



NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Central Nervous System Penetration of ARVs: Does it Matter?

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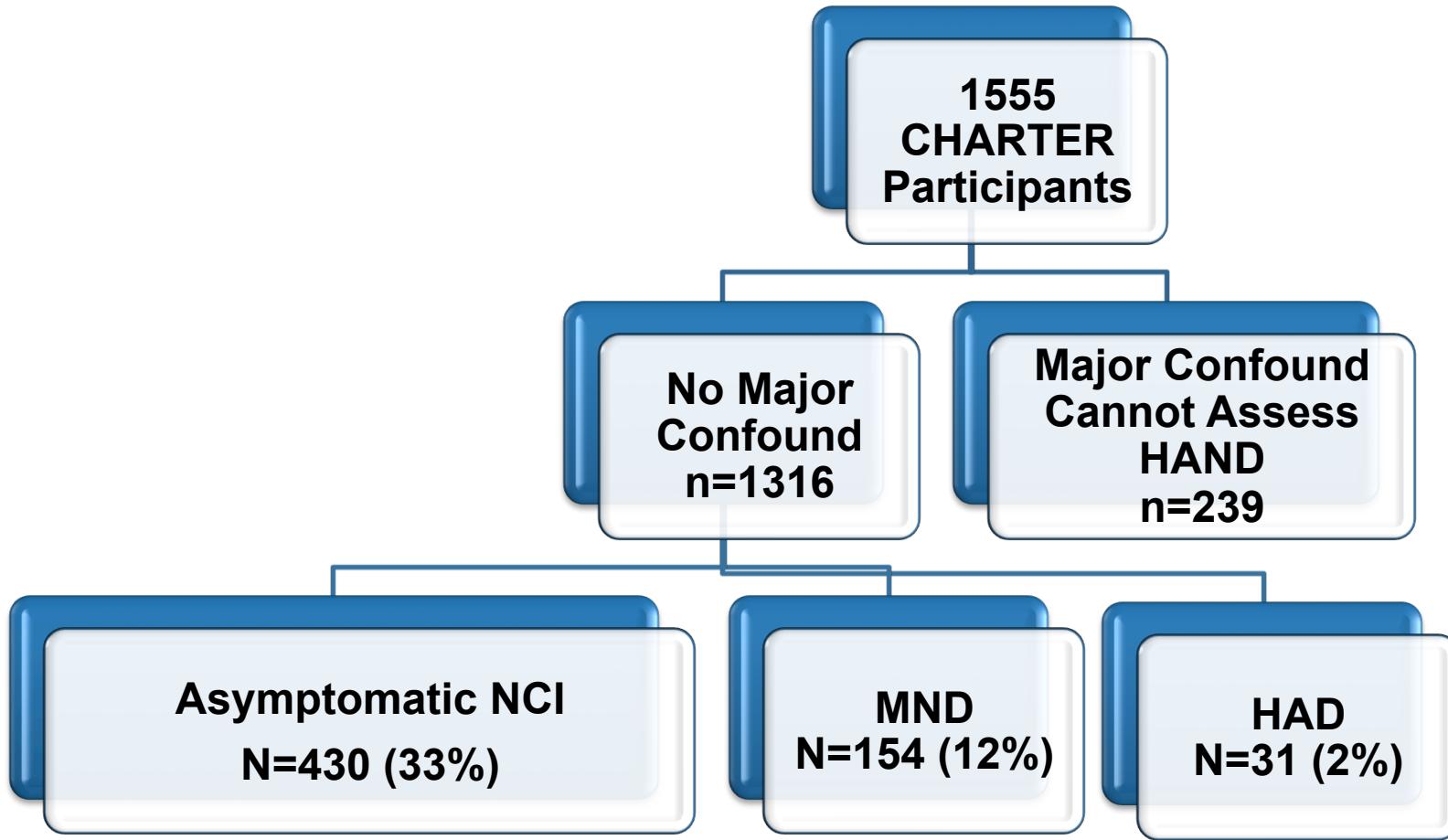
HAND: HIV-associated Neurocognitive Disorders

	Neuropsychological (NP) Tests	Everyday Function
Asymptomatic neurocognitive impairment (ANI)	At least mild impairment in 2 or more domains	No negative effects
Mild neurocognitive disorder (MND)	At least mild impairment in 2 or more domains	Two types of evidence of impaired function
HIV associated dementia (HAD)	At least moderate impairment in 2 or more domains	Two types of evidence of major functional decline
Not attributable to confounding conditions		

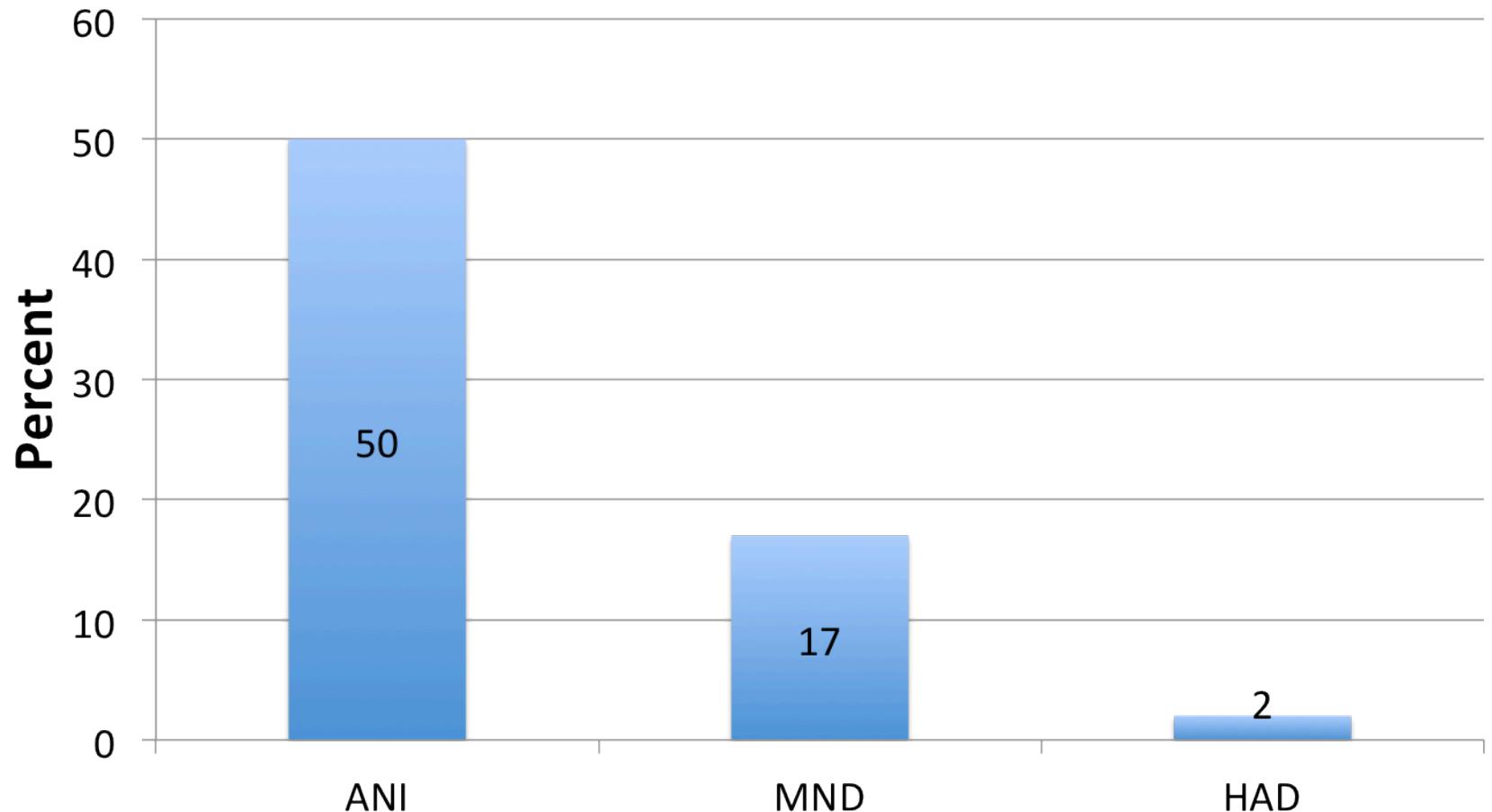
HAND in CHARTER

- Heaton R.K. et al. (Neurology 2010;75)
 - 1555 participants
 - Structured psychiatric interview
 - Comprehensive substance abuse history
 - Neuromedical assessment, including LP
 - Comprehensive NP battery
 - High ARV use
 - 71% current
 - 14% past only
 - 15% naive

HAND in CHARTER

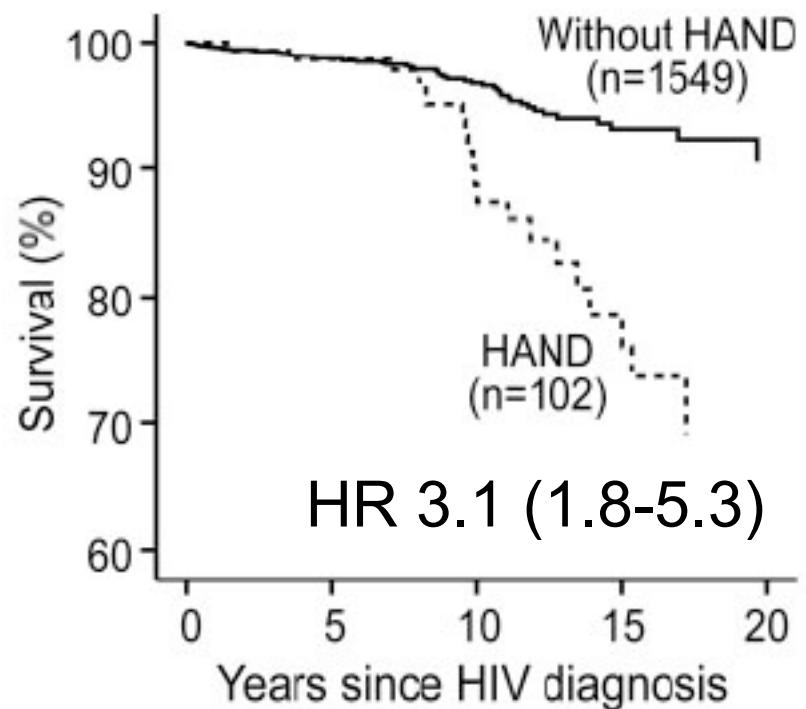


HAND in Aviremic Patients



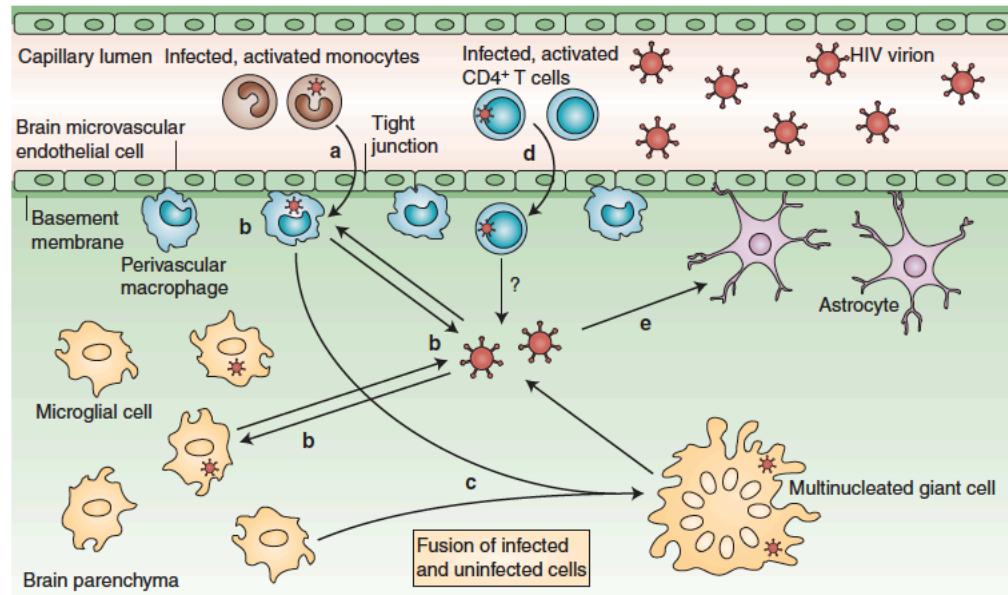
HAND Epidemiology

- High prevalence
 - Most is asymptomatic
- Increases risk of death
- Predictors
 - Lower current and nadir CD4
 - Shorter duration of ARV treatment
 - Shorter duration of being undetectable



HAND Etiology

- Productive infection of CNS
 - Drug resistance
 - Poor penetration
 - Poor adherence
- “Legacy” effect
 - Previous injury
- Comorbidities
 - Aging
 - Vascular disease
 - Cointfections
 - Drug abuse
- CART toxicities



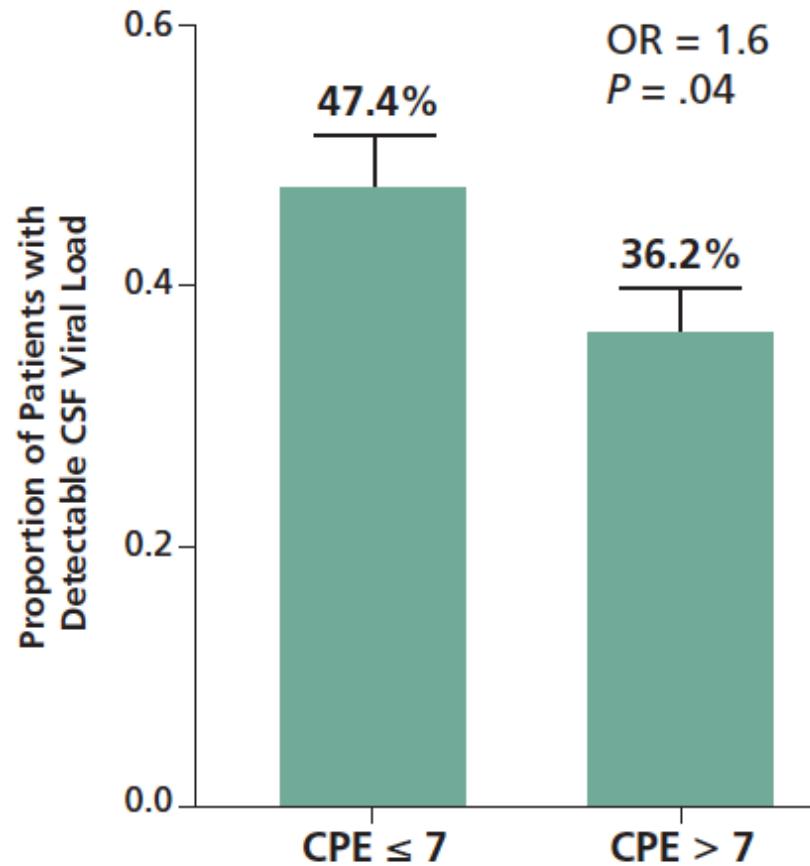
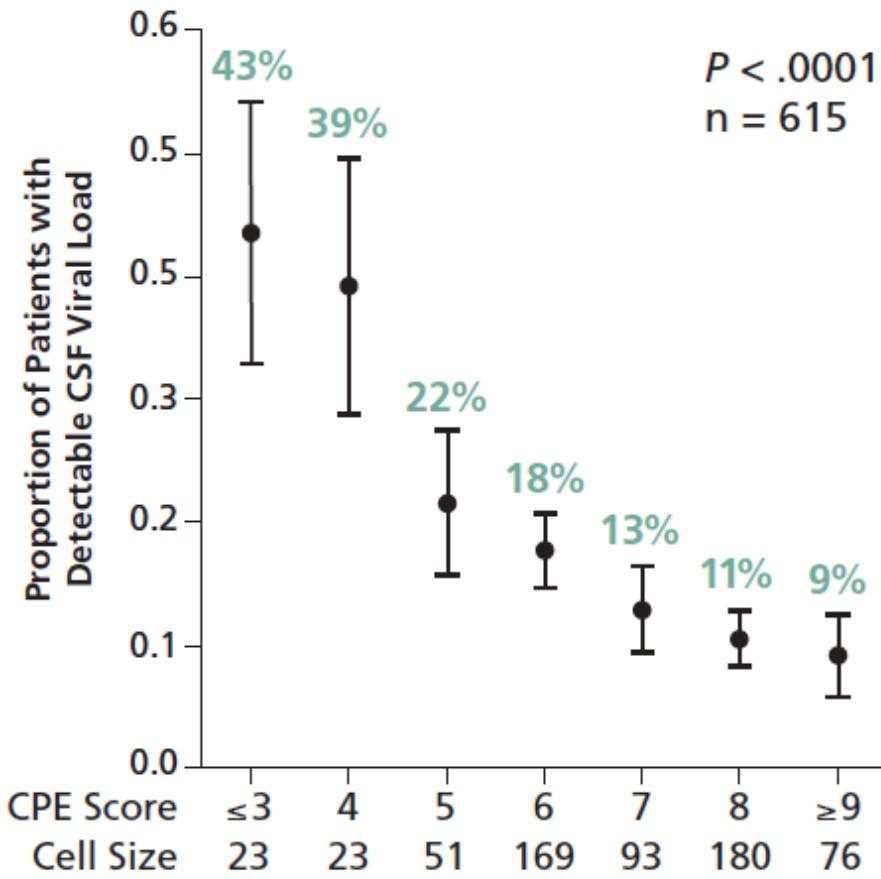
CNS Drug Penetration: 2008 CPE Rank

	1	0.5	0
NRTIs	Abacavir	Emtricitabine	Didanosine
	Zidovudine	Lamivudine	Tenofovir
		Stavudine	Zalcitabine
NNRTIs	Delavirdine	Efavirenz	
	Nevirapine		
PIs	Indinavir	Amprenavir-r	Amprenavir
	Indinavir-r	Atazanavir	Nelfinavir
	Lopinavir-r	Atazanavir-r	Ritonavir
			Saquinavir
			Saquinavir-r
			Tipranavir-r
Fusion/Entry			Enfuvirtide

2010 Revised CPE Rank

	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir-r	Nelfinavir
		Fosamp-r	Atazanavir	Ritonavir
		Indinavir	Fosamp	Saquinavir-r
		Lopinavir-r		Saquinavir
				Tipranavir-r
Fusion/Entry		Maraviroc		Enfuvirtide
Integrase		Raltegravir		

Regimens with Higher CPE More Effectively Suppress CSF HIV RNA



CPE and Cognitive Improvement

- Cysique LA et al. (Neurology 2009;73)
 - 37 NP impaired
 - 6 NPTs
 - Untreated or failing ARVs
 - CD4 196/ul
- Predictors of improvement
 - Lower baseline NP performance
 - 2008 CPE > 2

CPE and Cognitive Worsening

- Marra CM et al. (AIDS 2009;23)
 - 26 NP impaired
 - 4 NPTs
 - Untreated or failing ARVs
 - CD4 94/ μ l

ACTG 736: GEE Model		
	Z Score Estimate	P-value
Entry NPZ4	0.86	<0.001
# of ARVs	-0.38	0.001
2008 CPE \geq 2.0	-1.08	<0.001

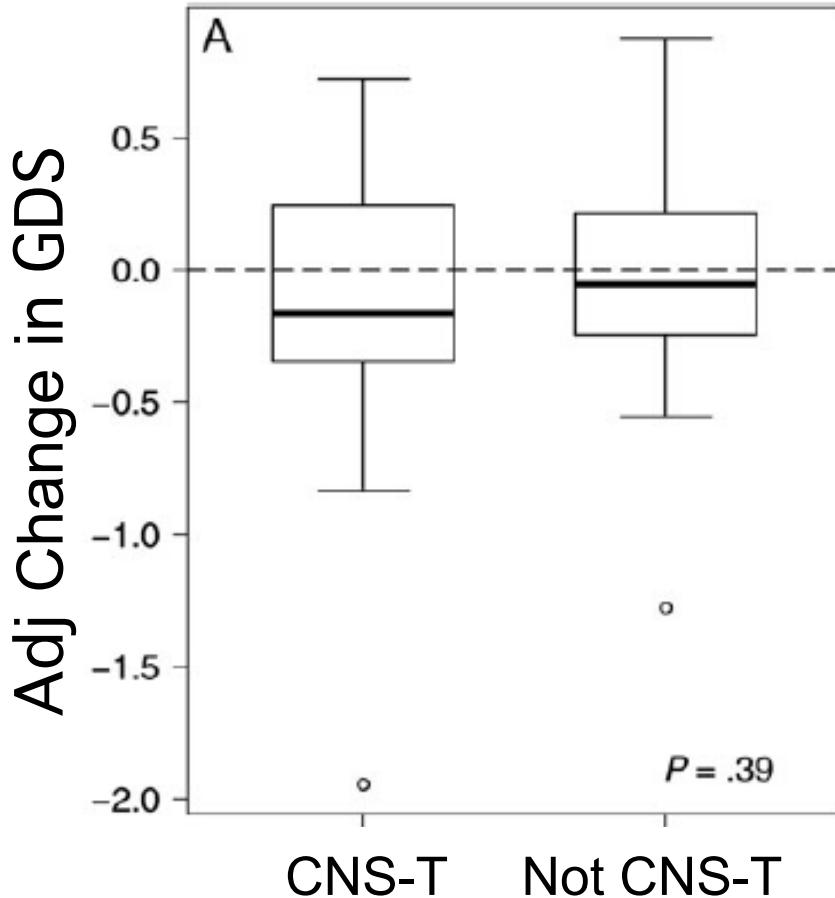
Limitations

- Study design differences
 - Cross-sectional vs. longitudinal
 - Observational
 - Bias in selection of CART regimens
- Inclusion and exclusion criteria differ
- Definitions of impairment differ
- Different NP batteries
- Population differences
 - Nadir CD4
 - Comorbidities

Trial of Neuro-targeted CART for HAND

- Multisite, randomized, controlled
- HAND
 - Initiating or changing ART
 - Randomized to CNS-Targeted (CNS-T) vs. not CNS-T
 - Median 2008 CPE 2.5 vs. 1.0
- Outcomes
 - Primary: change in NPT performance at 16 weeks
 - Secondary: proportion with virological suppression in plasma and CSF
- N=59
 - 26 CNS-T and 23 non CNS-T in ITT analysis
- Stopped because of slow recruitment

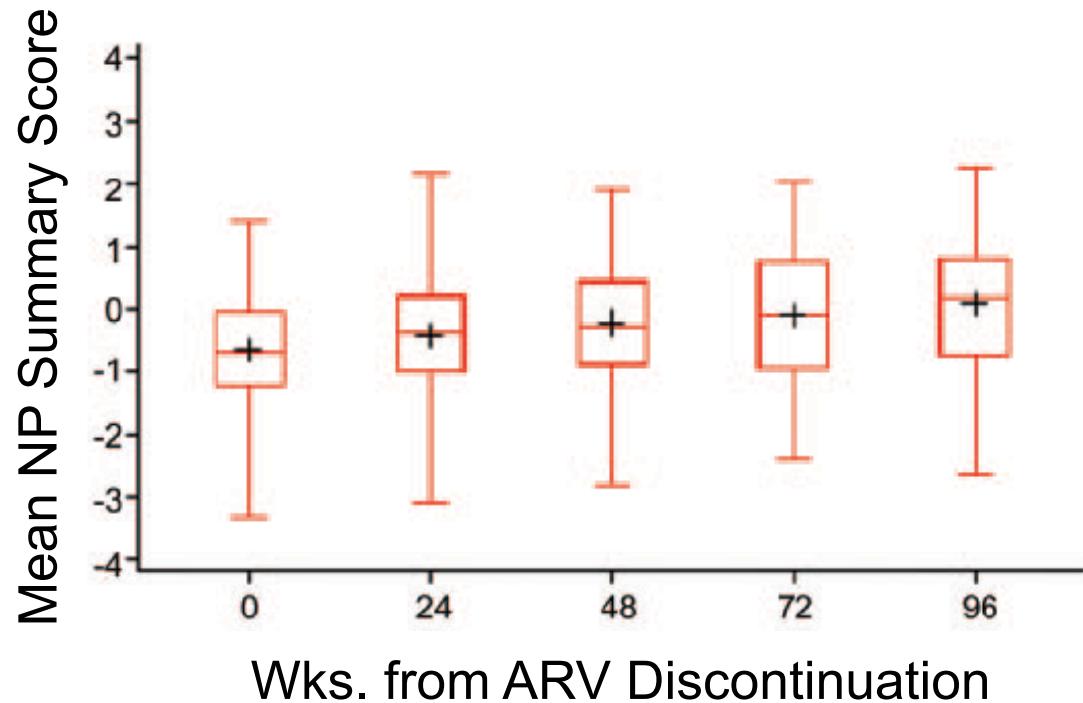
Neuro-targeted CART did not Improve Cognition



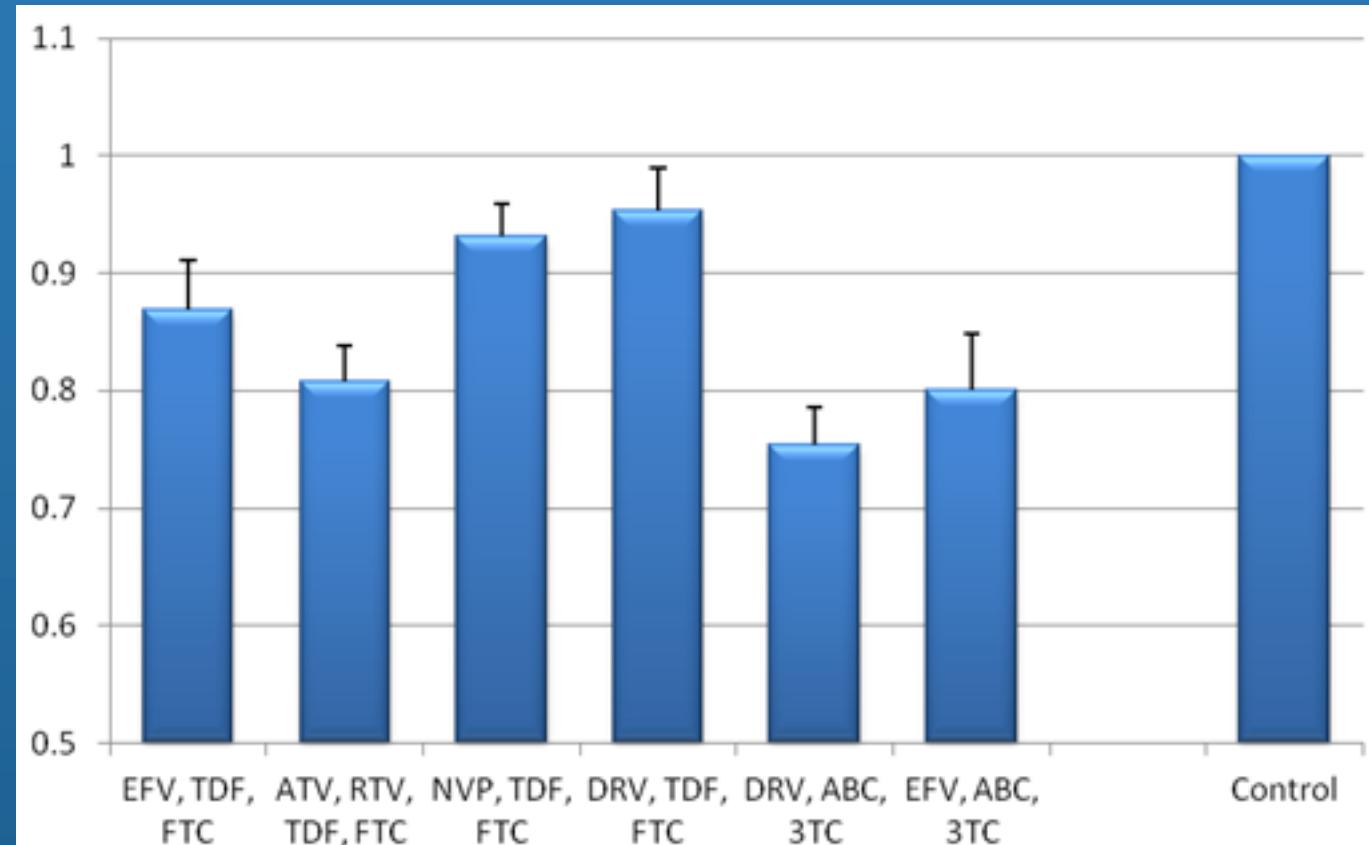
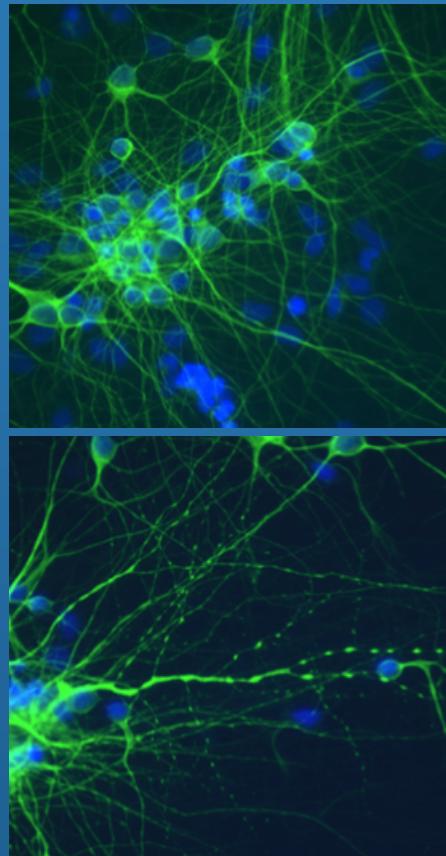
- Caveats
 - Incomplete accrual
 - Short follow-up
 - Baseline differences in CNS-T group
 - Lower nadir CD4
 - More HCV
 - Trend toward more agents
 - Trend toward poorer plasma suppression
- Is CNS-T CART neurotoxic?

CART Neurotoxicity: ACTG A5170

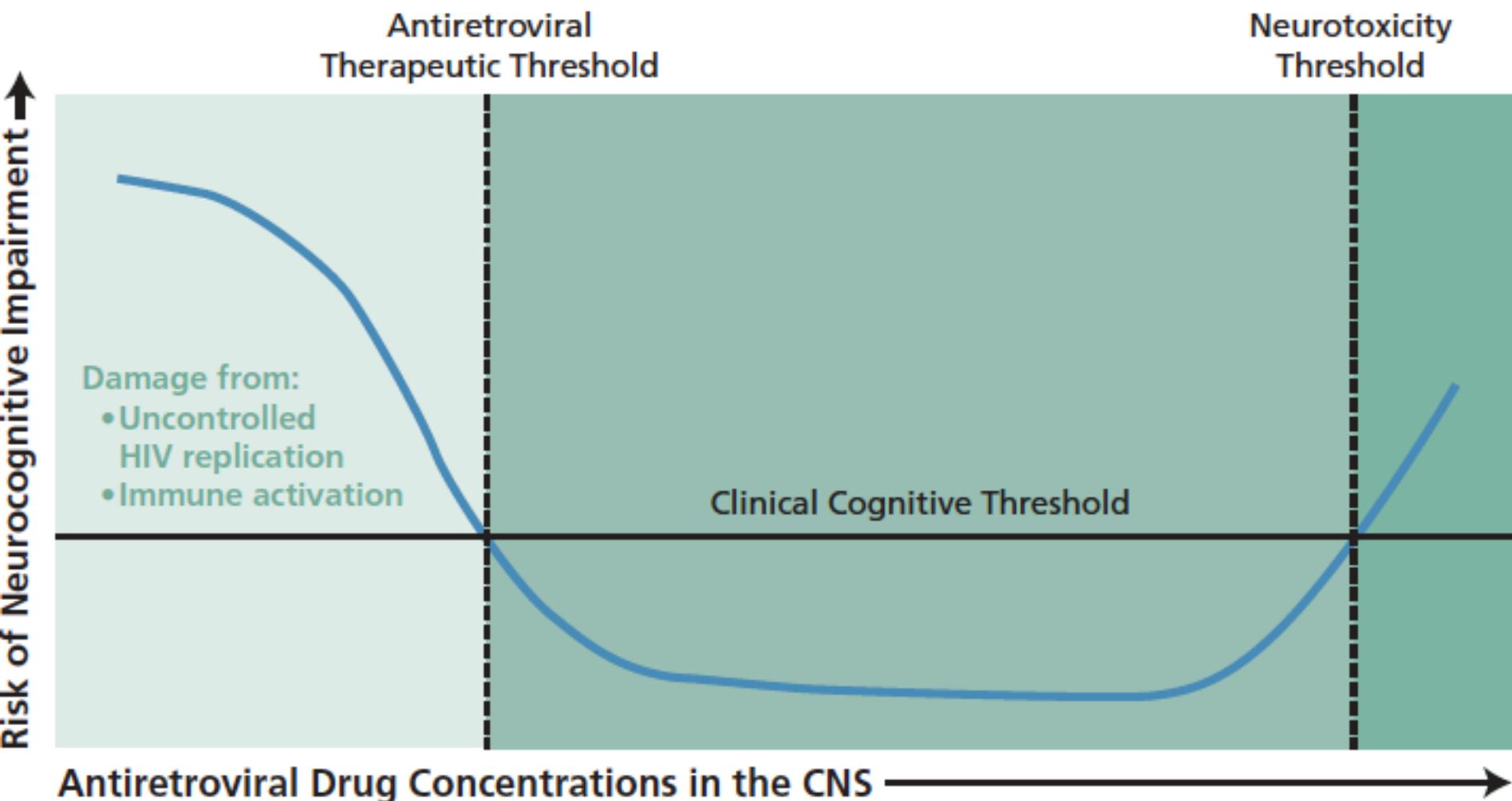
- 167 subjects
 - CD4 > 350/ μ l
 - Median 436/ μ l
 - HIV RNA < 55,000 c/ml
 - ≥ 2 ARVs X ≥ 6 months
 - DC ARVs, restart per investigator



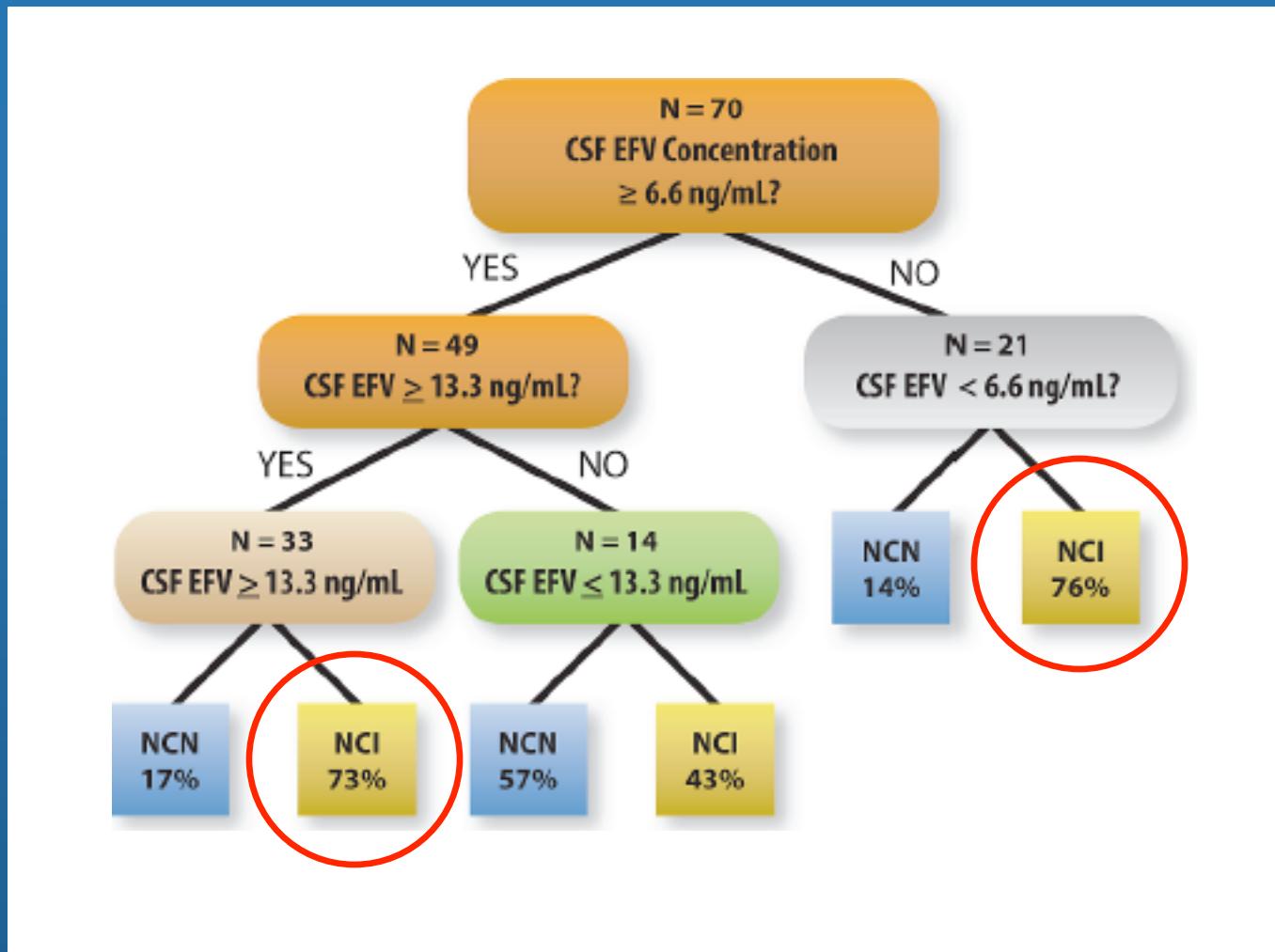
In vitro Neuronal Loss due to CART



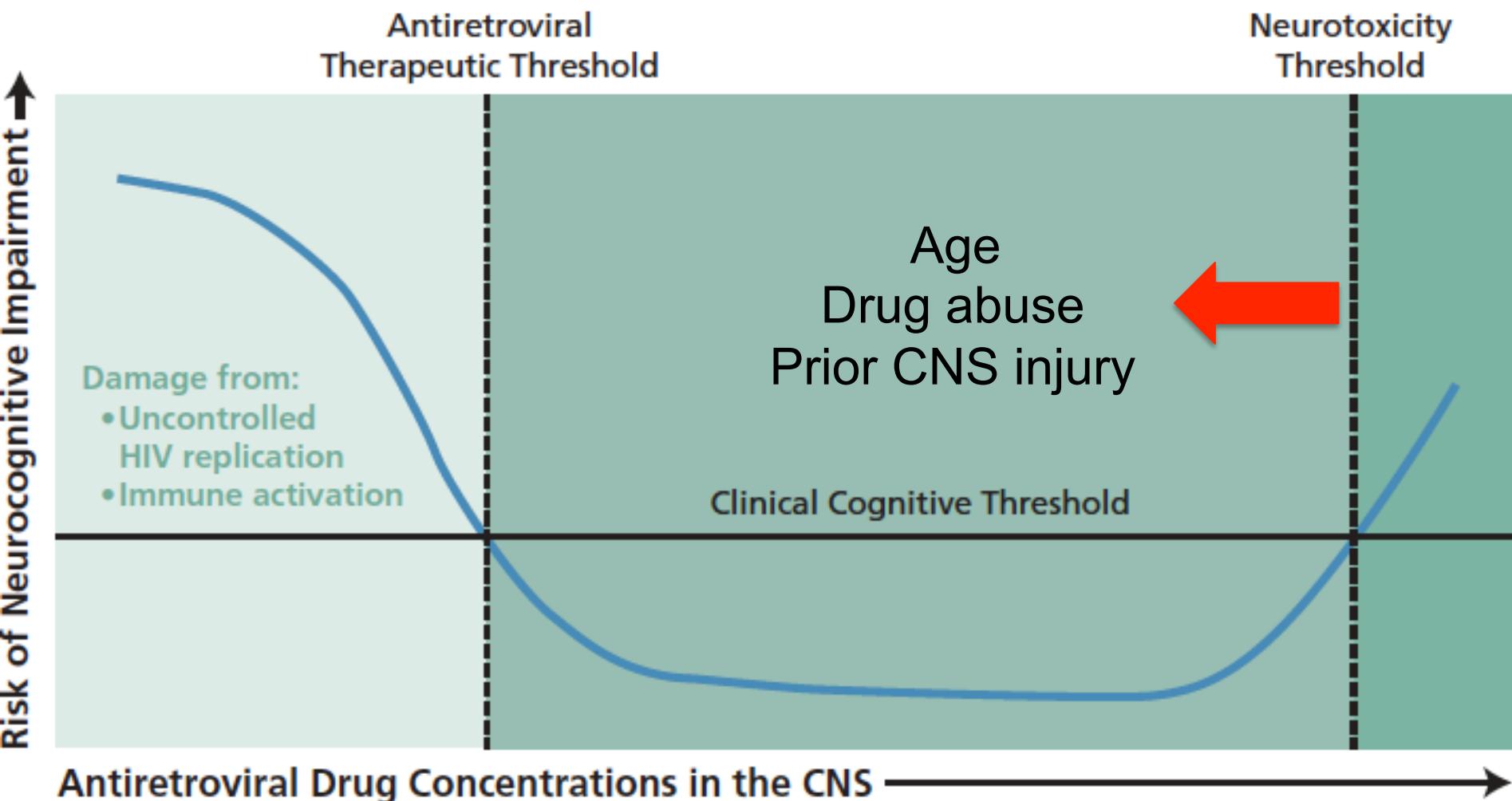
CART and Neurotoxicity



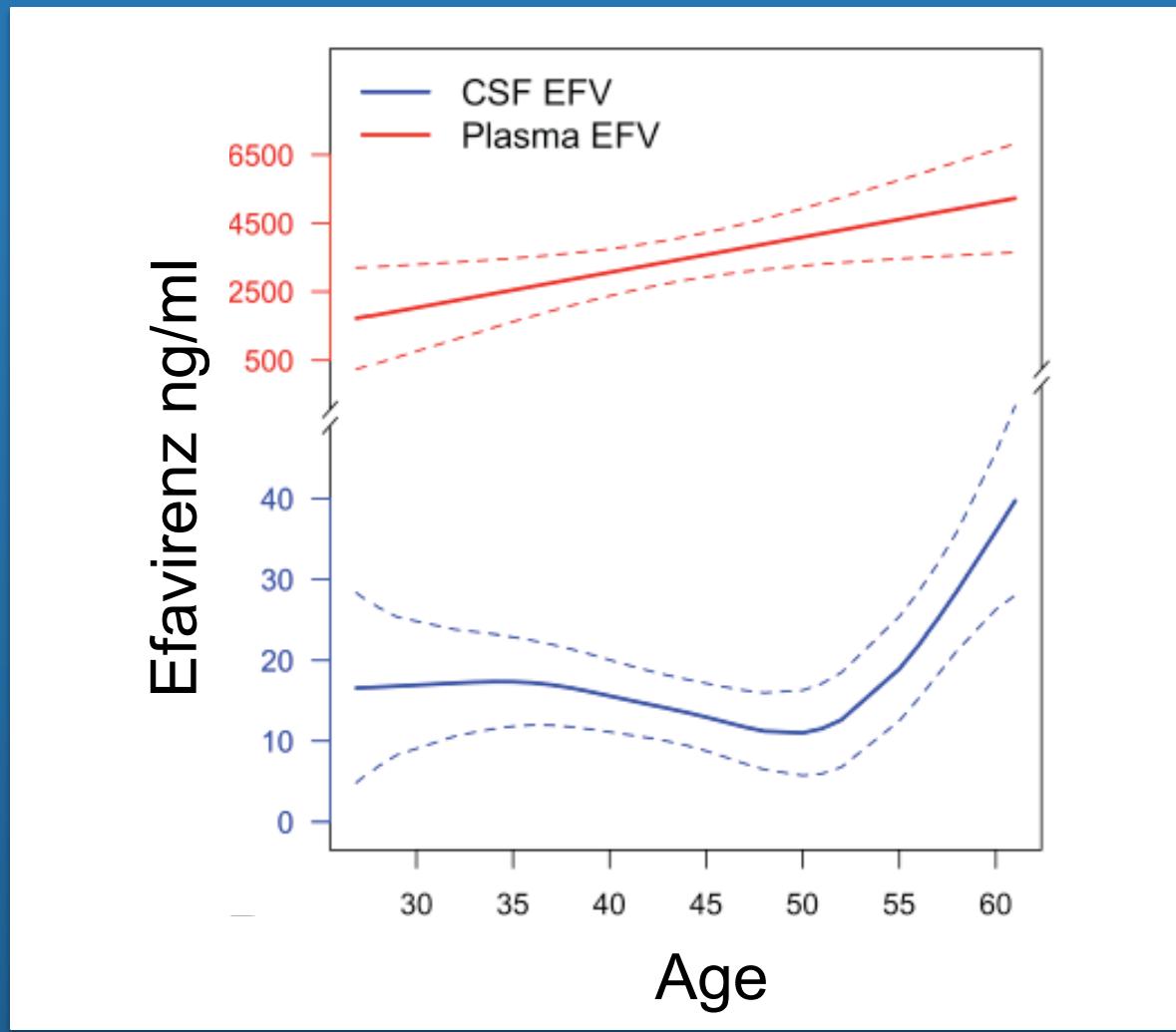
CNS Drug Concentrations can (theoretically) be Optimized



CART and Neurotoxicity



Increased CNS Drug Concentrations with Age



Summary

MY CLINIC 9 MAY 2014

- 53 year old MSM
- HIV-infected since 1998
- Nadir CD4 4 cells/ μ l
- Profoundly demented
- CD4 600/ μ l, RNA <20 c/ml
- On nevirapine and truvada (CPE=8)

WHAT TO DO?

- CNS penetration matters
- Can help or hurt
- Probably patient-dependent
- We lack the tools to tell the difference
- ?Should we measure CSF drug concentrations