89	0.5-1.83	0.24-1.49	0.34	7.6	4.0
Lamivudine	229	< 36	4.37-8.74	0.05-1.14	0.78-4.90	0.01	1.5	0.74
Stavudine	224	"Negligible"	3.35-6.43	0.20-0.36	0.34-2.12	0.09	1.1	0.58
Didanosine	236	< 5	2.12-11	0.17-0.51	2.53-15.84	0.01	0.20	0.11
Zalcitabine	211	< 4	0.05-0.18	0.003-0.03	0.19-1.22	0.00	0.16	0.08
Non-Nucleoside Analogue Reverse Transcriptase Inhibitors								
Nevirapine	266	60	7.52-16.92	1.3-10.9	0.023-0.142	8.9	474	241
Delavirdine	516	98	15-55	0.02-0.22	0.0006-0.0036	5.6	367	186
Efavirenz	316	99.5	9.2-16.6	0.006-0.09	0.008-0.052	0.12	11	5.7
Protease Inhibitors								
Indinavir	712	60	12.2-13.0	0.03-0.66	0.0031-0.0195	1.5	213	108
Amprenavir	506	90	10.6-19.2	BDL*-0.36	0.0046-0.0289	0	78	39
Nelfinavir	568	> 99	5.63-8.45	BDL*-0.012	0.0014-0.0088	0	8.6	4.3
Saquinavir	767	98	1.85-3.23	BDL*-0.008	0.001-0.006	0	8.0	4.0
Ritonavir	721	98-99	10.5-26	BDL*-0.032	0.0049-0.0308	0	6.5	3.3

Letendre, et al. 8th CROI 2001, Abstract 614

Pre-CPE comparisons of estimated CNS distribution to HIV RNA in CSF

Author	Year	Design	N	Effect	Penetration Measure
Letendre	2004	P	31	**Lower**	No. of penetrators
Eggers	2003	P	40	Similar	Multiple methods
Marra	2003	P	25	Similar	ZDV, IDV
Antinori	2002	P	29	**Lower**	≥ 3 Penetrators
DeLuca	2002	P	50	**Lower**	No. of penetrators
Gisolf	2000	P	27	**Lower**	SQV-r+d4T vs. SQV-r
Murphy	2000	P	27	**Lower**	APV-ZDV-3TC vs. APV
von Giesen	2005	C-S	71	Similar	ZDV, d4T
Solas	2003	C-S	41	Similar	IDV
Lafeuillade	2002	C-S	41	Similar	IDV vs. LPV-r or NFV
Robertson	2002	C-S	98	Similar	No. of penetrators
Antinori	2002	C-S	75	**Lower**	IDV
DeLuca	2002	C-S	134	Similar	No. of penetrators

- Method of estimating CNS distribution varied substantially
- Results were mixed but prospective analyses were more likely to link greater distribution to lower HIV RNA levels

Pre-CPE comparisons of estimated CNS distribution to NP performance

Author	Year	Design	N	Effect	Penetration Measure
Letendre	2004	P	31	**Better**	No. of penetrators
Cysique	2004	P	97	**Better**	≥ 3 Penetrators
Evers	2004	P	110	**Better***	Multiple methods
Robertson	2004	P	29	Similar	No. of penetrators
Sevigny	2004	P	147	Similar	No. of penetrators
Marra	2003	P	25	**Better**	ZDV, IDV
Chang	2003	P	33	Similar	≥ 2 Penetrators
Dougherty	2002	P	30	**Better***	Single vs. Multiple
Sacktor	2001	P	73	Similar	Single vs. Multiple
von Giesen	2005	C-S	71	Similar	ZDV, d4T
Antinori	2004	C-S	165	Similar	No. of penetrators
Evers	2004	C-S	306	**Better**	Multiple methods

- Both CNS distribution estimates and NP methods varied
- Relatively fewer studies reported benefit but again more likely if prospective or larger

Drug Characteristics

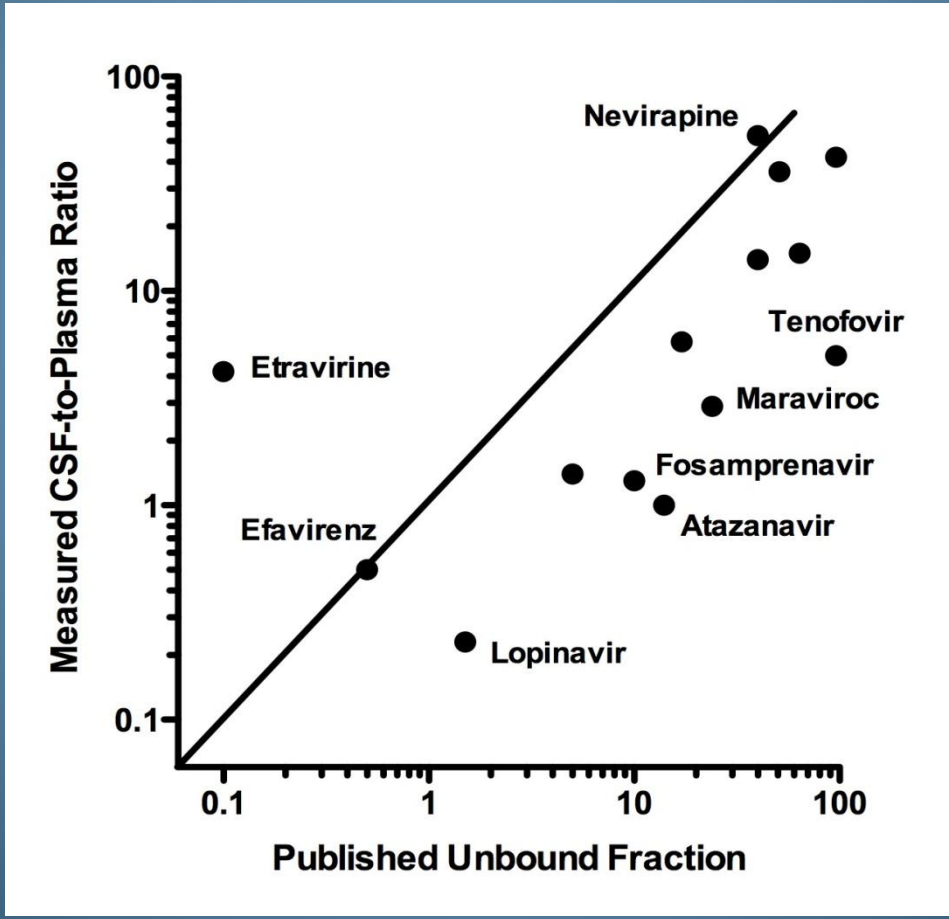
Protease Inhibitors

	IDV	LPV	DRV	ATV	APV	SQV	TPV
Unbound Fraction	40%	1%	5%	14%	10%	2%	< 0.1%
Molecular Weight							
Octanol-Water Coeff. (KowWin)							
Acid Dissociation Constant (pK_a)							
Est. [Drug] $_{CSF}$ (nM)*							
CSF IQ**							

** Unbound Fraction x Plasma C_{min}*

*** Est. CSF [Drug] / IC_{50}*

Estimates Based on Plasma Protein Binding Tend to Overestimate CSF Concentrations



Refining an Approach for Comparison

- Enting et al. suggested a standard for judging the extent of antiretroviral distribution into CSF
  - » Protein binding < 90%: Only 2 PIs meet this standard
  - » Molecular weight < 500: No PIs meet this standard
- The CPE was based on traditional HAART (2 NRTIs + PI or NNRTI)
  - » Relative approach *within class*
  - » Limited to human adult data
  - » Three categories instead of two
  - » Simple method of combining estimates for a combination regimen

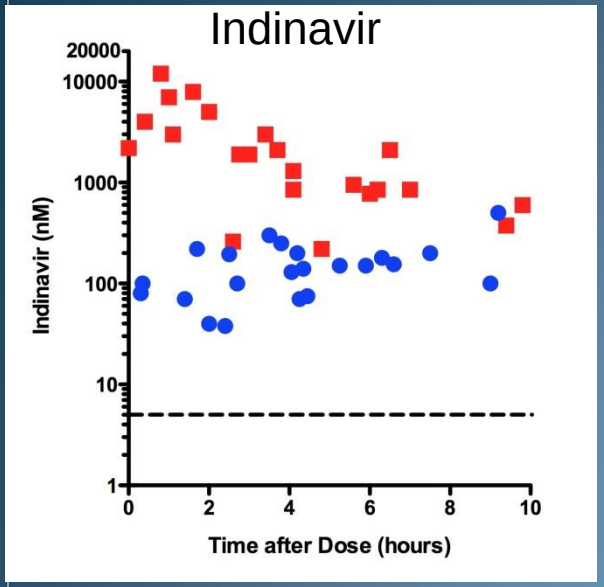
CPE Tabulation
Protease Inhibitors

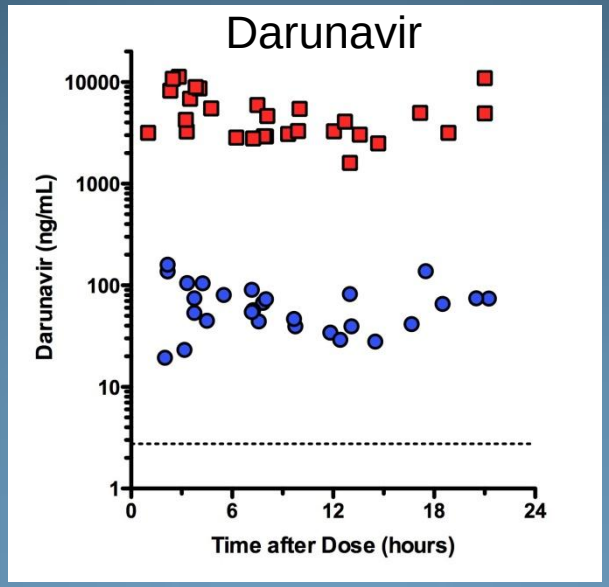
	IDV	LPV	DRV	ATV	APV	SQV	TPV
Drug Characteristics	1	0.5	0.5	1	0.5	0.5	0
Pharmacokinetics							
Pharmacodynamics							
Overall							

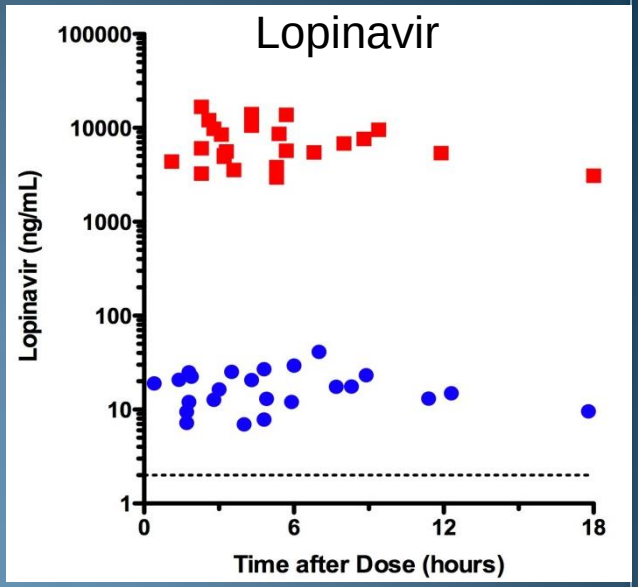
Early CSF Pharmacology Data

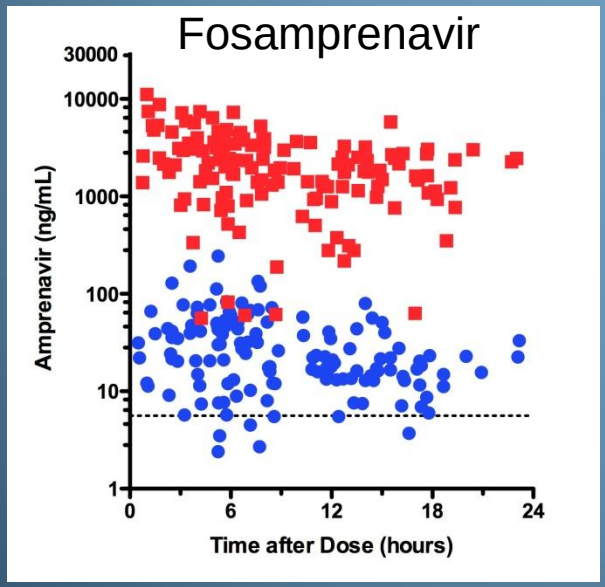
- **Saquinavir** in CSF below 0.29 nM in 26 of 28 individuals[1]
- **Nelfinavir** in CSF below 88 nM in 12 individuals[2]
- **Ritonavir** in CSF below 34.5 nM in 19 of 22 individuals[3]

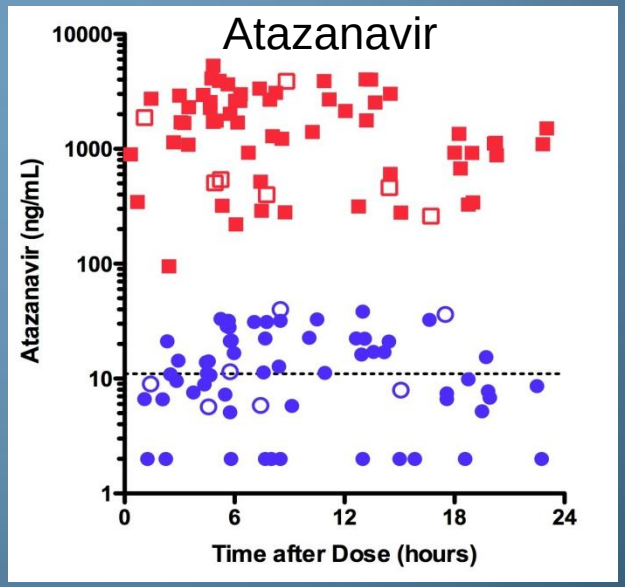
[1]Kravcik et al, JAIDS 1999
[2]Lafeuillade et al, HIV Clin Trials 2002
[3]Gisolf et al, AIDS 2000











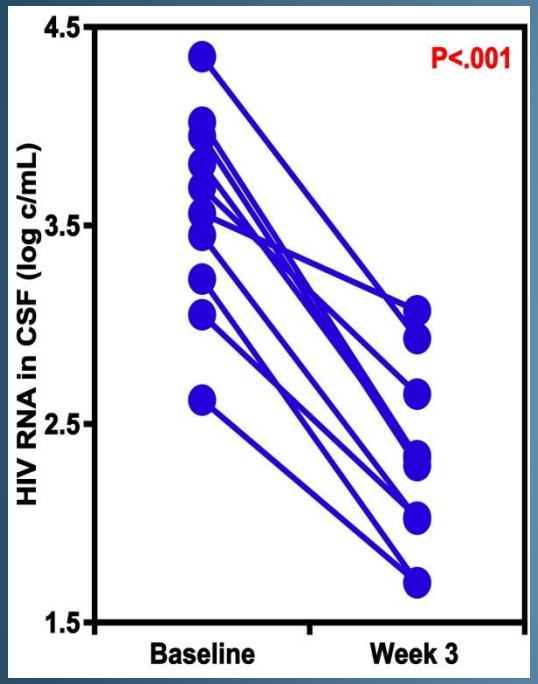
Best et al, AIDS 2009; 23: 83-87; Capparelli et al, AIDS 2005; 19:949–952; Letendre et al, 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2009; Letendre et al, 9th Intl Workshop on Clinical Pharmacology of HIV Therapy, 2009; Letendre et al, Antimicrobial Agents and Chemotherapy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

CPE Tabulation
Protease Inhibitors

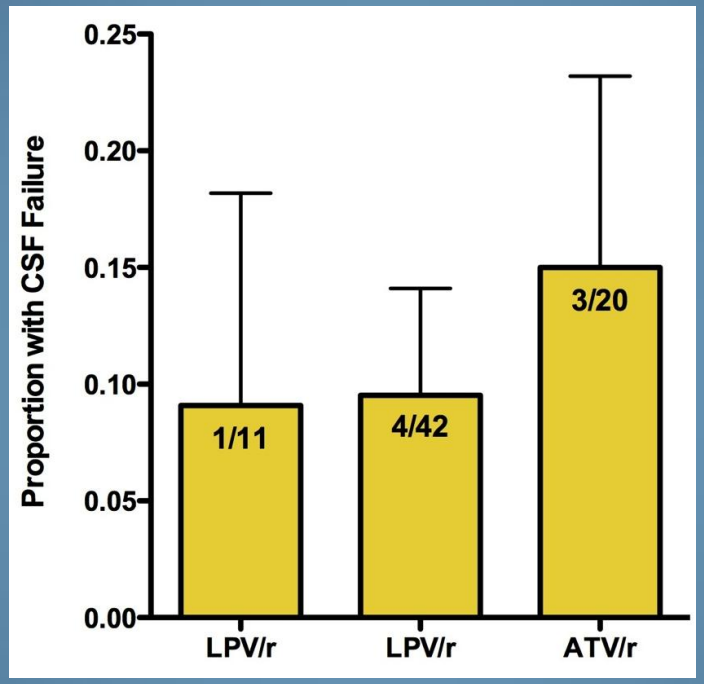
	IDV	LPV	DRV	ATV	APV	SQV	TPV
Drug Characteristics	1	**0.5**	**0.5**	**1**	0.5	**0.5**	0
Pharmacokinetics	1	**1**	**1**	**0.5**	0.5	**0**	-
Pharmacodynamics							
Overall							

Pharmacodynamics in the CNS

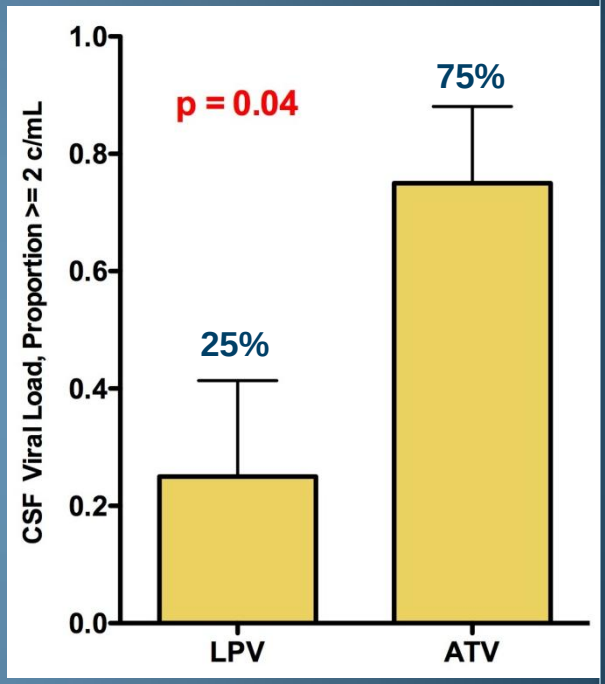
Protease Inhibitor Examples



Letendre et al., Clinical Infectious Diseases, 2007



Yeh et al, 14th CROI 2006, Abstract 381
Gutmann et al, AIDS 2010, 24: 2347-54
Vernazza et al, AIDS 2007, 21: 1309-15



Letendre et al, 14th CROI 2007, Abstract 369

CPE Tabulation
Protease Inhibitors

	IDV	LPV	DRV	ATV	FPV	SQV	TPV
Drug Characteristics	1	0.5	0.5	1	0.5	0.5	0
Pharmacokinetics	1	1	1	0.5	0.5	0	-
Pharmacodynamics	-	1	-	0.5	-	0	-
Overall	**1**	**1**	**1**	**0.5**	**0.5**	**0**	**0**
Strength of Evidence	PK	**PD**	PK	**PD**	PK	**PD**	DC

- Most drugs do not have Pharmacodynamic data
- Pharmacodynamic data do not typically alter the Pharmacokinetic categorization

Drug Characteristics
Nucleoside/Nucleotide RTIs

	ZDV	ABC	FTC	3TC	D4T	DDI	TDF
Drug Characteristics	0.5	0.5	1	1	1	0	1
Pharmacokinetics	1	0.5	1	0.5	0.5	0.5	0
Pharmacodynamics	1	0.5	-	-	-	0.5	-
Overall	**1**	**0.5**	**1**	**0.5**	**0.5**	**0.5**	**0**
Strength of Evidence	**PD**	**PD**	PK	PK	PK	**PD**	DC

Drug Characteristics
Non-Nucleoside RTIs

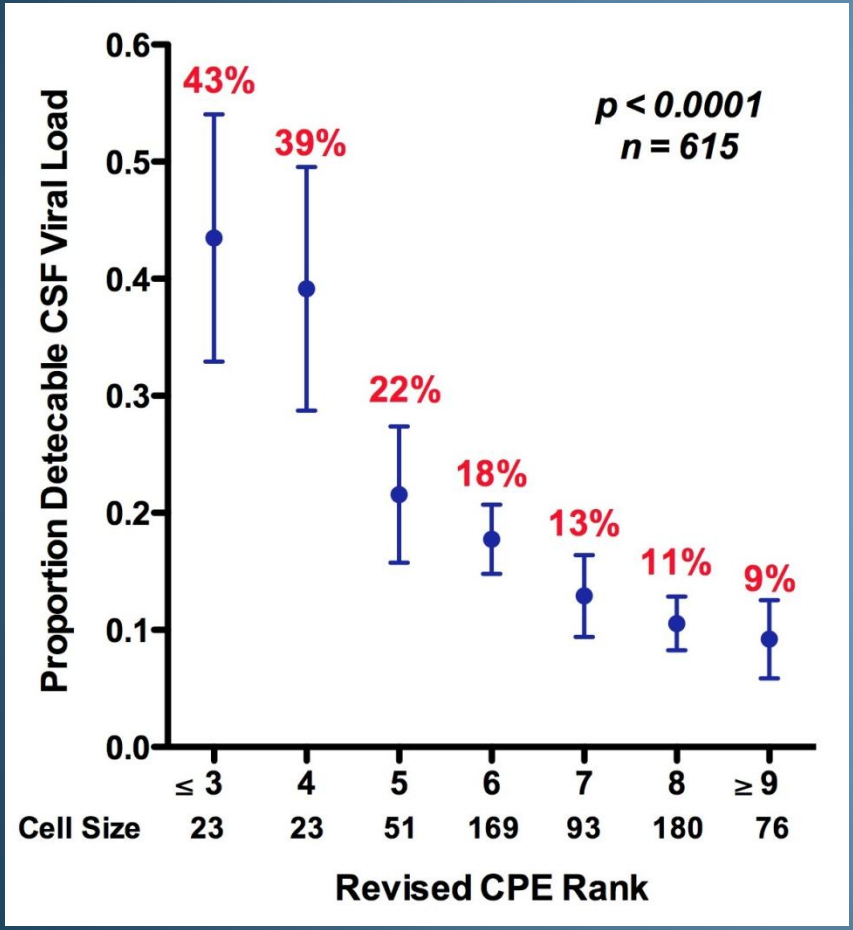
	NVP	EFV	ETR	RPV
Drug Characteristics	1	0.5	0	0.5
Pharmacokinetics	1	0.5	0.5	-
Pharmacodynamics	-	-	-	-
Overall	**1**	**0.5**	**0.5**	**0.5**
Strength of Evidence	PK	PK	PK	DC

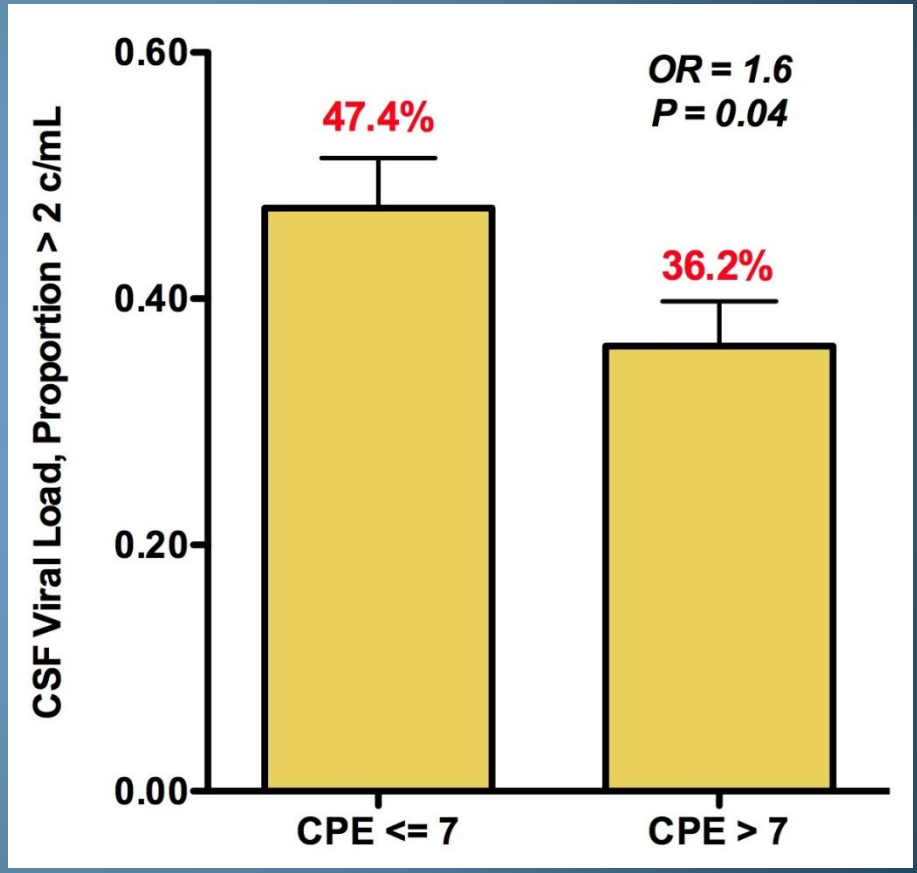
CNS Penetration Effectiveness Ranks 2010

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

Letendre SL, et al. 17th CROI 2010, Abstract 172

Higher CPE Values Are Associated with Lower HIV RNA Levels in CSF



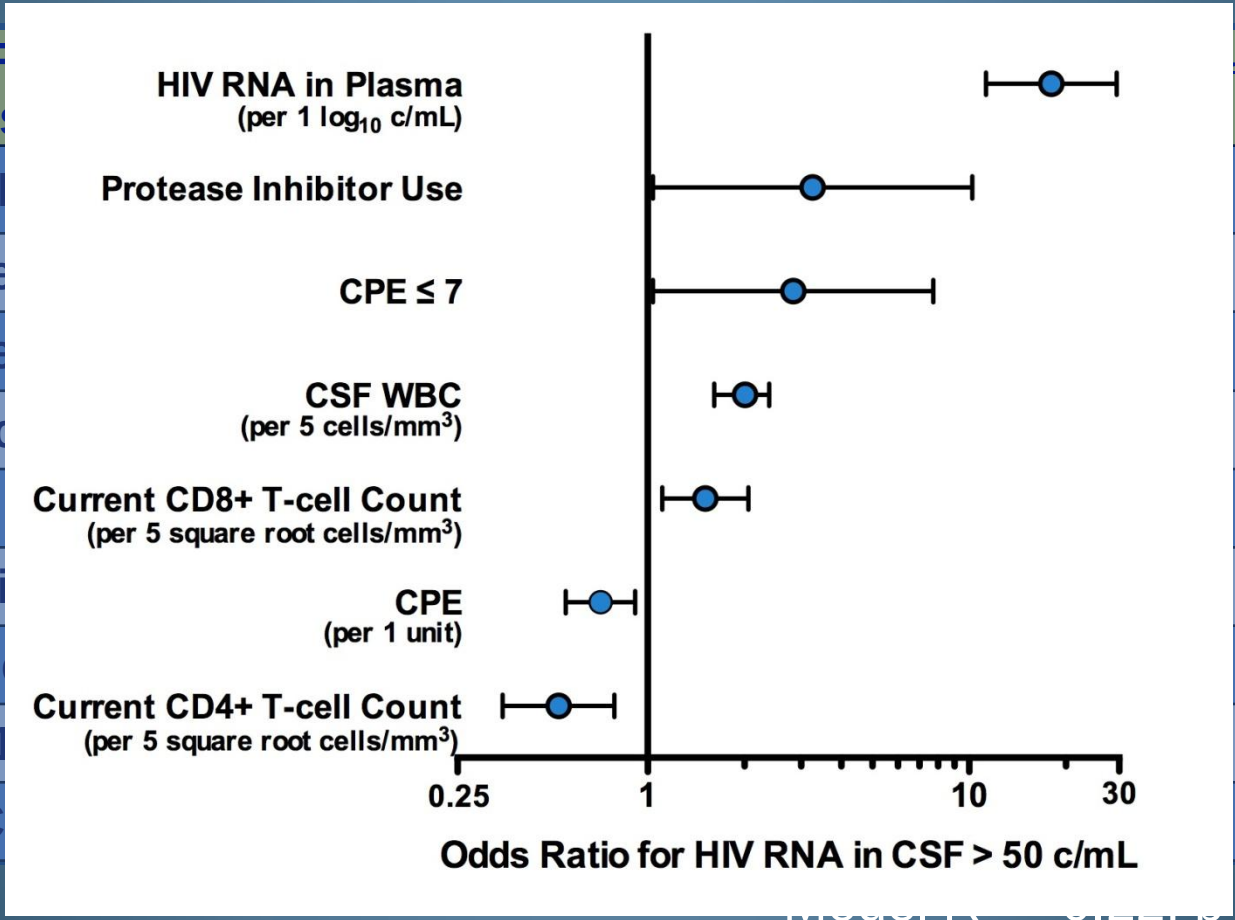


Letendre S et al, 17th CROI 2010, Abstract 172

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

Correlates of Detectable CSF Viral Loads Over Time During ART

2,207 CSF Volunteers	riable P
Plasma HI	< 0.0001
CD4+ T-ce	0.002
CD8+ T-ce	0.009
Duration c	-
CPE 2010	0.008
Protease i	0.04
Adherenc	-
Age (per 1	-
CSF WBC	< 0.0001

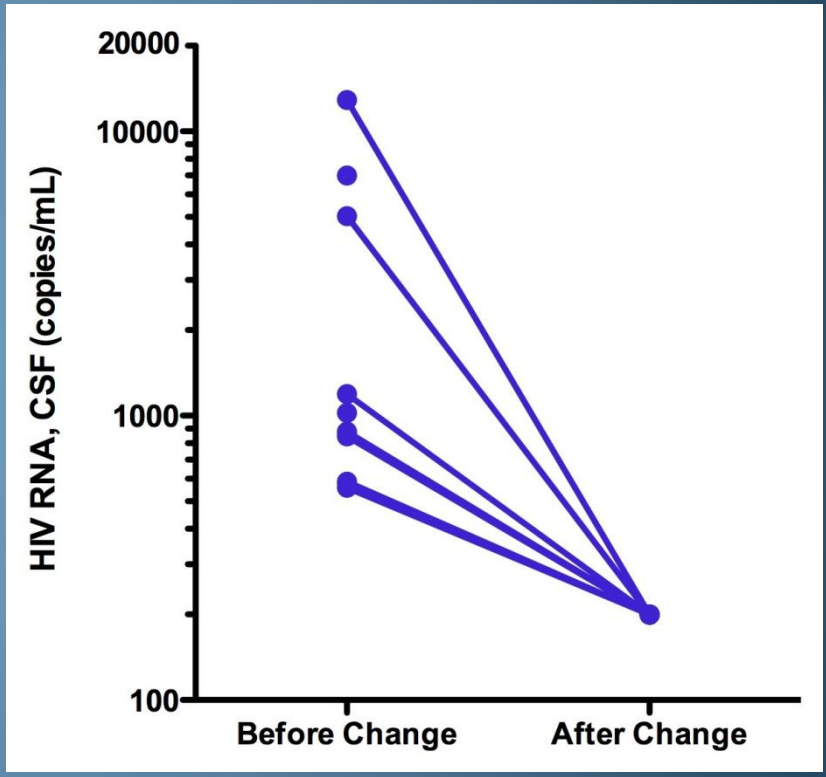


< 0.0001

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

Lower CPE may also be Associated with "Viral Escape" in CSF during ART

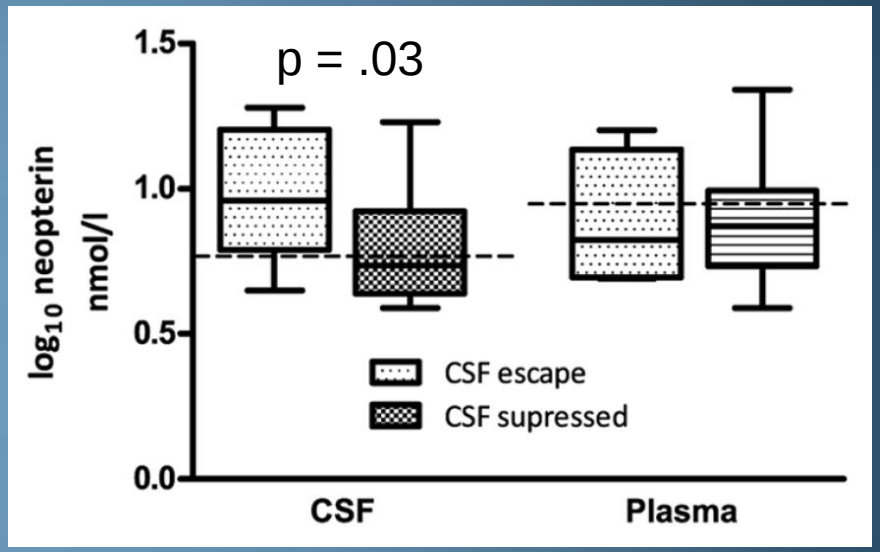
- 11 patients with new neurological symptoms and CSF viral escape during ART
- Drug resistance mutations found in CSF in 7 of 8
- ART modified based on drug resistance testing and CPE
- All patients clinically improved with reduction of HIV in CSF



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

“Viral Escape” in CSF also Occur without Symptoms

- 69 individuals on 2 NRTIs with either EFV, LPV/r, or ATV/r with HIV RNA in plasma <50 c/ml for >6 months
- 11% had CSF viral escape
  - HIV RNA up to 213 c/ml
  - No association with CPE but viral escape did not occur in anyone taking ZDV or LPV/r



Edén et al, J Infect Dis. 2010;202:1819-1825.

CSF "Viral Escape" in Patients Undergoing LP for Clinical Indications

- 142 HIV+ individuals undergoing LP in London between 2008 and 2010
- CSF viral escape* was present in 30 (21%)
  - » 13% when plasma HIV RNA < 50 c/mL
- When plasma HIV RNA < 50 c/mL, only CPE was associated with detectable CSF HIV RNA (p = 0.04)

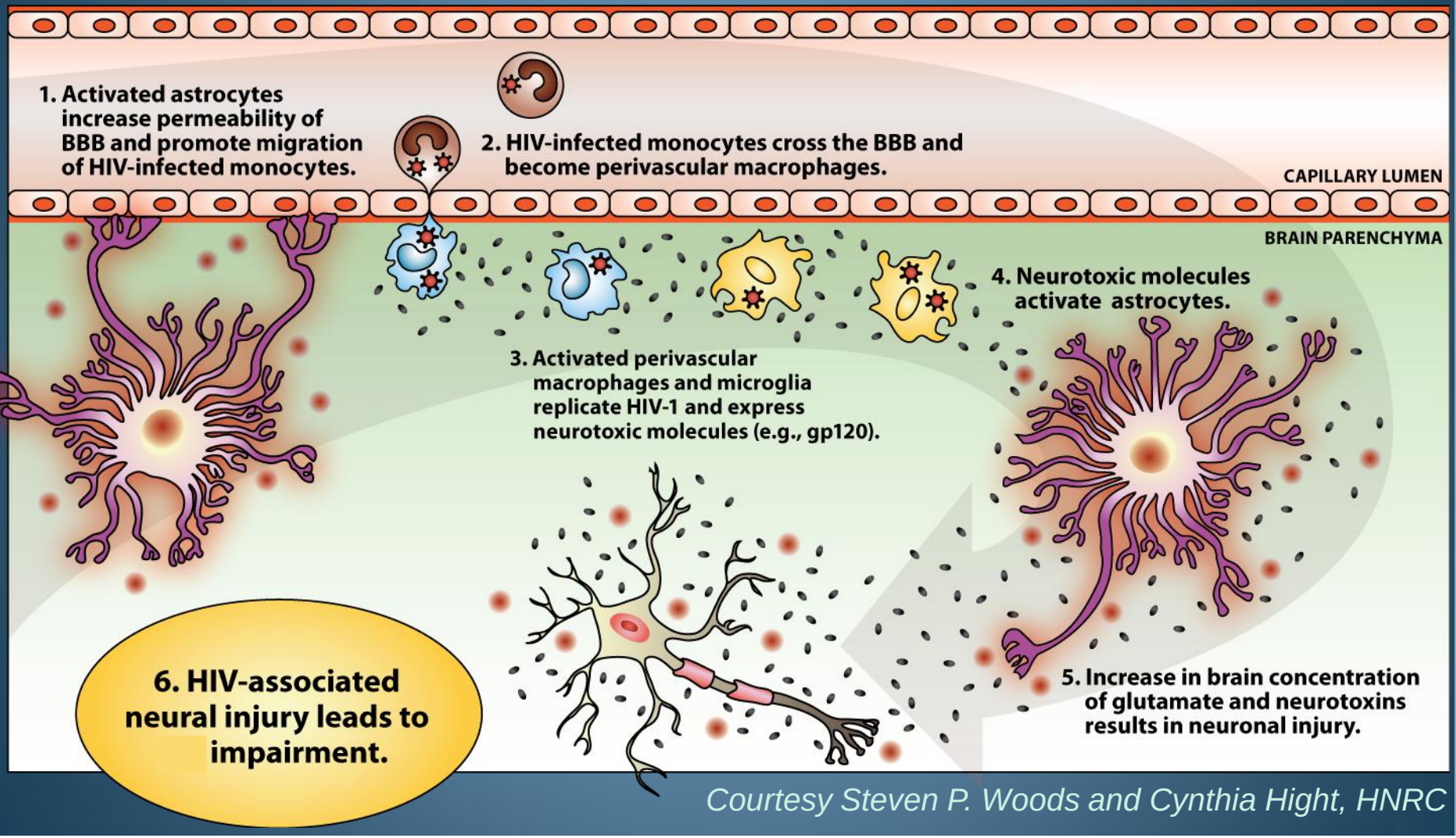
Factors Associated with CSF HIV RNA in subjects with suspected HIV encephalopathy

	β	p
Plasma HIV RNA	0.438	0.02
Age	-0.095	0.17
CPE	-0.511	0.003

* Defined as CSF RNA > 0.5 $\log_{10}$ c/mL greater than plasma HIV RNA or CSF RNA > 200 c/mL when plasma HIV RNA < 50 c/mL

Rawson T, et al., J Infect (2012), doi:10.1016/j.jinf.2012.04.007

Model of HIV Neuropathogenesis



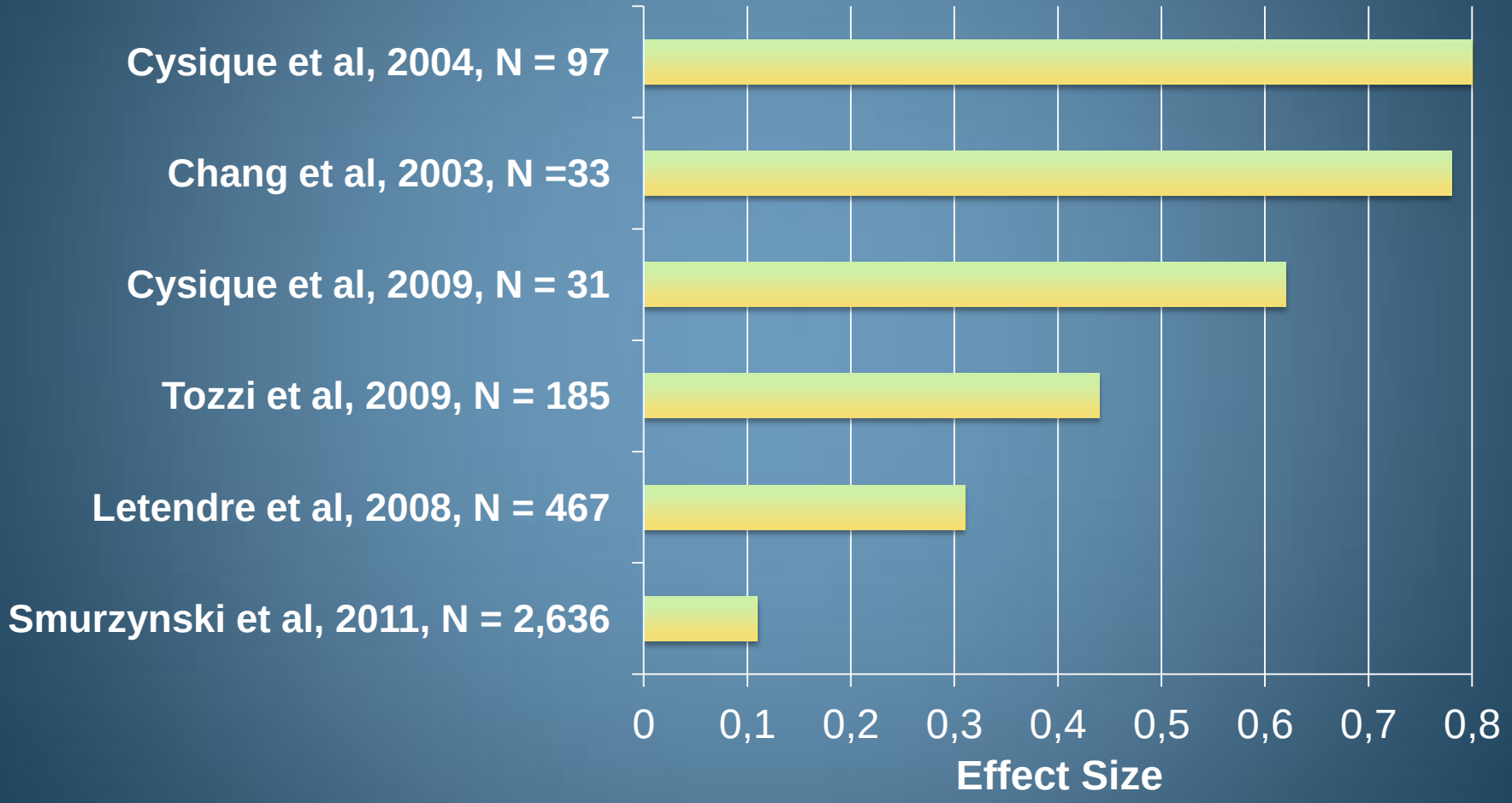
Courtesy Steven P. Woods and Cynthia Hight, HNRC

HAND is Composed of 3 Disorders Which May Not Have Common Pathogenesis

	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	✔	✔

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

Published Studies of Acceptable Quality had Mostly Medium to Large Effect Sizes



Cysique et al, BMC Neurology, 2011 Nov 22;11:148

Summary of Comparisons of CPE to Different Outcomes

Outcome	Findings	Influences
CSF HIV RNA	Associated with CPE Cross-Sectionally and Longitudinally	Number of ARVs Drug Resistance
Host CSF Biomarkers	Limited Analyses	Detectable HIV RNA
Imaging Biomarkers	Limited Analyses	None Identified
HAND	Mixed Findings	Many Modifiers
Survival	Mixed Findings	Detectable HIV RNA, Date

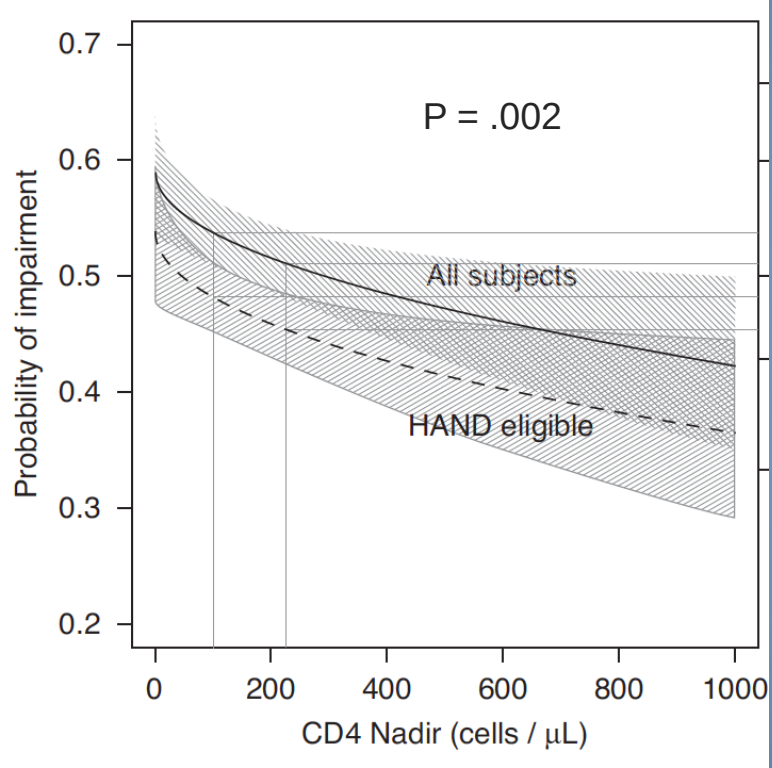
Mitigating Circumstances

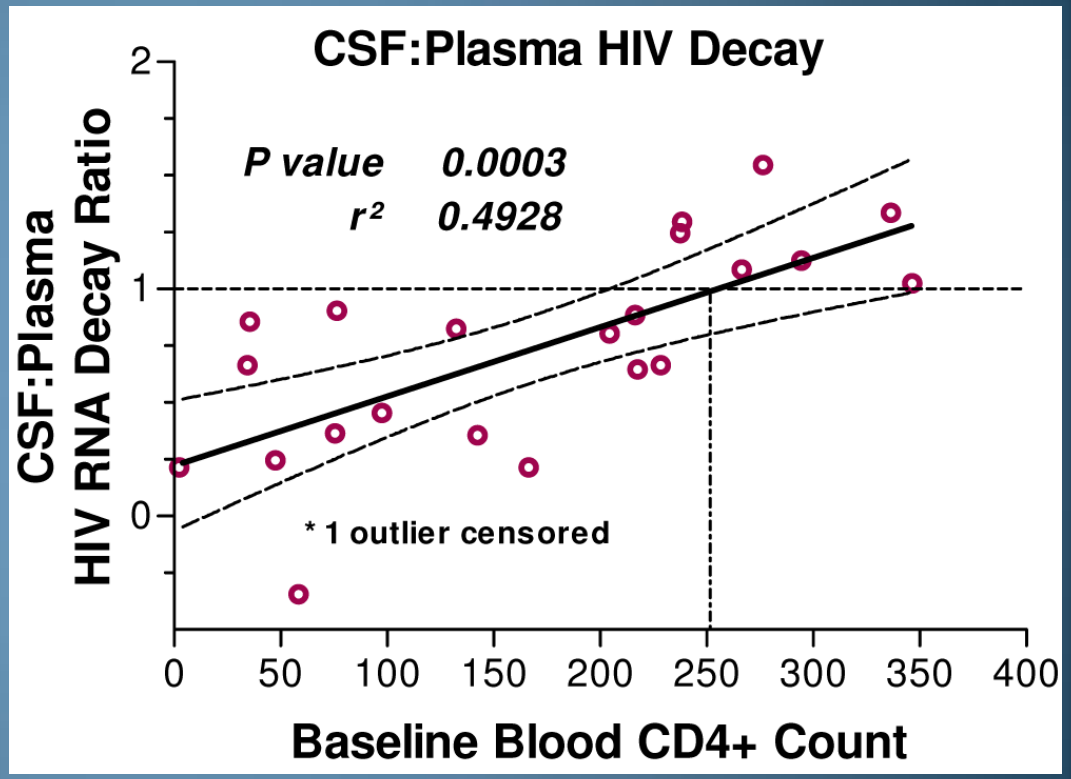
What Influences Relationships Between CPE and Outcomes?

- Neuroadapted HIV
  - » Nadir CD4 Count
- Other antiretroviral effects
  - » Monocyte efficacy
  - » Neurotoxicity
- BBB permeability
- Neurorelevant comorbidities
  - » Aging
  - » Vascular Disease
  - » Co-infections
- Human genetics
  - » Neuroinflammation
  - » Molecular transporters

Mitigating Circumstances

Lower CD4+ T-cell Counts





Ellis, et al. AIDS, 2011, 25: 1747-51

Spudich, et al. BMC Infect Dis, 2005, 5: 98

Mitigating Circumstances

Monocyte/Macrophage Efficacy

	EC_{50} (μM)		Fold
	PBL	MDM	Difference
Zidovudine	0.2	0.02	**10.0**
Didanosine	0.5	0.05	**10.0**
Zalcitabine	0.04	0.003	**13.3**
Lamivudine	0.04	0.02	**2.0**
Stavudine	0.8	0.24	**3.3**
Abacavir	0.9	0.3	**3.0**
Tenofovir	0.37	0.02	**18.5**

Perno et al., Antiviral Research, 2006

Mitigating Circumstances
Drug Neurotoxicity

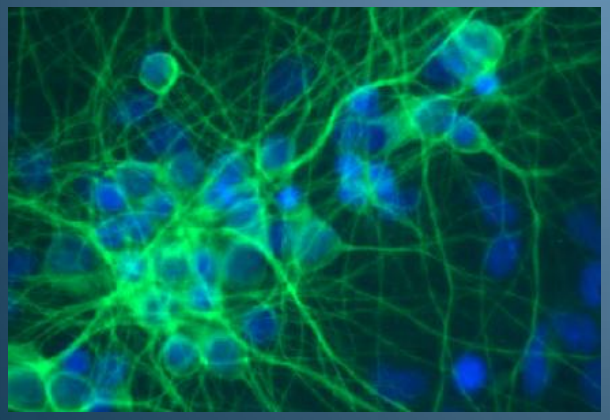
ACTG 5170

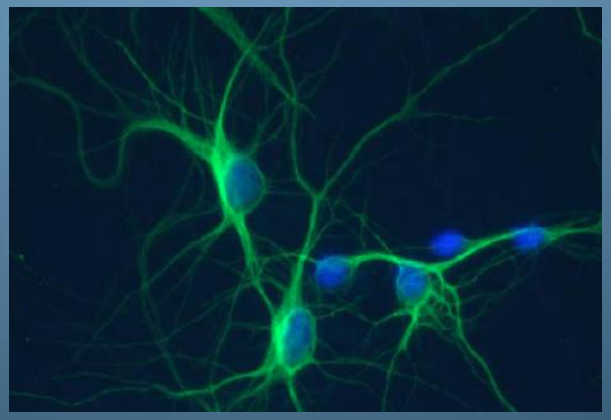
- 167 people interrupting ART
- Performance on 2 NP tests improved over 96 weeks, particularly among those who took efavirenz

Robertson et al, Neurology 2010, 74: 1260

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

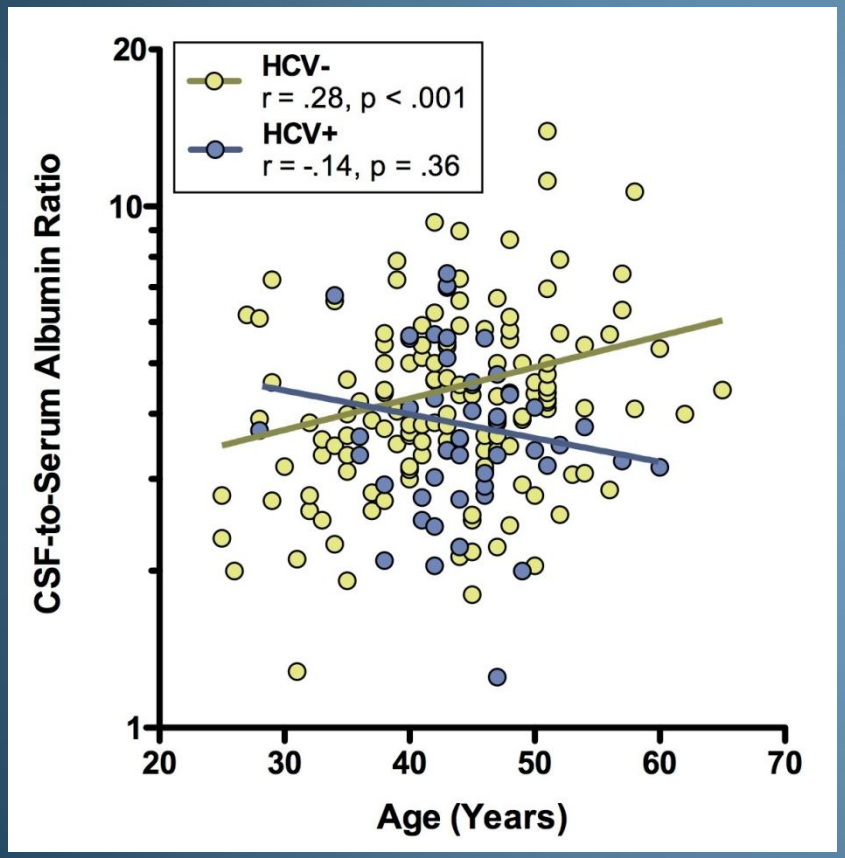


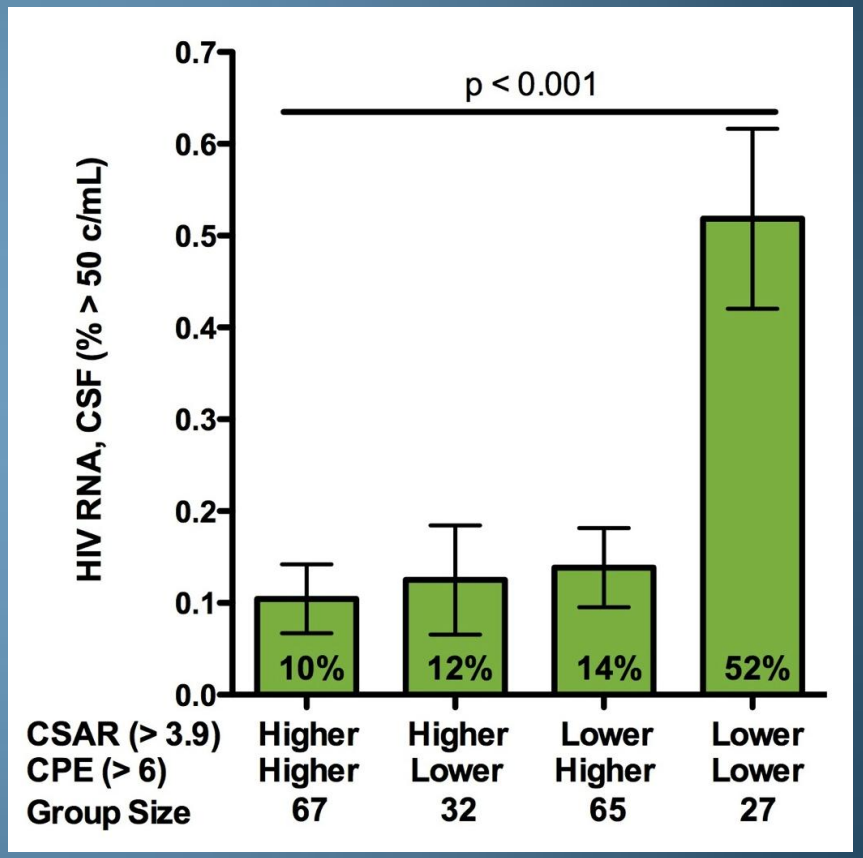


Liner et al, 17th CROI 2010, Abstract 435

Mitigating Circumstances

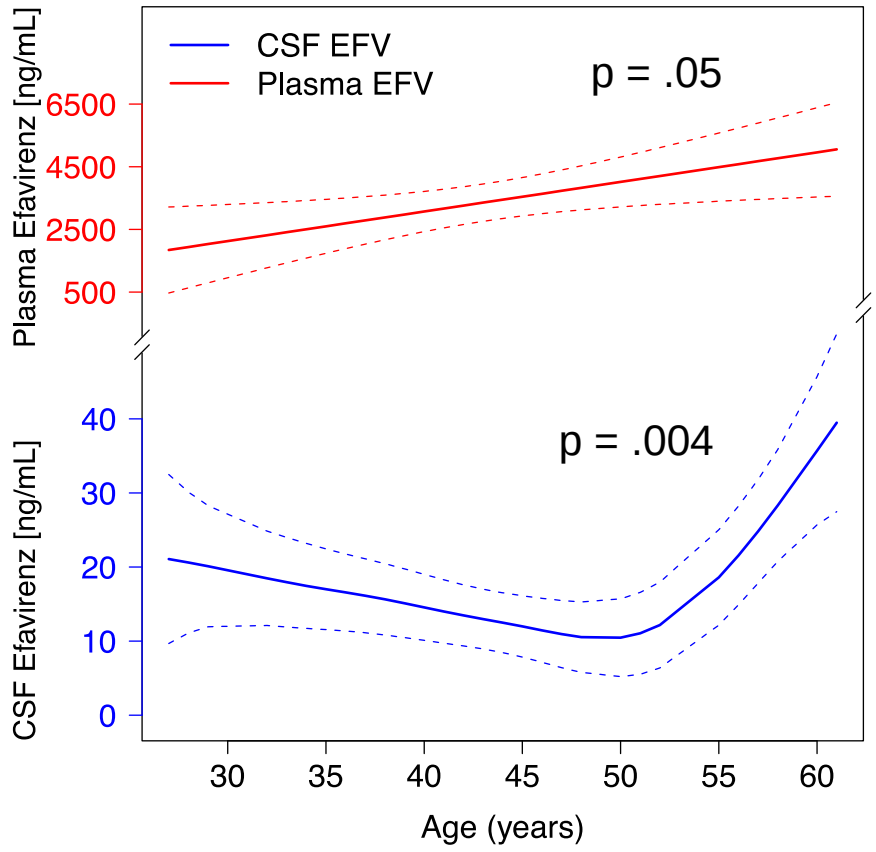
BBB Permeability

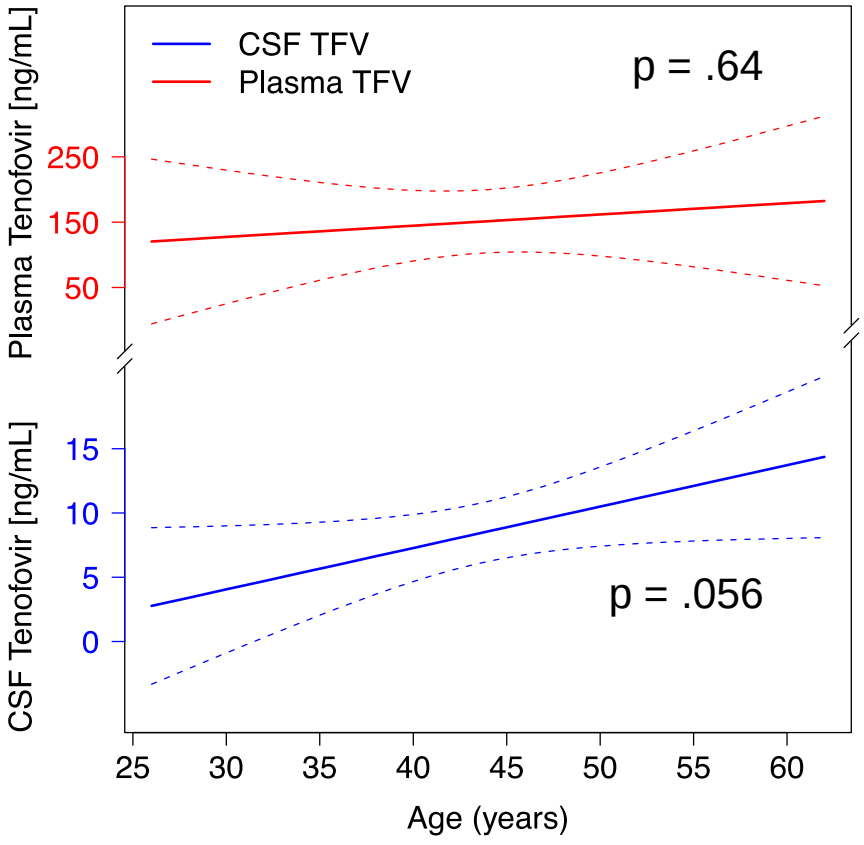




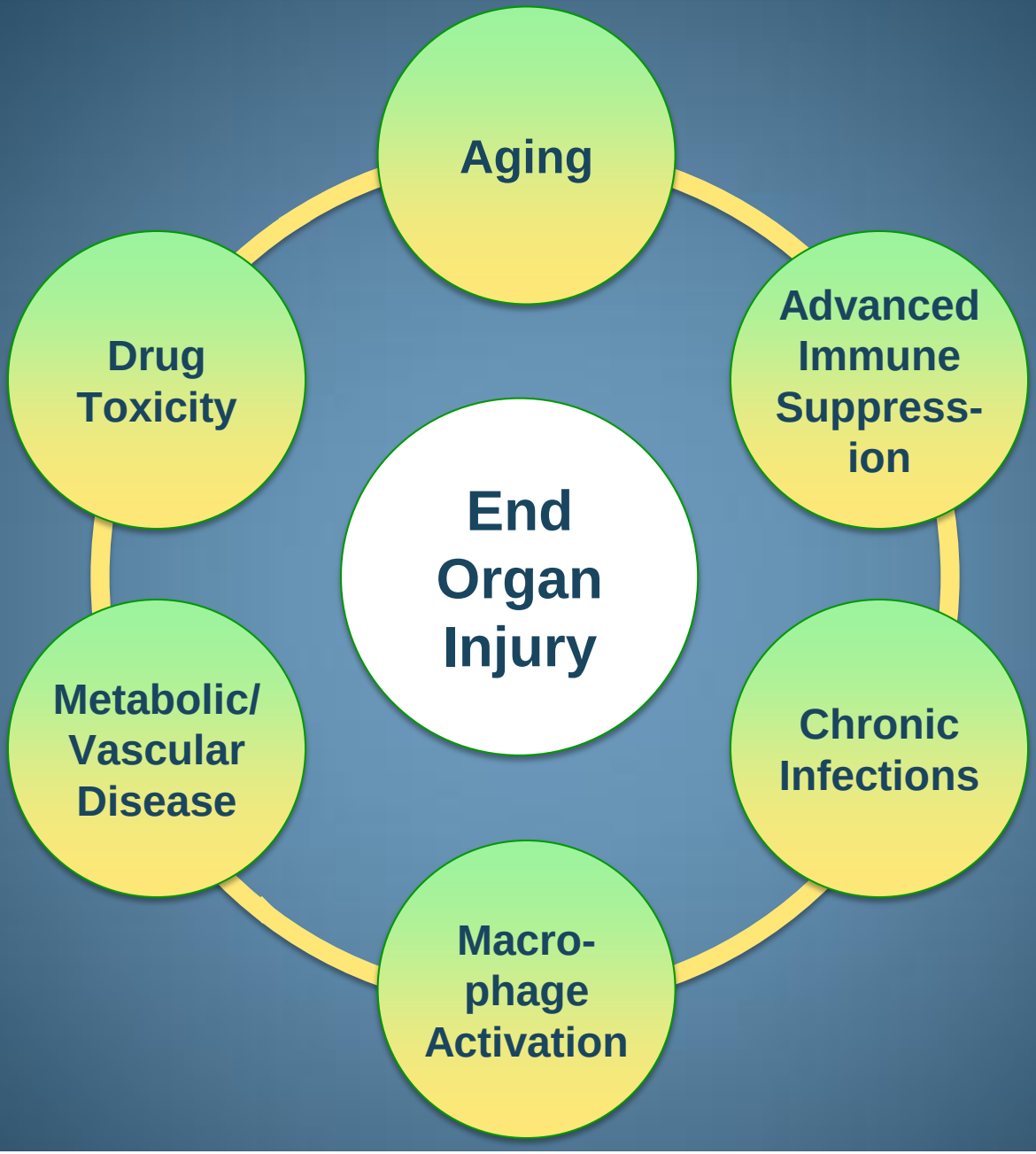
Letendre et al, 18th CROI, 2011, Abstract 408

Aging seems to influence antiretroviral concentrations in CSF

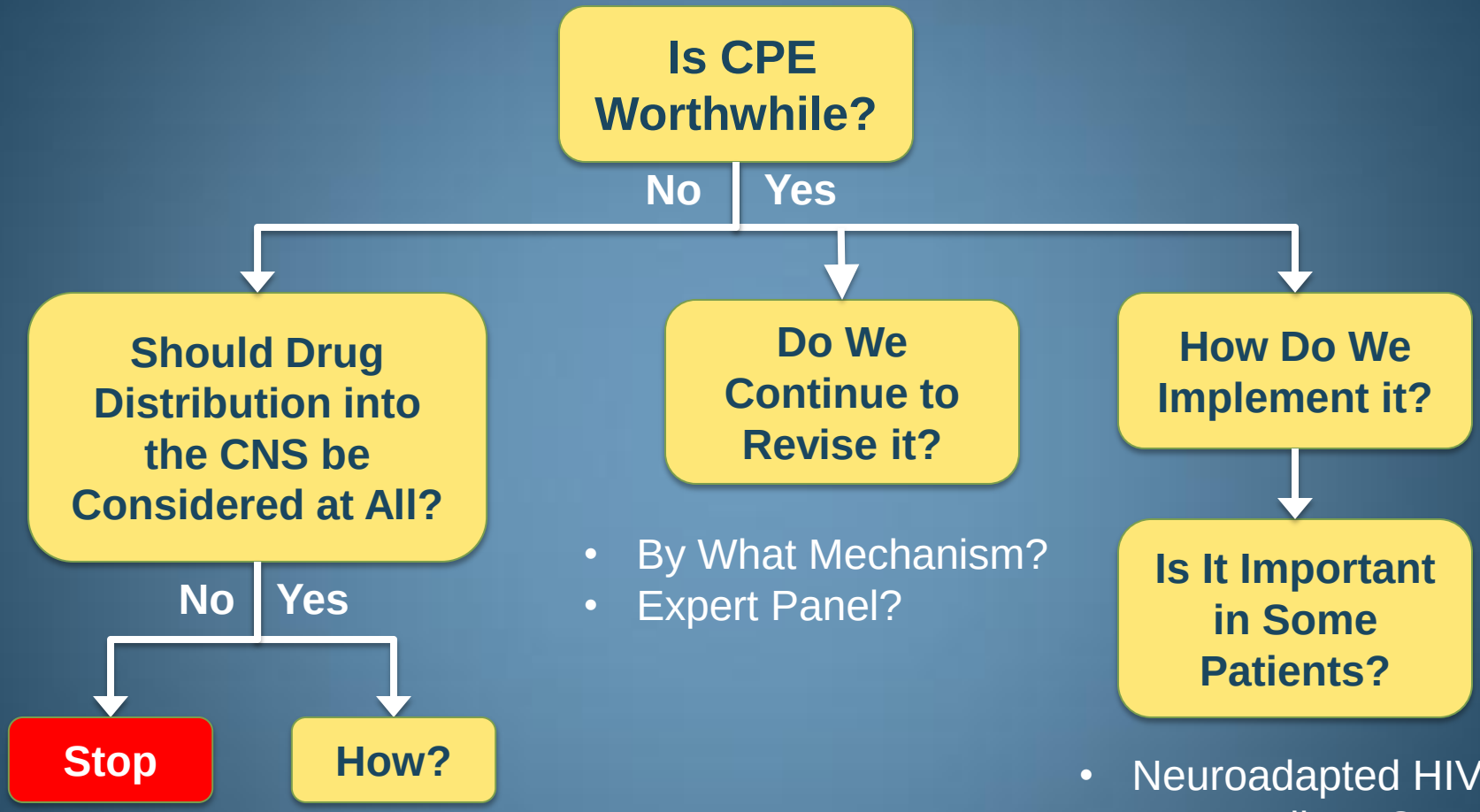




Croteau et al, 19th CROI, 2012, Abstract 592


Aging
Advanced Immune Suppress-ion
Chronic Infections
Macro-phage Activation
Metabolic/ Vascular Disease
Drug Toxicity
End Organ Injury

The Future of CPE



2011 EACS Recommended ART

Treatment Naive Individuals

- ABC-3TC
- TDF-FTC

- NVP
- EFV
- DRV-r
- LPV-r
- ATV-r
- RAL

2011 EACS Recommended ART

Treatment Naive Individuals

ABC-3TC

- Therapeutic CSF concentrations with bid dosing
- Concerns about vascular disease

TDF-FTC

- Subtherapeutic CSF TDF concentrations
- Therapeutic CSF concentrations of FTC
- Good monocyte activity for TDF

NVP

- Therapeutic CSF concentrations
- Hypersensitivity

EFV

- Short- and Long-term Neurotoxicity

DRV-r

- Therapeutic CSF concentrations

LPV-r

- Therapeutic CSF concentrations

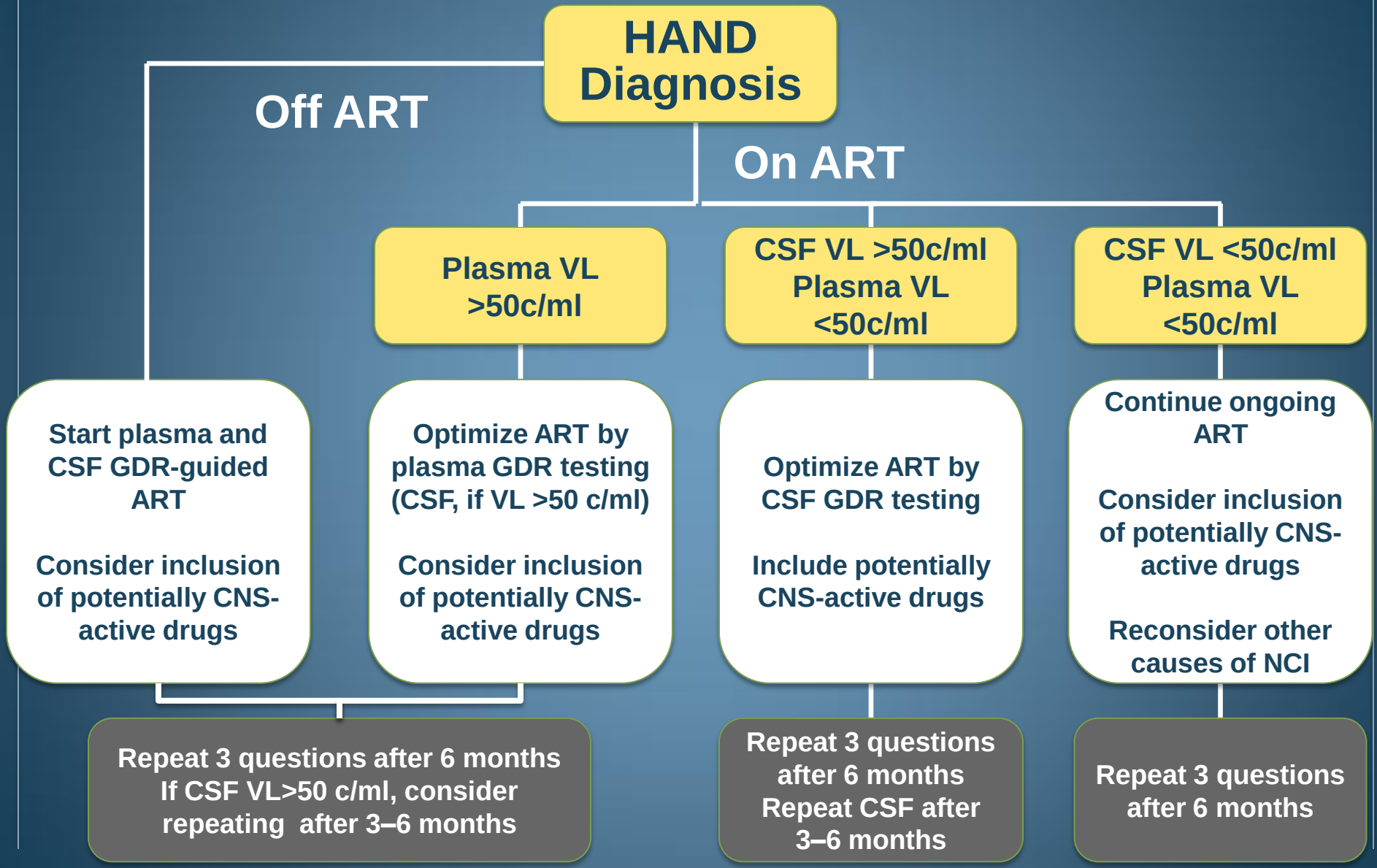
ATV-r

- Subtherapeutic CSF concentrations

RAL

- Possibly therapeutic CSF concentrations

2011 EACS Management of HAND



October 2011; Available at www.europeanaidsclinicalsociety.org/ [accessed 15 Nov 2011]

GDR = Genotypic Drug Resistance

BHIVA Guidelines
30 April 2012

- Start ART in patients with symptomatic HAND irrespective of CD4+ lymphocyte counts
  - » Adequate support to optimise adherence is essential
- Start standard combination ART regimens
  - » CPE score should not influence therapeutic decisions in subjects with NC impairment commencing ART
- With ongoing or worsening NC impairment despite ART
  - » Re-assess for confounding conditions
  - » Obtain CSF and measure HIV RNA
  - » In subjects with detectable CSF HIV RNA
  - » Measure HIV genotropism and genotyping
  - » Based ART modification on plasma and CSF genotypic and genotropism results

Mind Exchange: Evidence Based Guidelines to Assist in Clinical Decisions

Q1	Which patients should be screened for HAND, and when? How often should patients be screened?
Q2	How can I identify patients at greatest risk of HAND? To what extent do different factors affect the risk of HAND?
Q3	Which tools should be used to screen for HAND?
Q5	How can HAND be differentiated from neurodegenerative diseases in older patients?
Q8	When should lumbar puncture be performed in the management of HAND?
Q9	How often should I monitor patients who have been diagnosed with HAND?
Q11	What interventions should I consider in treated patients with persistent or worsening HAND and CSF viral load <50 copies/mL?

Challenges & Future Directions

- **What is the pathogenesis of HAND, particularly with respect to the role of HIV itself and for the milder HAND categories?**
  - » Continue to perform cohort studies that include lumbar punctures and biomarker objectives
  - » Refine the definition of HAND based on the risk of change, either progression or improvement. Should we deconflate ANI from MND and HAD?
- **How does pathogenesis vary by environment and comorbidities? (e.g., human and viral genetics, endemic infections, metabolic and vascular disease, treatment practices)**
  - » Continue to perform cohort studies in LMICs that are designed to investigate locally relevant risk conditions. Why do different HIV subtypes differently affect the CNS?

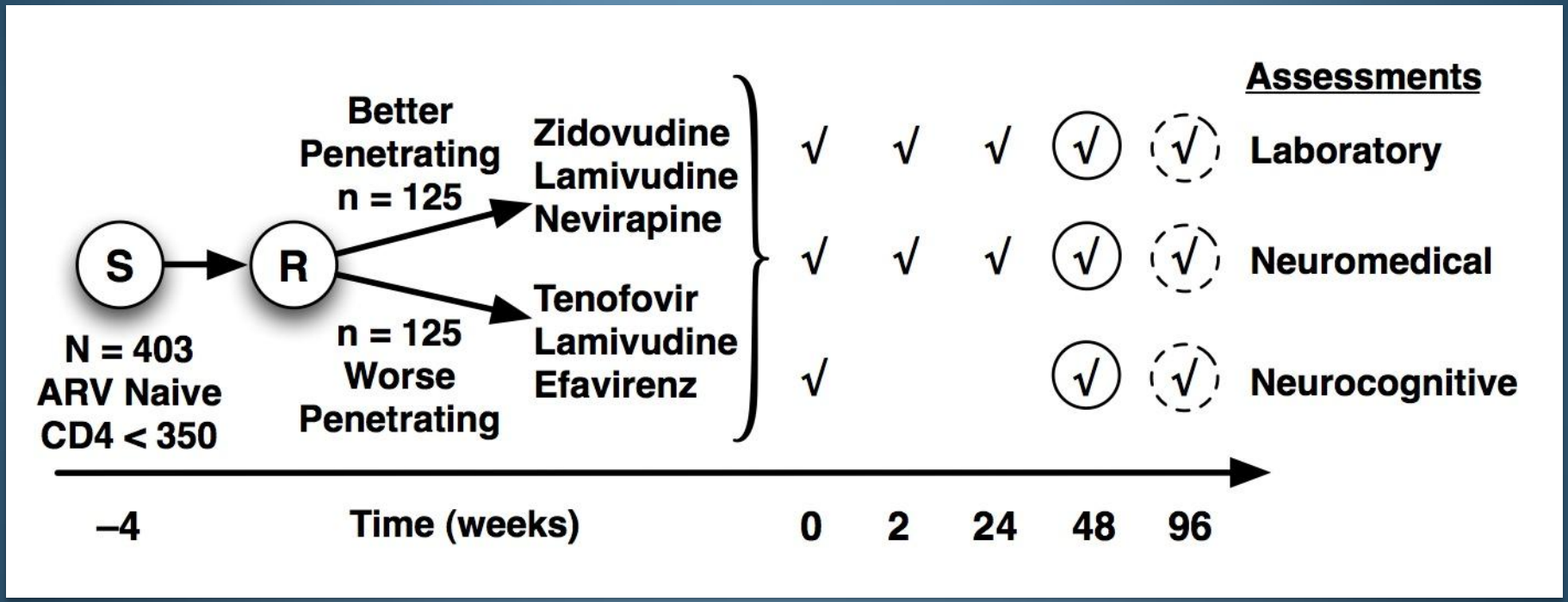
Challenges & Future Directions

- **What are the determinants, correlates, and effects of drug distribution into CSF?**
  - » Compare CSF and brain tissue drug concentrations
  - » **Develop imaging methods that can estimate drug distribution into brain tissue**
  - » **Perform longitudinal analyses of antiretroviral concentrations in CSF that account for other drugs in the regimen**
  - » **Perform pharmacogenomic analyses to better understand the role of genetic variation in determining drug distribution**
  - » **Devise an evidence-based approach to implement drug distribution into clinical practice in a way that benefits patients**

Challenges & Future Directions

- **What is the best approach to preventing and treating HAND?**
  - » Perform dedicated interventional studies, either treatment trials targeted at those with a specific risk profile or prevention trials
  - » Add neurocognitive and lumbar puncture objectives to HIV treatment trials when feasible
  - » Investigate treatments other than drugs, such as cognitive rehabilitation and exercise
- **Is the CNS important for eradication of HIV?**

Design of Actively Enrolling Clinical Trial on HAND Prevention in China



S = Screening
R = Randomization

Acknowledgements

Study Volunteers

UCSD HNRC

- Ronald J. Ellis
- Igor Grant
- Allen McCutchan
- Bob Heaton
- Edmund Capparelli
- Brookie Best
- Davey Smith
- Tom Marcotte
- Cris Achim
- Steven Woods
- Eliezer Masliah

CHARTER and CIT2

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

National Institutes of Health

- …Mental Health
- …Drug Abuse
- …Neurological Disorders and Stroke

Pharma

- Abbott Laboratories
- GlaxoSmithKline
- Merck, Inc.
- Janssen
- Gilead Sciences