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

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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

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

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

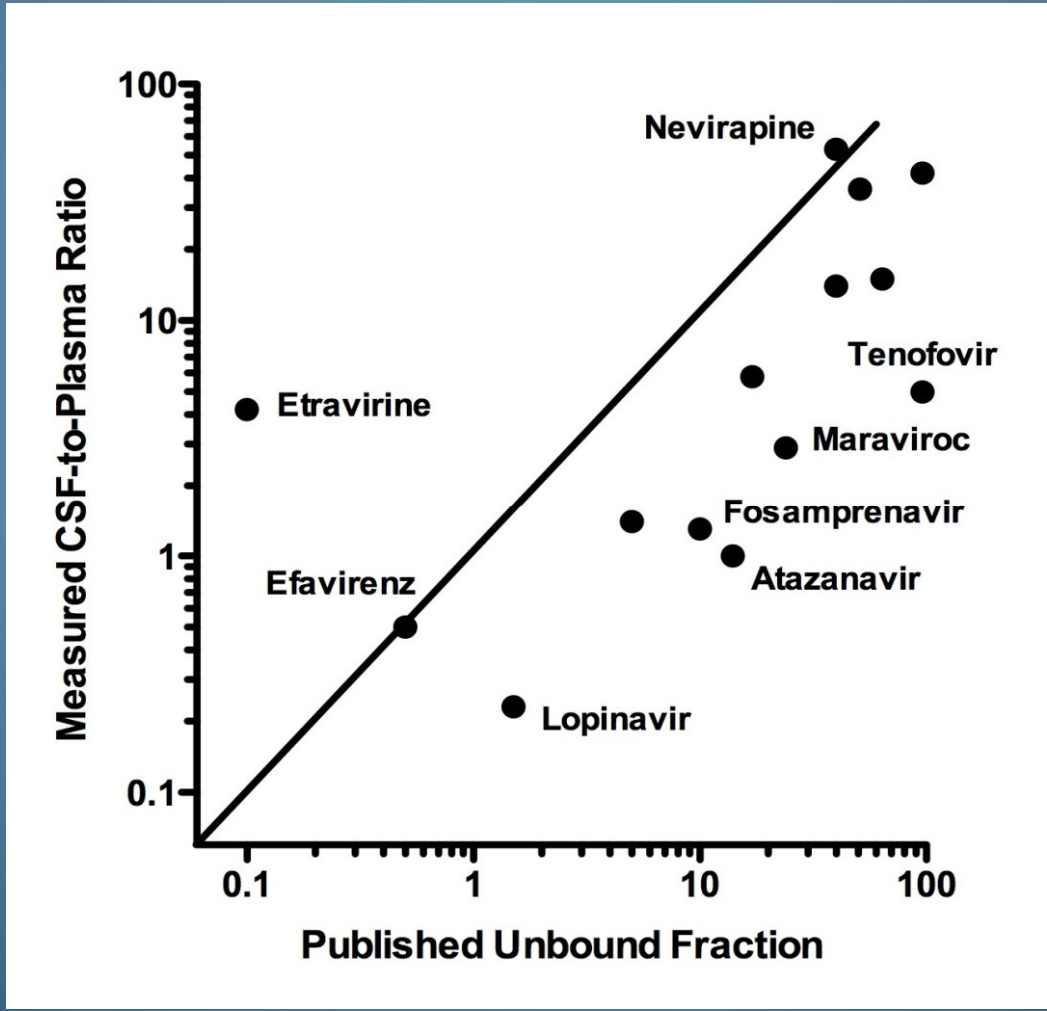
Drug Characteristics
Protease Inhibitors

	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

- Based on the standard suggested by Enting et al, two PIs would meet the protein binding standard and none would meet the molecular weight standard
  - » Protein binding < 90%
  - » Molecular weight < 500
- CPE developed based on traditional HAART (2 NRTIs + PI or NNRTI)
  - » Relative approach within class
  - » Limited to human data
  - » Three categories instead of two
  - » Simple method of combining estimates for a combination regimen

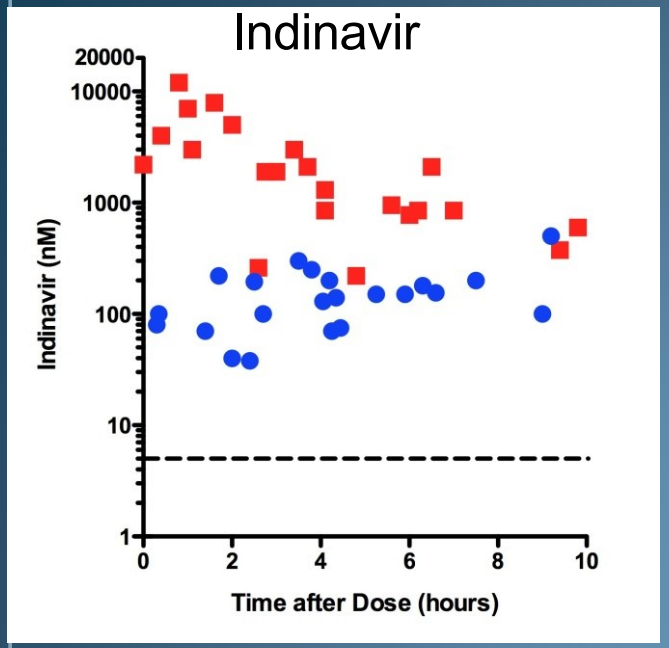
CPE Tabulation
Protease Inhibitors

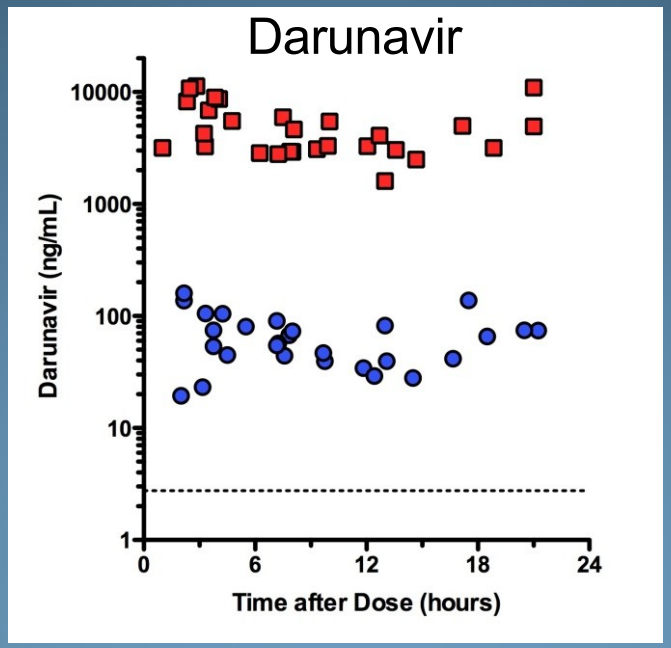
	IDV	LPV	DRV	ATV	APV	SQV	TPV
Drug Characteristics	1	0.5	0.5	1	0.5	0.5	0
Pharmacokinetics							
Pharmacodynamics							
Overall							

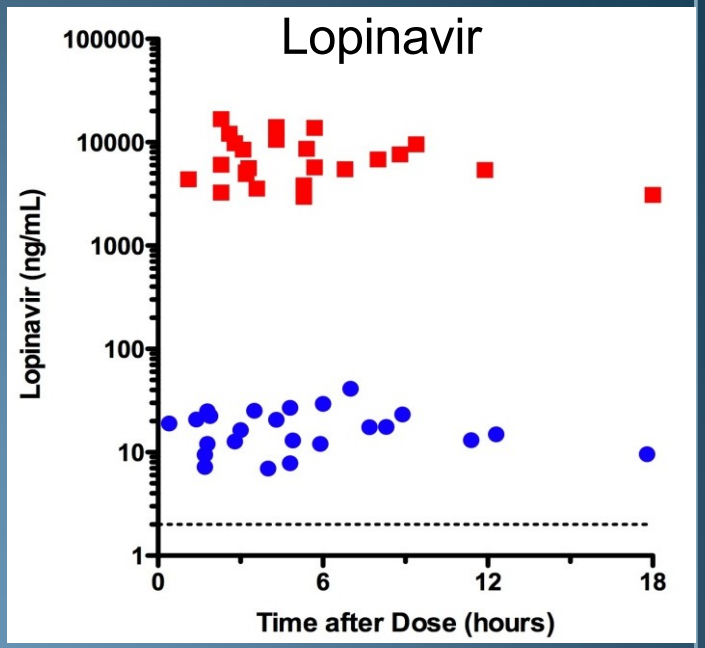
Early CSF Pharmacology Data

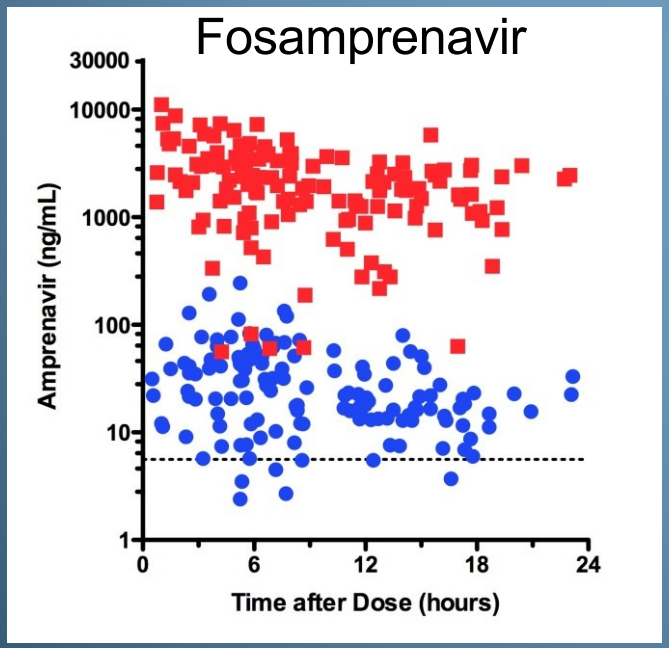
- **Saquinavir** in CSF below 0.29 nM in 26 of 28 individuals[1]
- **Nelfinavir** in CSF below 88 nM in 12 individuals[2]
- **Ritonavir** in CSF below 34.5 nM in 19 of 22 individuals[3]

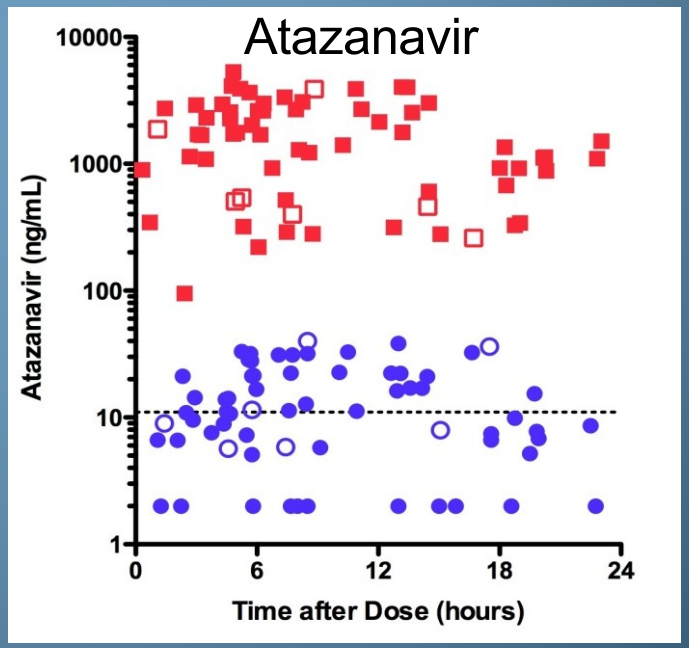
[1]Kravcik et al, JAIDS 1999
[2]Lafeuillade et al, HIV Clin Trials 2002
[3]Gisolf et al, AIDS 2000











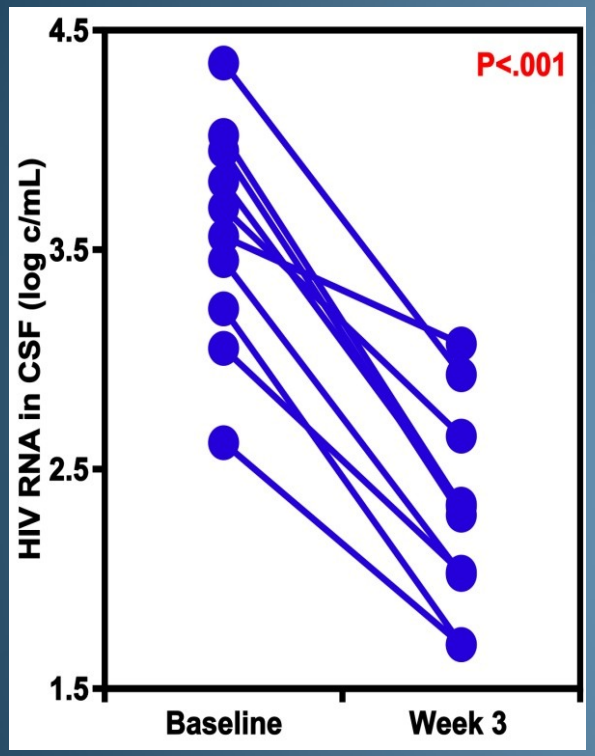
Best et al, AIDS 2009; 23: 83-87; Capparelli et al, AIDS 2005; 19:949–952; Letendre et al, 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2009; Letendre et al, 9th Intl Workshop on Clinical Pharmacology of HIV Therapy, 2009; Letendre et al, Antimicrobial Agents and Chemotherapy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

CPE Tabulation
Protease Inhibitors

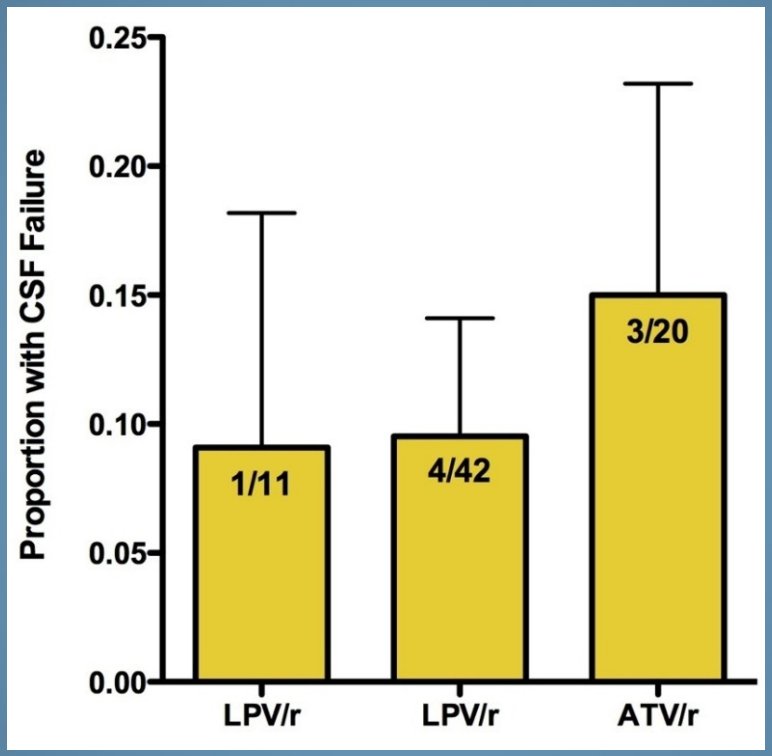
	IDV	LPV	DRV	ATV	APV	SQV	TPV
Drug Characteristics	1	**0.5**	**0.5**	**1**	0.5	**0.5**	0
Pharmacokinetics	1	**1**	**1**	**0.5**	0.5	**0**	-
Pharmacodynamics							
Overall							

Pharmacodynamics in the CNS

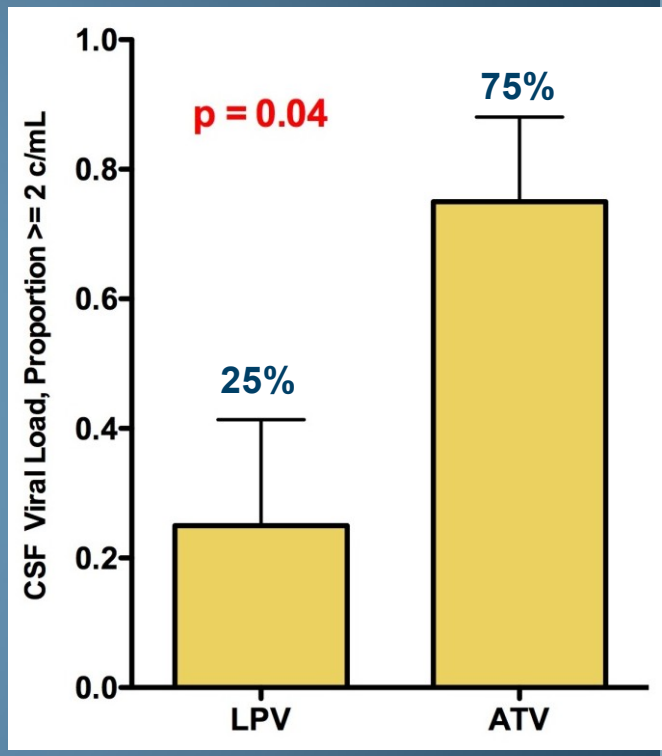
Protease Inhibitor Examples



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

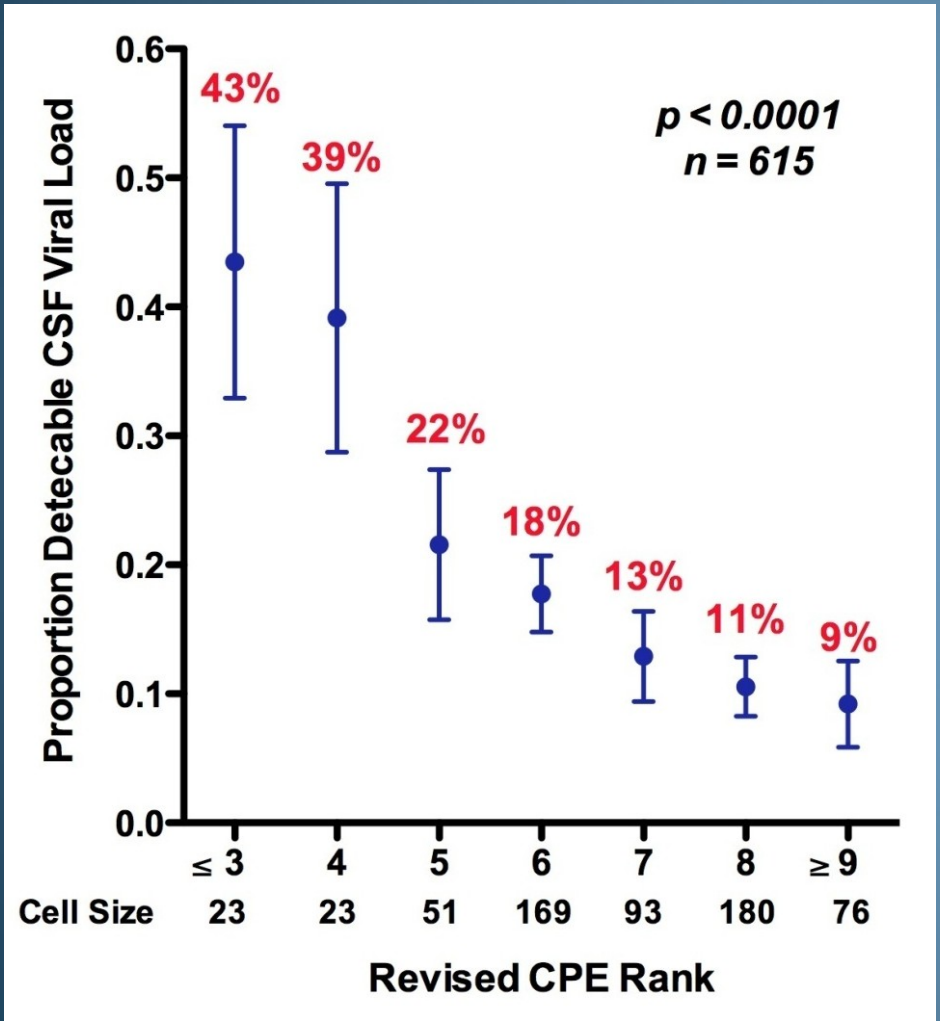
	NVP	EFV	ETR	RPV
Drug Characteristics	1	0.5	0	0.5
Pharmacokinetics	1	0.5	0.5	-
Pharmacodynamics	-	-	-	-
Overall	**1**	**0.5**	**0.5**	**0.5**
Strength of Evidence	PK	PK	PK	DC

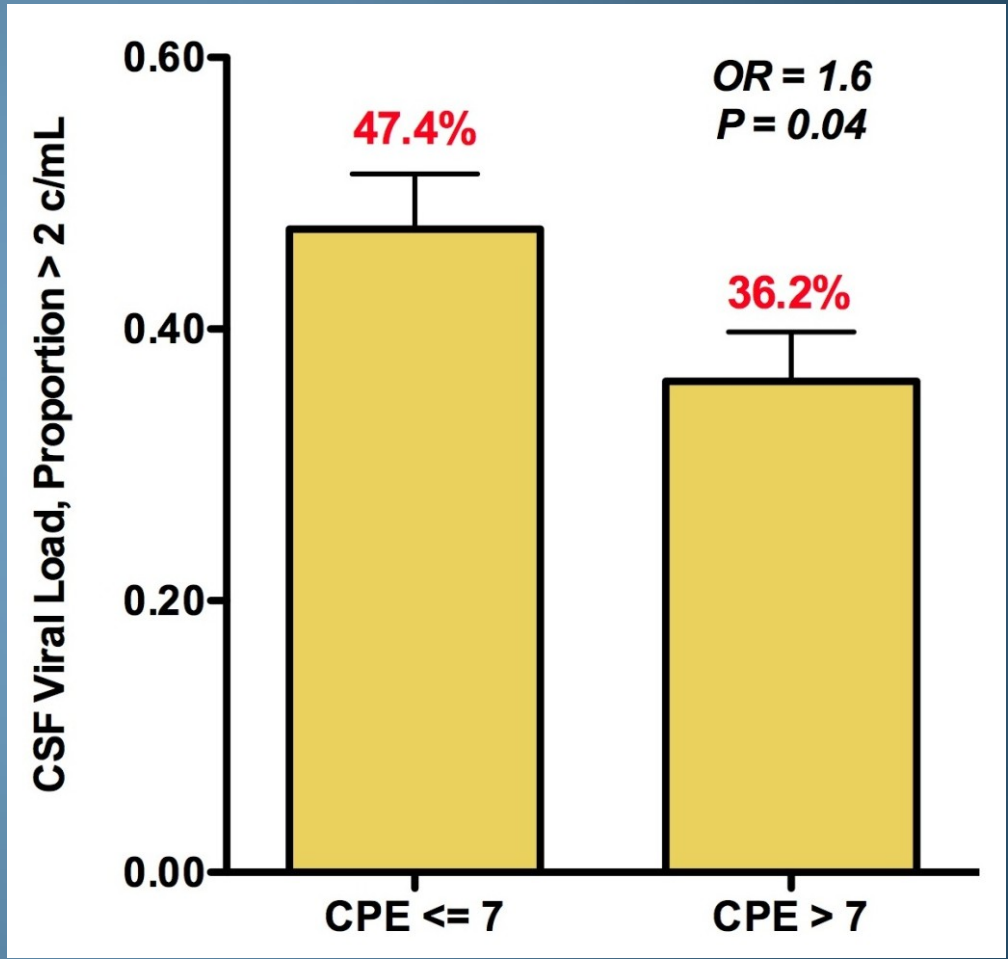
CNS Penetration Effectiveness Ranks 2010

	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

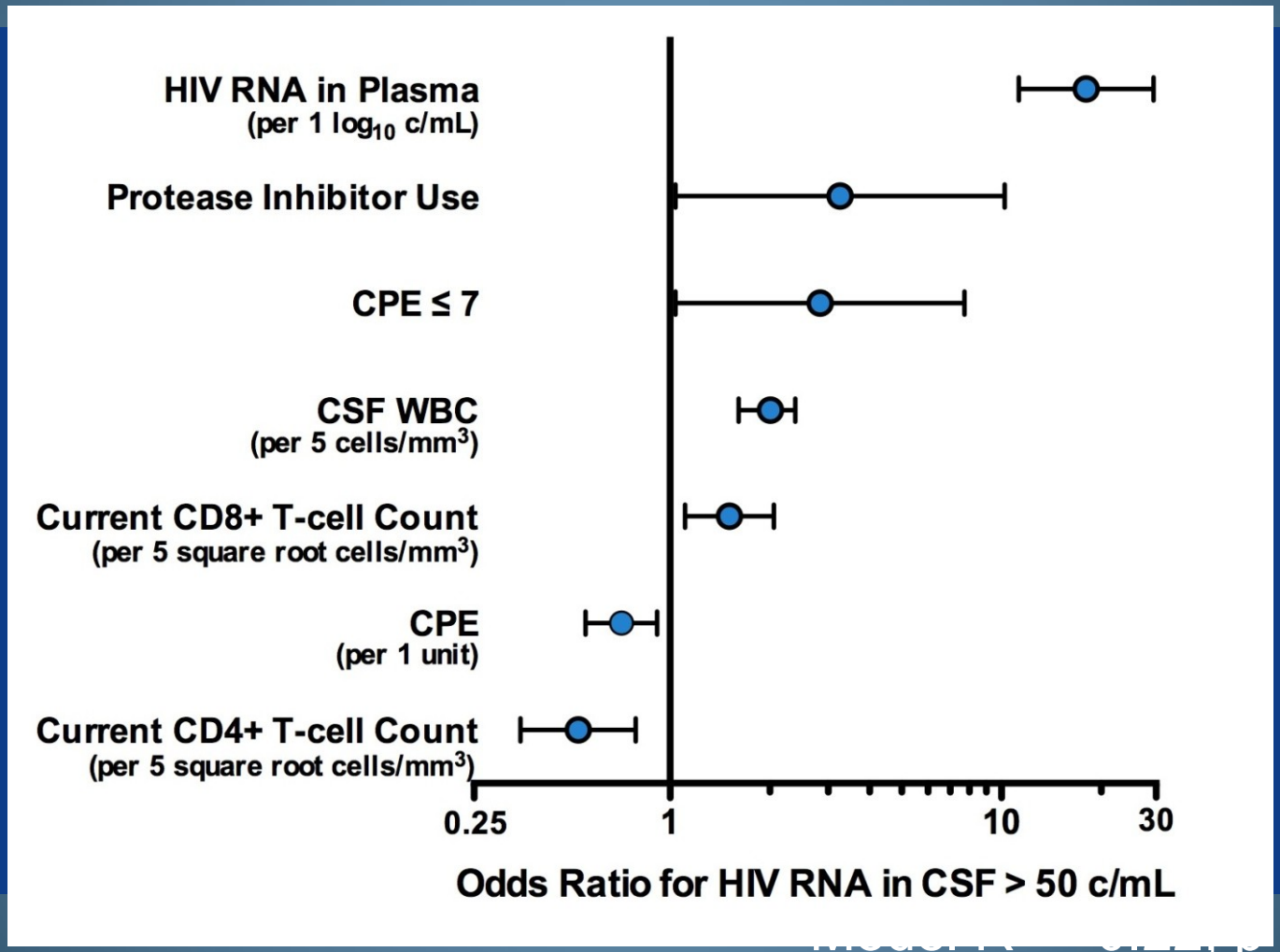




Letendre S et al, 17th CROI 2010, Abstract 172

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

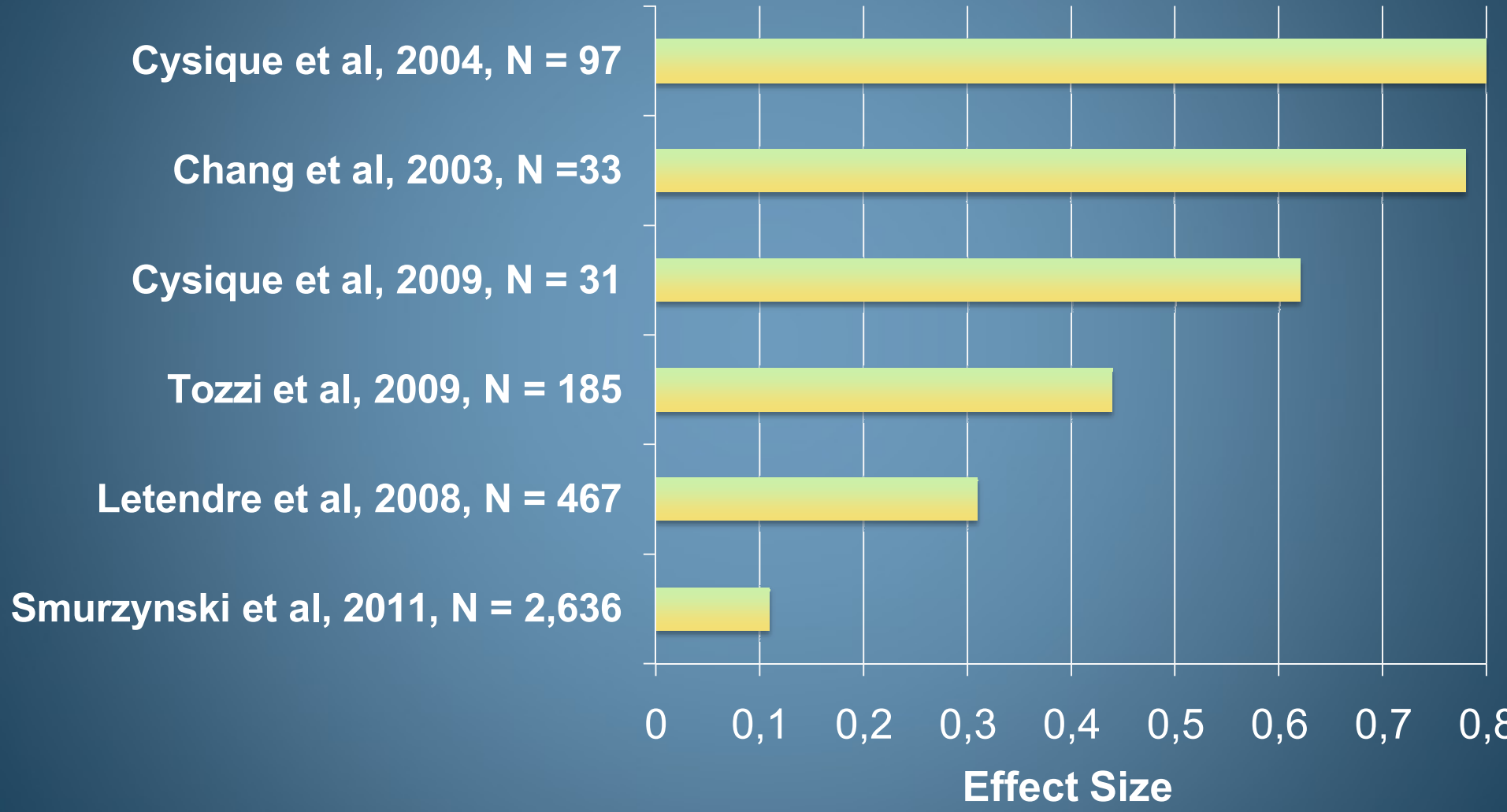
Correlates of Detectable CSF Viral Loads Over Time During ART



< 0.0001

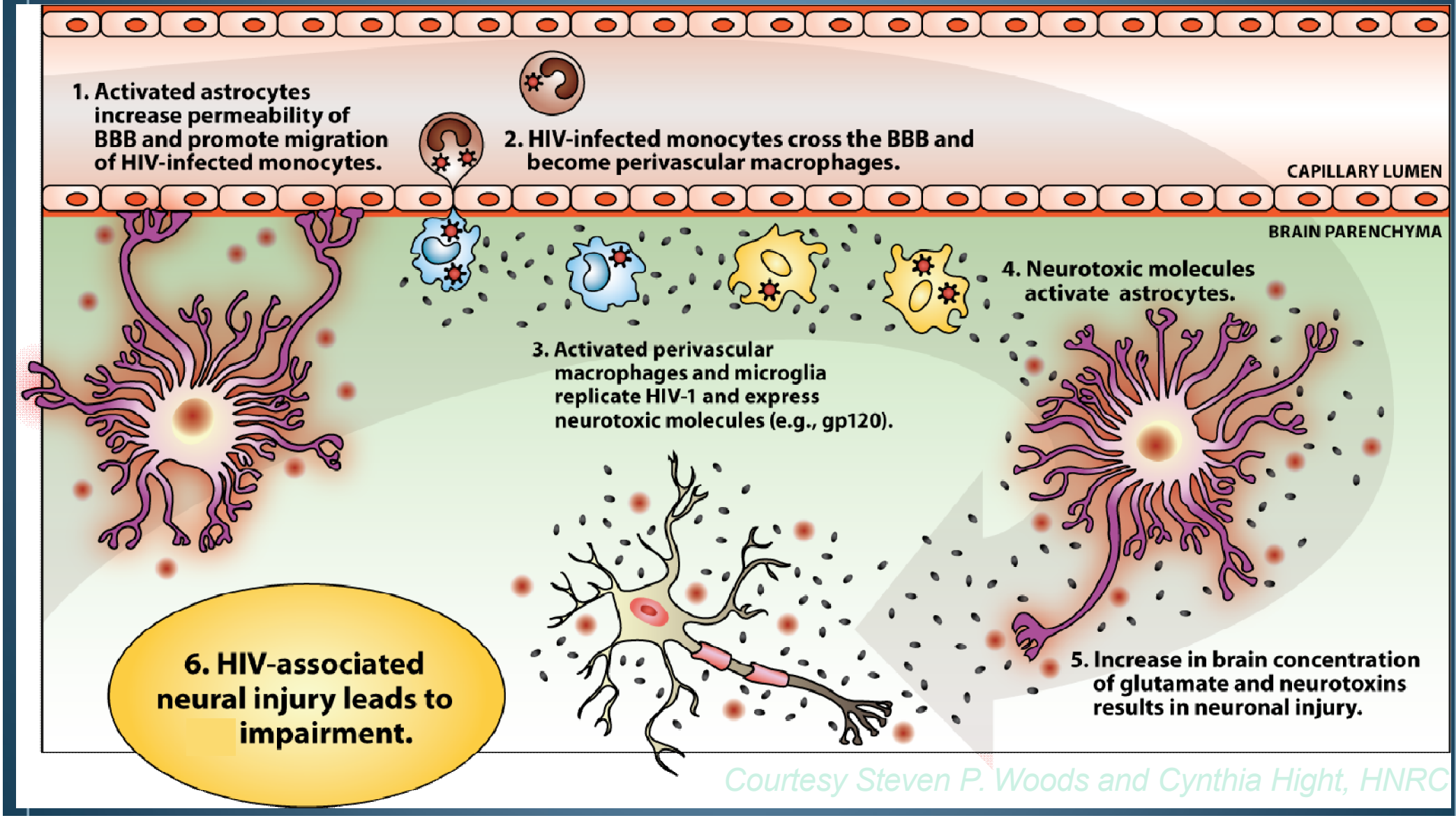
Letendre et al, 19th CROI, 2012, Abstract 473

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



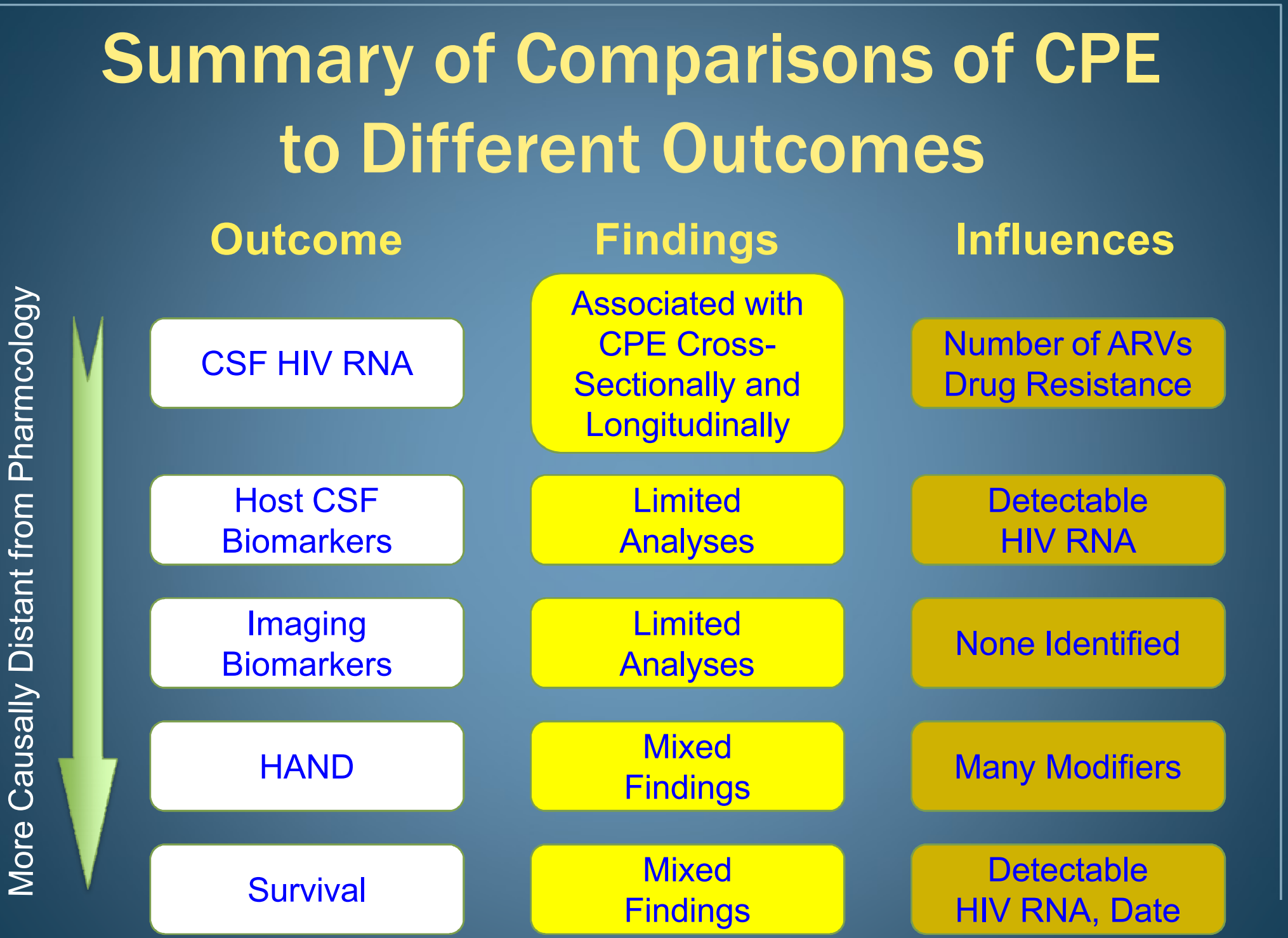
Cysique et al, BMC Neurology, 2011 Nov 22;11:148

Model of HIV Neuropathogenesis



Courtesy Steven P. Woods and Cynthia Hight, HNRC

Summary of Comparisons of CPE to Different Outcomes



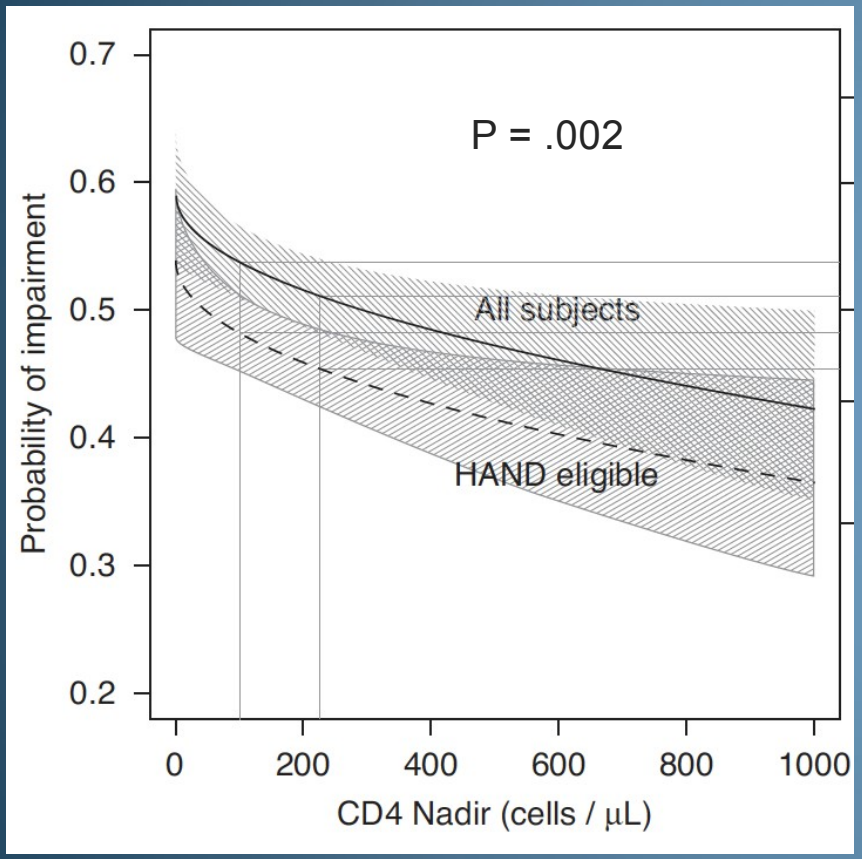
Mitigating Circumstances

What Influences Relationships Between CPE and Outcomes?

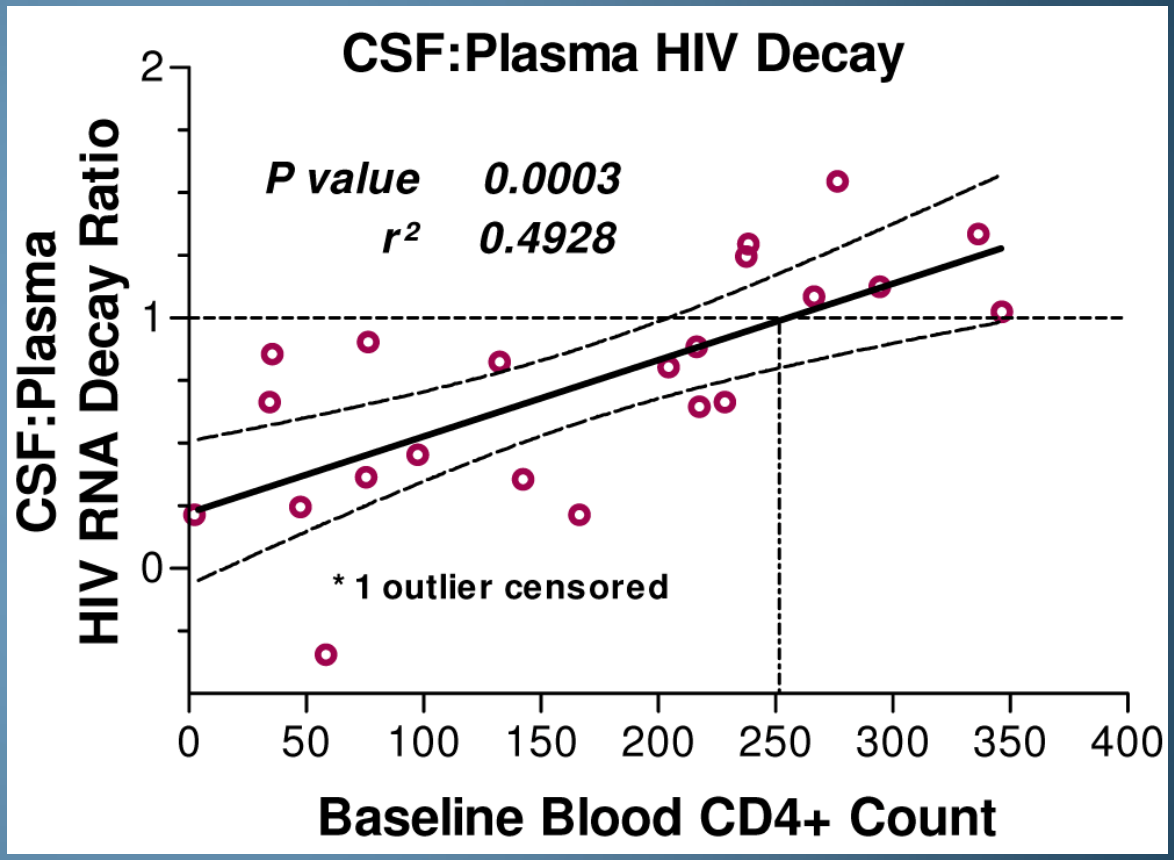
- Neuroadapted HIV
  - » Nadir CD4 Count
- Other effects of antiretrovirals
  - » Monocyte efficacy
  - » Neurotoxicity
- BBB permeability
- Neurorelevant comorbidities
  - » Aging
  - » Vascular Disease
  - » Co-infections
- Human Genetics
  - » Neuroinflammation
  - » Molecular transporters

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

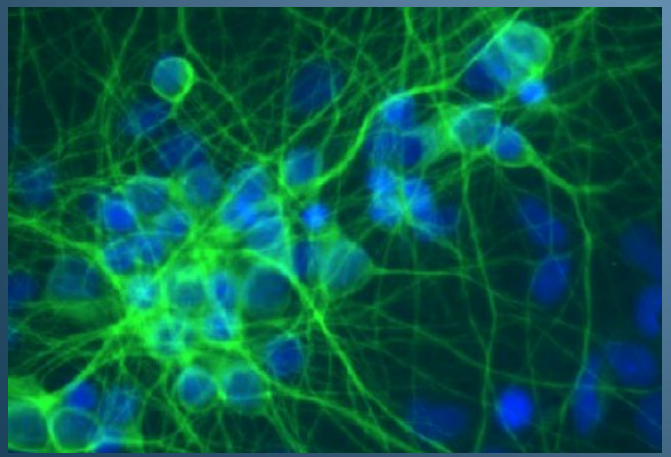
ACTG 5170

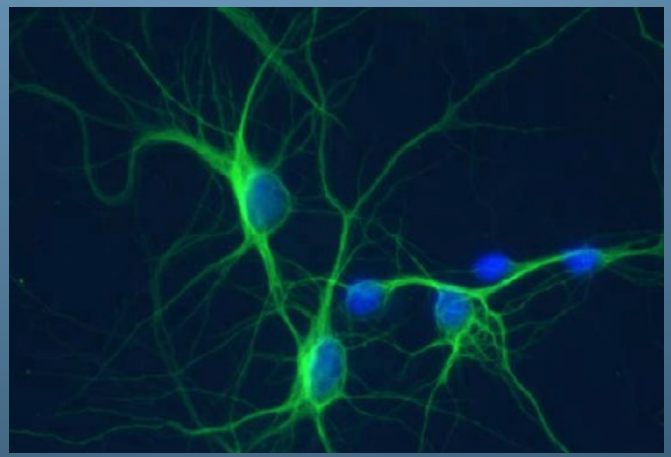
- 167 people interrupting ART
- Performance on 2 NP tests improved over 96 weeks, particularly among those who took efavirenz

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

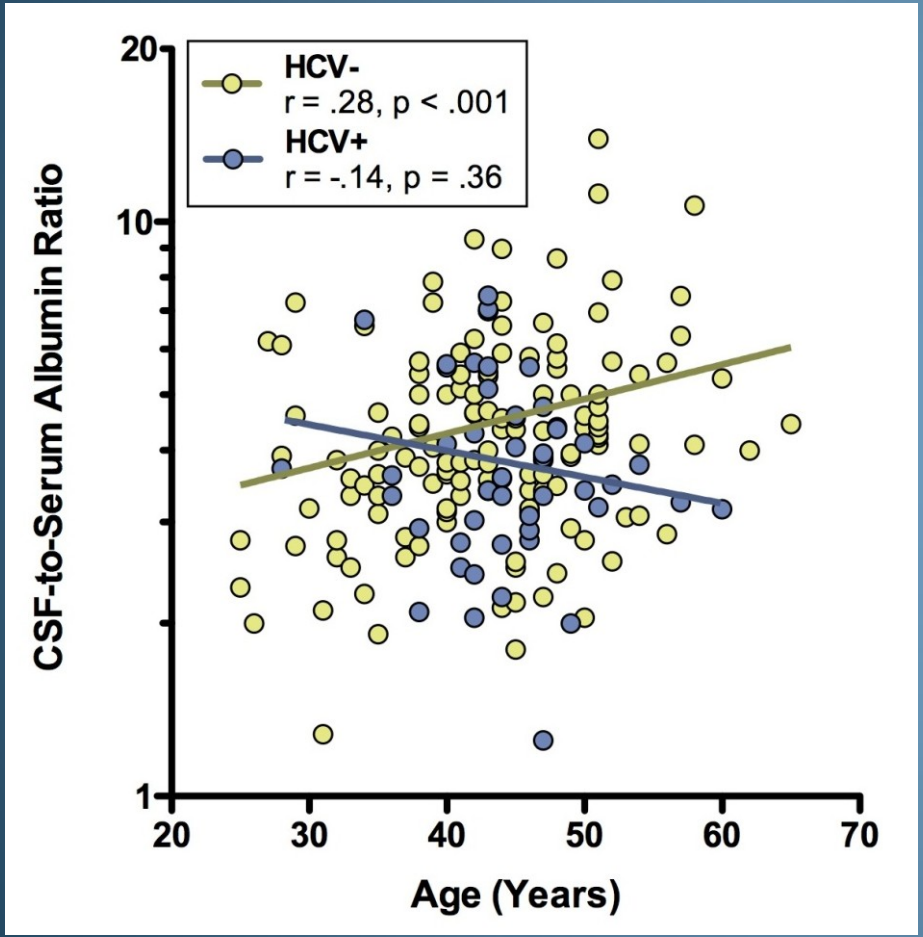




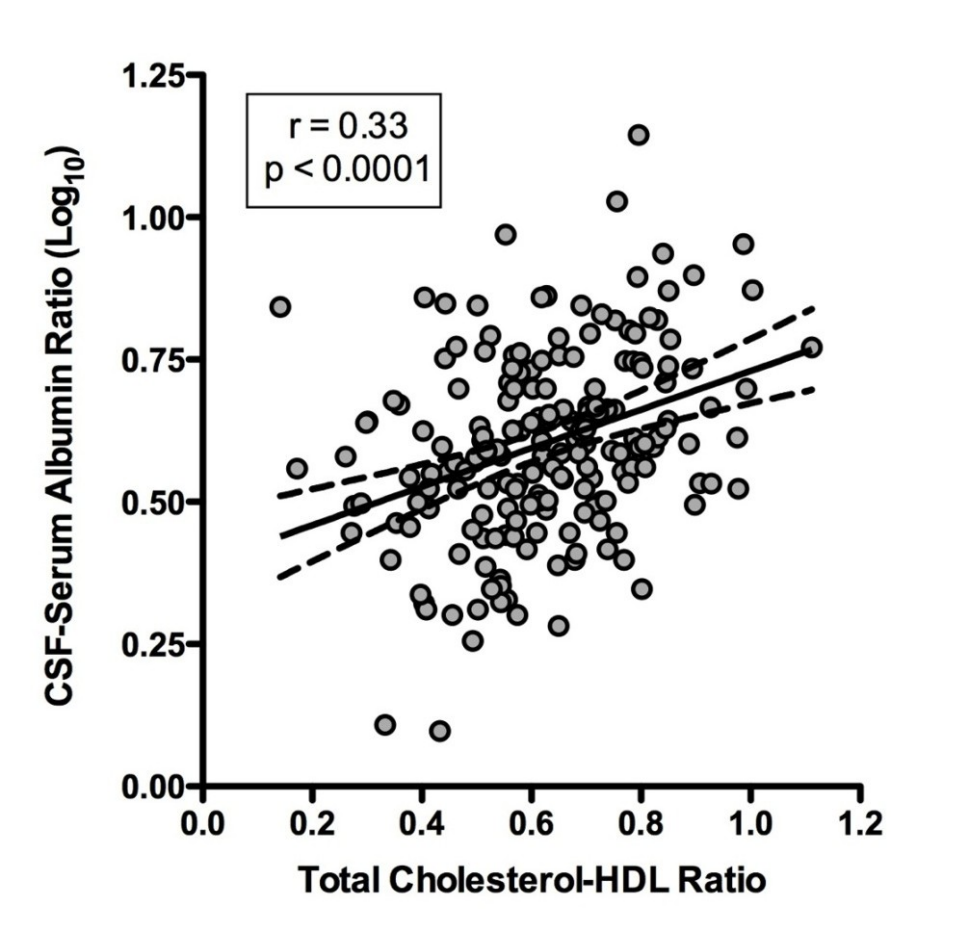
Liner et al, 17th CROI 2010, Abstract 435

Mitigating Circumstances

BBB Permeability

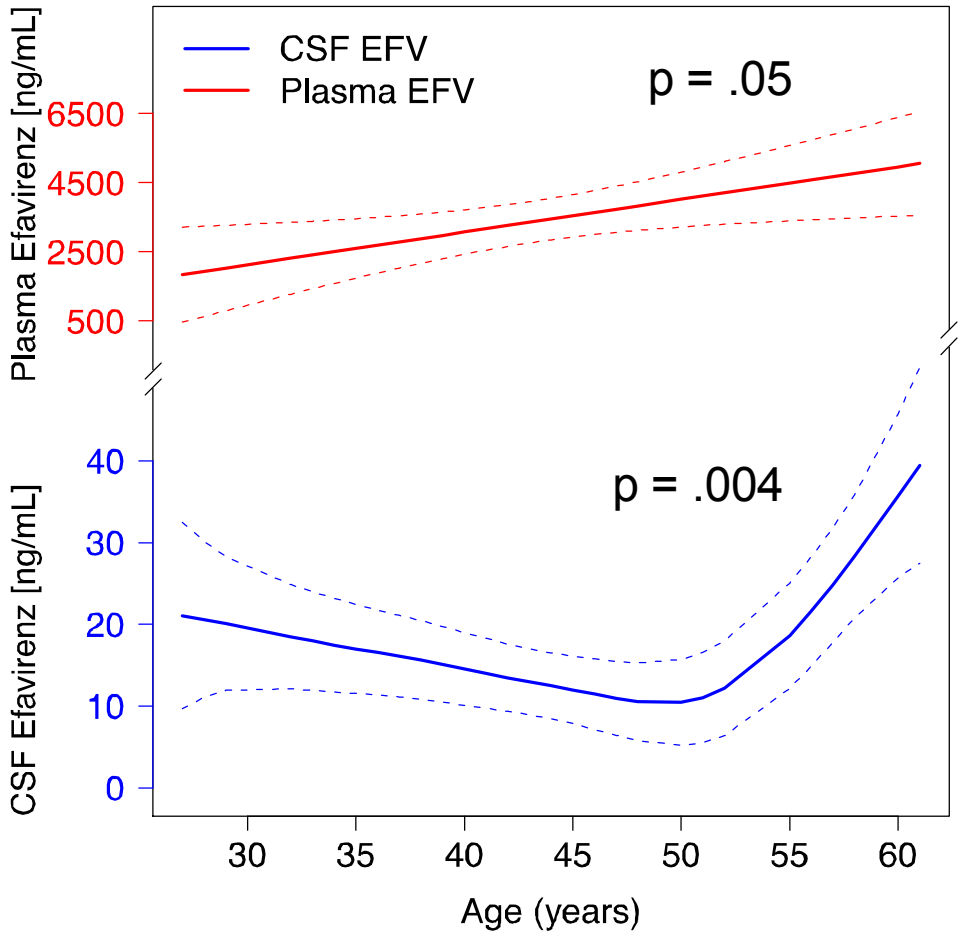


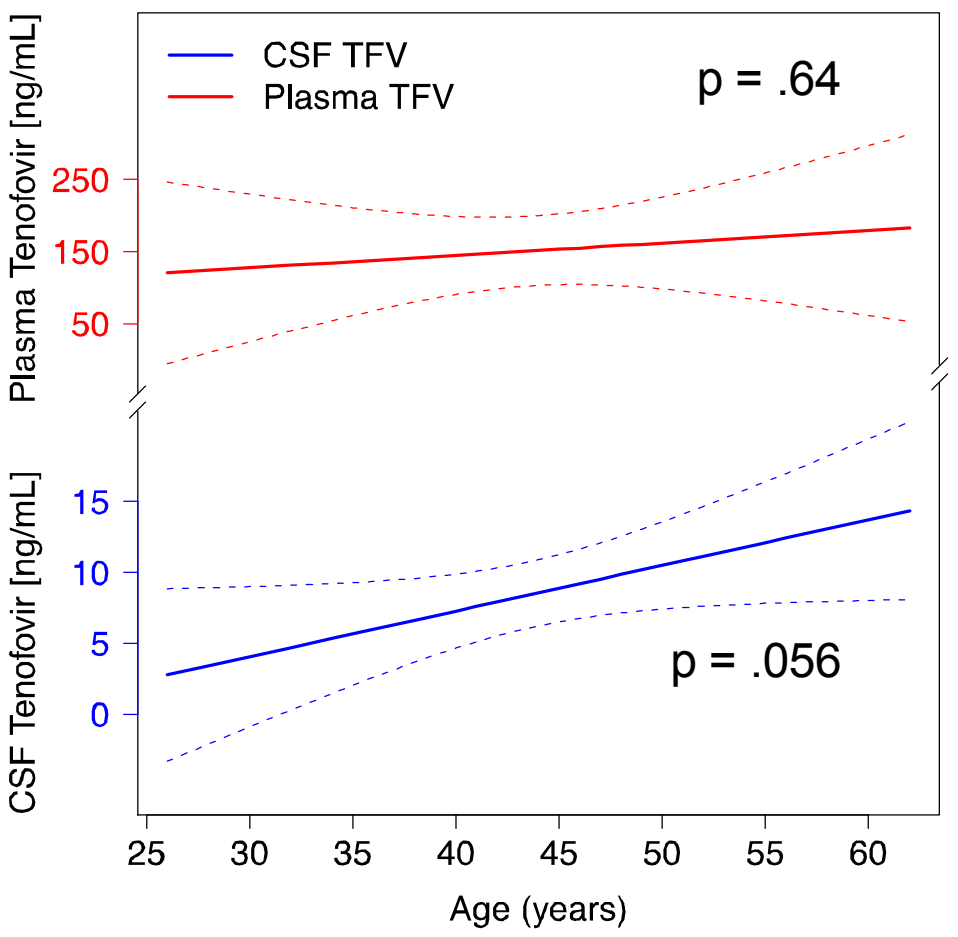
Letendre et al, 18th CROI, 2011, Abstract 408



Letendre et al, Unpublished CHARTER Data

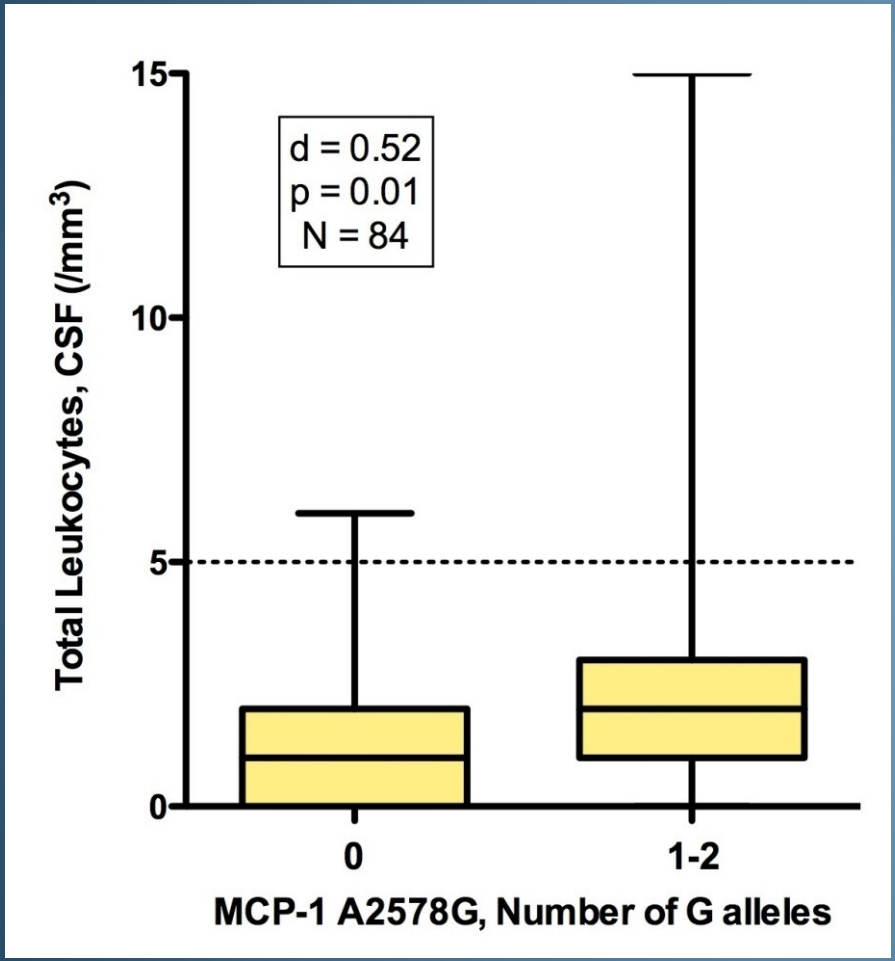
Aging seems to influence antiretroviral concentrations in CSF

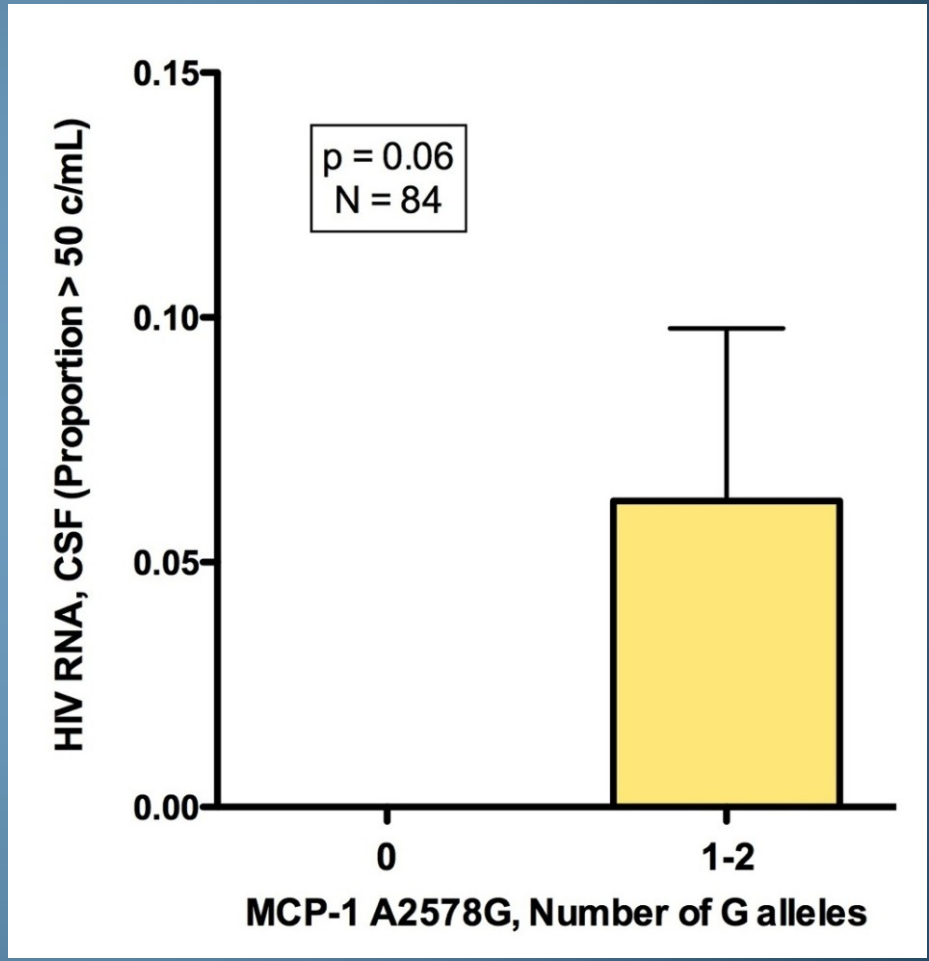




Croteau et al, 19th CROI, 2012, Abstract 592

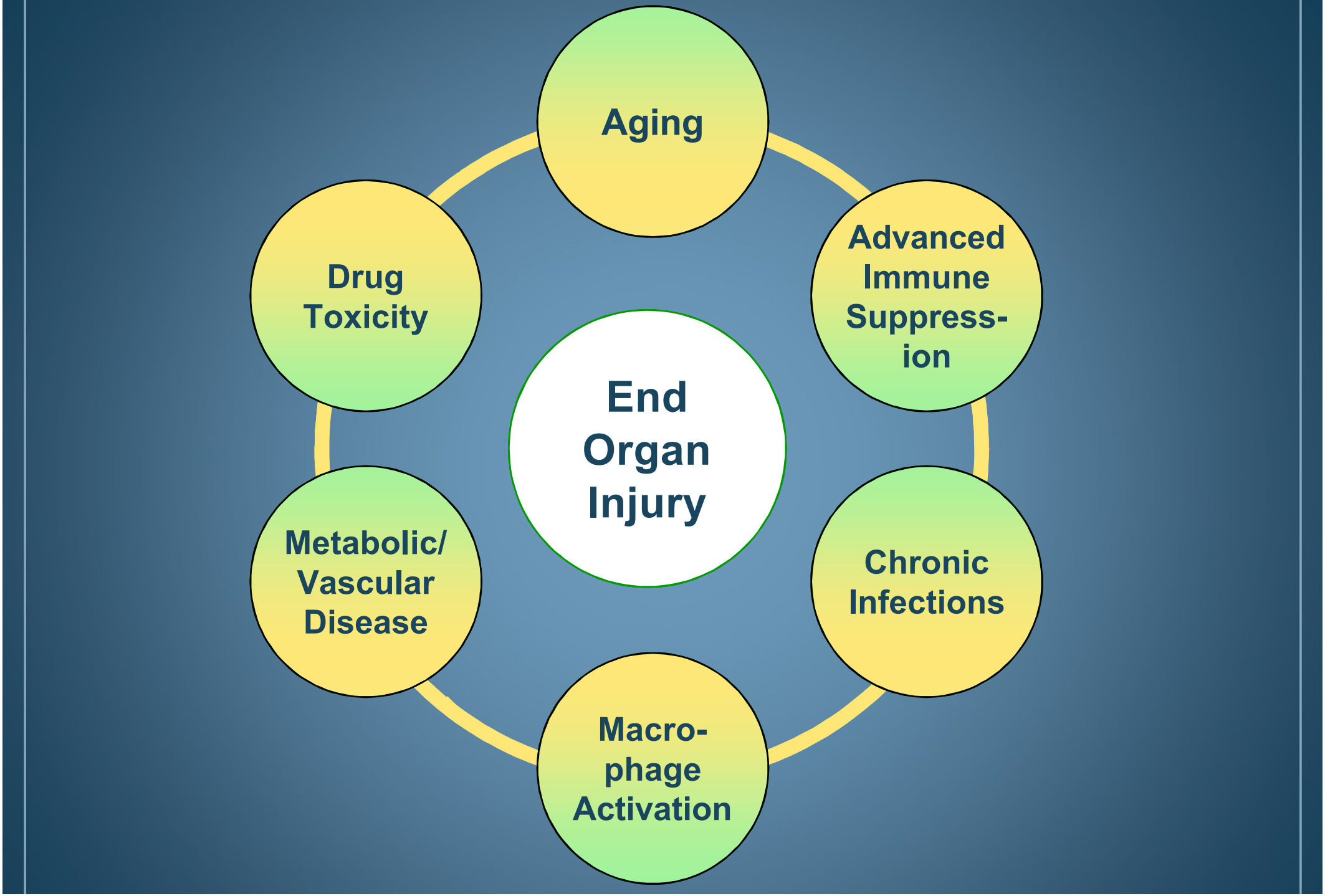
Mitigating Circumstances
Human Genetics



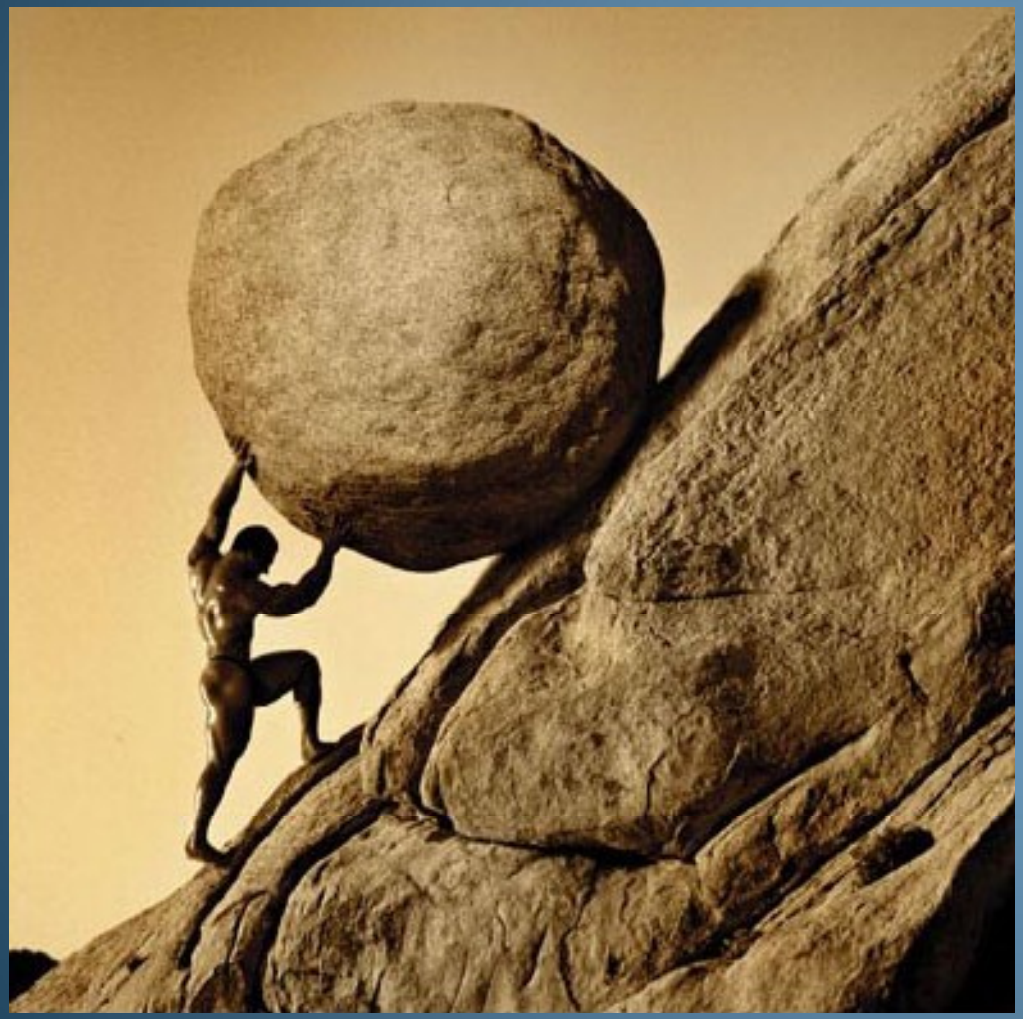


On ART, Plasma HIV RNA < 50
Only in people with CD4 > 550

Letendre et al, Unpublished CHARTER Data


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

How Do We Move Forward?



Should We Reformulate the Phenotypes?

	Presymptomatic	Symptomatic Mild	Symptomatic Moderate to Severe
Immune Activation	✔	✔	✔
Comorbid Diseases	±	±	±
Drug Neurotoxicity	±	±	±
Neuronal/Synaptic Injury		✔	✔
HIV Adaptation			✔

The Future of CPE

Is CPE Worthwhile?

No

Should Drug Distribution into the CNS be Considered at All?

Do we move beyond simple numbering and identify better and worse regimens?

Yes

How Do We Implement it?

Do We Continue to Revise it?

By What Mechanism? Expert Panel?

Is It Important in Some Patients?

- Neuroadapted HIV
- Low CD4+ T-cell Count (Current or Nadir?)
- HAD
- Impermeable BBB

What is Most Achievable?

US DHHS Preferred Regimens

TDF-FTC	EFV	• Neurotoxicity
	ATV-r	• Subtherapeutic concentrations in CSF are common
	DRV-r	• Therapeutic concentrations in CSF
	RAL	• Therapeutic concentrations in CSF*

What is Most Achievable?

US DHHS Alternative Regimens

ABC-3TC

- CSF PK data based on bid dosing
- Cardiovascular concerns
- Unsupportive clinical trial

RPV

- No CSF PK data
- CNS AEs lower than EFV

LPV-r

- Supportive PK and PD data
- CSF PK data based on soft gel formulation

FPV-r

- Good PK data with 90+% supratherapeutic levels in CSF
- Acceptance issues among treaters

ZDV-3TC

- Acceptable regimen
- Bone marrow suppression
- Lower dose than in ADC trial
- Acceptance issues among treaters

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