Selecting the Right Drugs (for the CNS)

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		DHHS	EACS	BHIVA	WHO
TDF-FTC	EFV[1]	✓	✓	✓	✓
	ATV/r[1]	✓	✓	✓	
	DRV/r	✓	✓	✓	
	RAL	✓	✓	✓	
	EVG/c	✓	✓	✓	
	RPV[2]	✓	✓		
	DTG	✓	✓		
ABC-3TC	DTG	✓	✓		

[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

Recent CPE Reports Have Mixed Findings

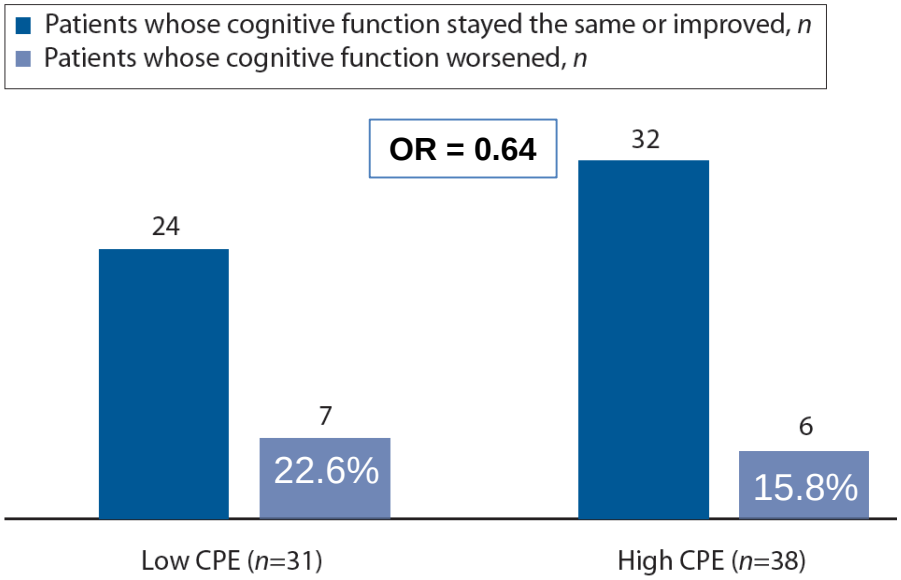
		N	NP	Duration	Principal Finding	Notes
Ciccarelli[1]	C-S	101	C	-	Beneficial	2010 version stronger than 2008 version
Ciccarelli[2]	C-S	215	C	-	Beneficial	Adjusted CPE using GSS
Casado[3]	C-S	69	B	-	Trend toward benefit	Beneficial when CD4 < 200
Vassallo[4]	L	96	C	22 months	Beneficial	~25% were not virologically 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.*

Two Uncontrolled Longitudinal Studies Found Similar Effect Sizes but Came to Different Conclusions

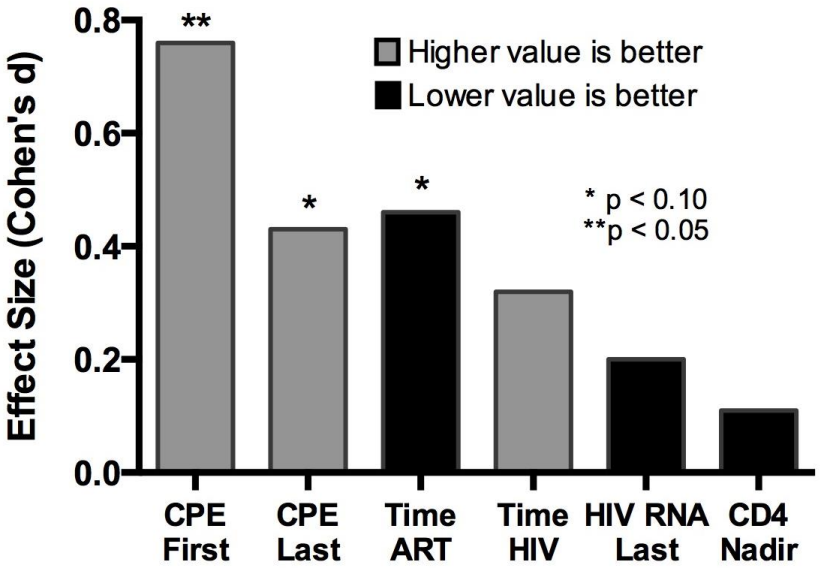
South Africa



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

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The relationship of CPE to HIV dementia

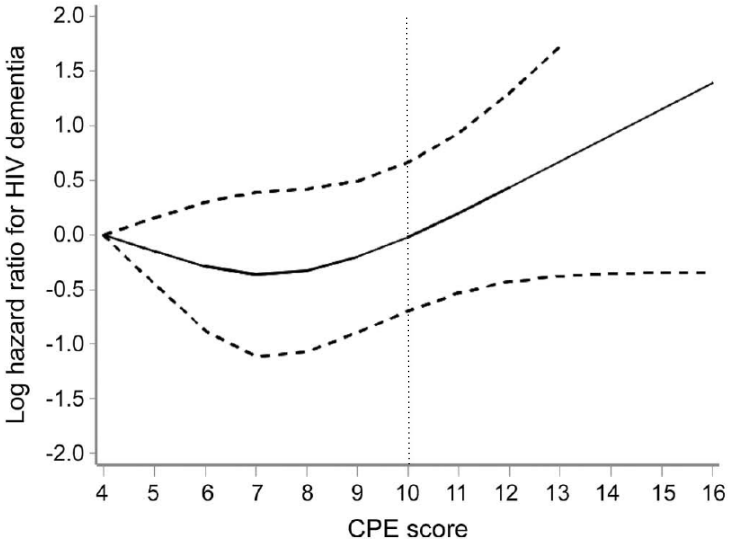
Slain by an ugly fact?

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”-like analysis
- CPE transformed into 3 categories
  - “Low”: ≤ 7
  - “Medium”: 8-9
  - “High”: ≥ 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?

- **Excluded subjects from 4 cohorts that had no neuroAIDS events**
- **Did not use standardized assessments for diagnosing "HAD"**
  - "…diagnostic procedures that reflect standard clinical practice"
- **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
- **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 important 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

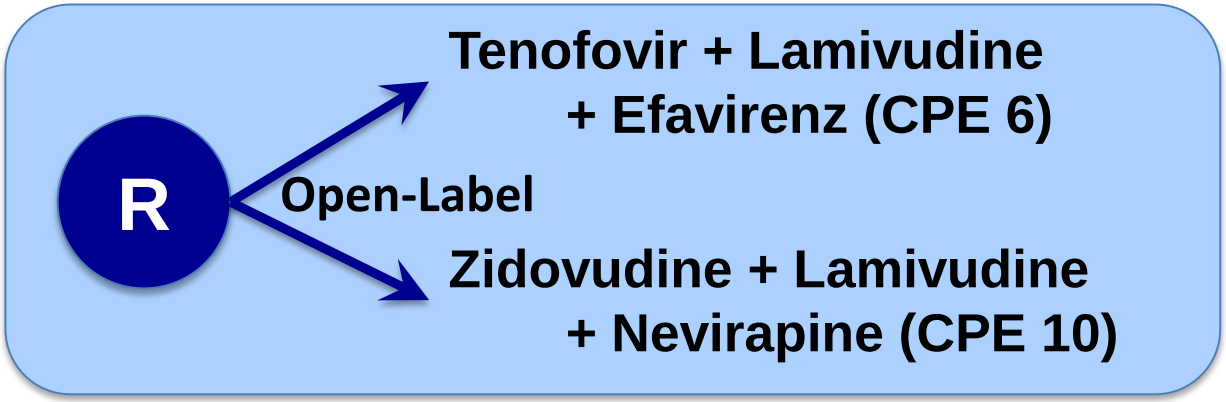
Caniglia et al, Neurology 2014;83:1–8; Berger & Clifford, Neurology 2014;83:1–2

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

- **Studies should be randomized and longitudinal**
- **Power and duration should be sufficient to test the hypothesis**
- **Assessments should be standardized and comprehensive**
- **Drug regimen potency and toxicity of comparator regimens should be similar**
  - For those that focus on CPE, regimens should have the same number of drugs

Clinical Trial of CNS Penetrating ART to *Prevent* NeuroAIDS in China

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



Follow-up: 96 Weeks at 2 Hospitals in Beijing
Safety Assessments
Neurocognitive and Mood Testing
Functional Assessments
Limited Pharmacogenetics
Inflammation Biomarkers

Funded by NIH R01 MH92225 (PI: Letendre)

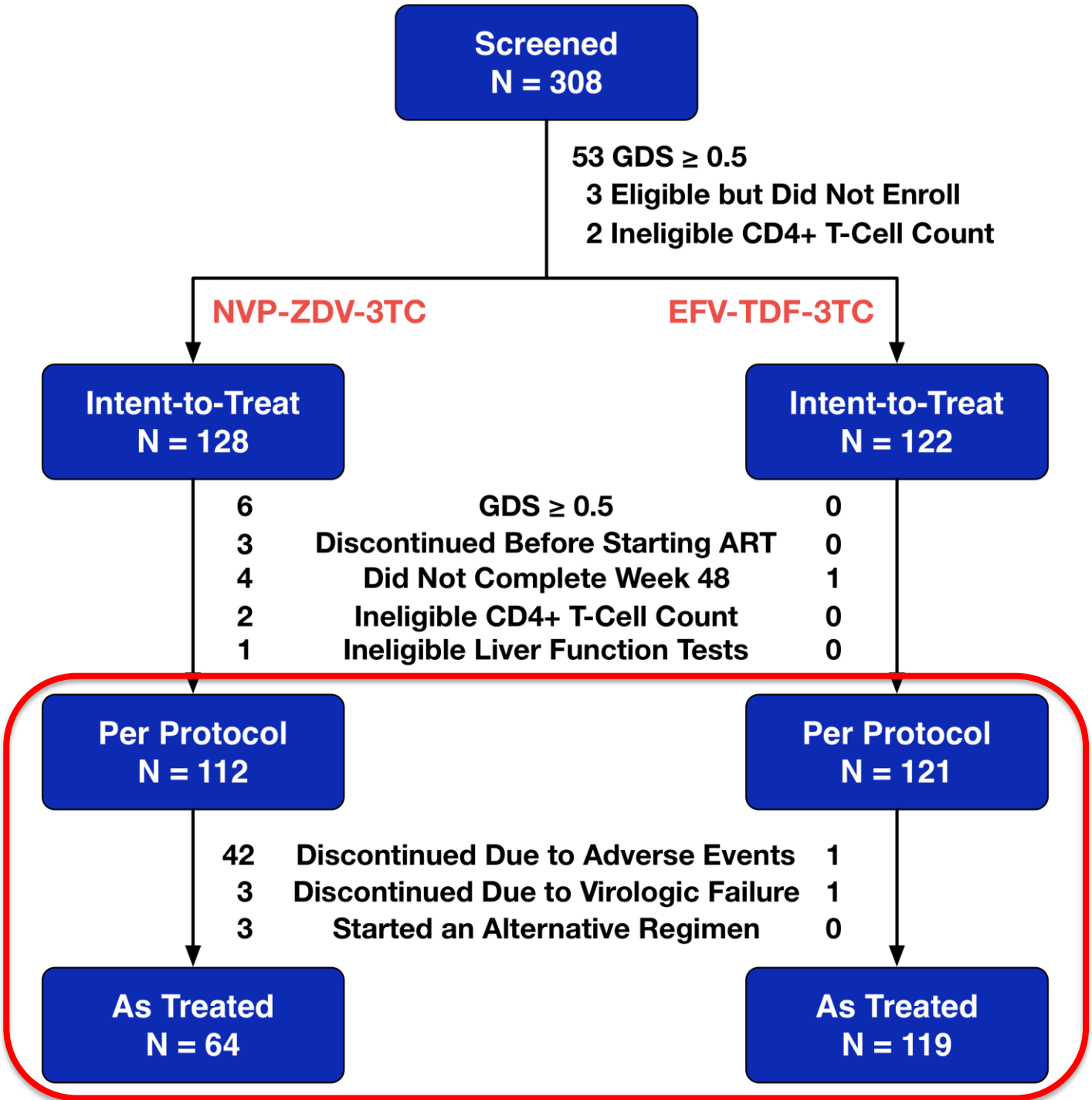
Zhang et al, CROI, 2015, Accepted

Neurocognitive Methods

- **An 8-test battery that assessed 5 cognitive abilities was administered along with a symptom questionnaire and functional assessment**
  - Assessments performed at 48 and 96 weeks
- **Cross-sectional & longitudinal normative data**
  - Adjust for effects of age, gender, education, and ethnicity in the HIV- population in China
- **Results were summarized by 3 methods**
  - Regression-based Summary Change Score*
  - Global deficit scores (GDS, continuous)
  - GDS-based neurocognitive impairment (binary)

Zhang et al, CROI, 2015, Accepted

* Primary outcome


Screened
N = 308
53 GDS ≥ 0.5
3 Eligible but Did Not Enroll
2 Ineligible CD4+ T-Cell Count
NVP-ZDV-3TC
EFV-TDF-3TC
Intent-to-Treat
N = 128
Intent-to-Treat
N = 122
6 GDS ≥ 0.5 0
3 Discontinued Before Starting ART 0
4 Did Not Complete Week 48 1
2 Ineligible CD4+ T-Cell Count 0
1 Ineligible Liver Function Tests 0
Per Protocol
N = 112
Per Protocol
N = 121
42 Discontinued Due to Adverse Events 1
3 Discontinued Due to Virologic Failure 1
3 Started an Alternative Regimen 0
As Treated
N = 64
As Treated
N = 119

Treatment Arms were Comparable

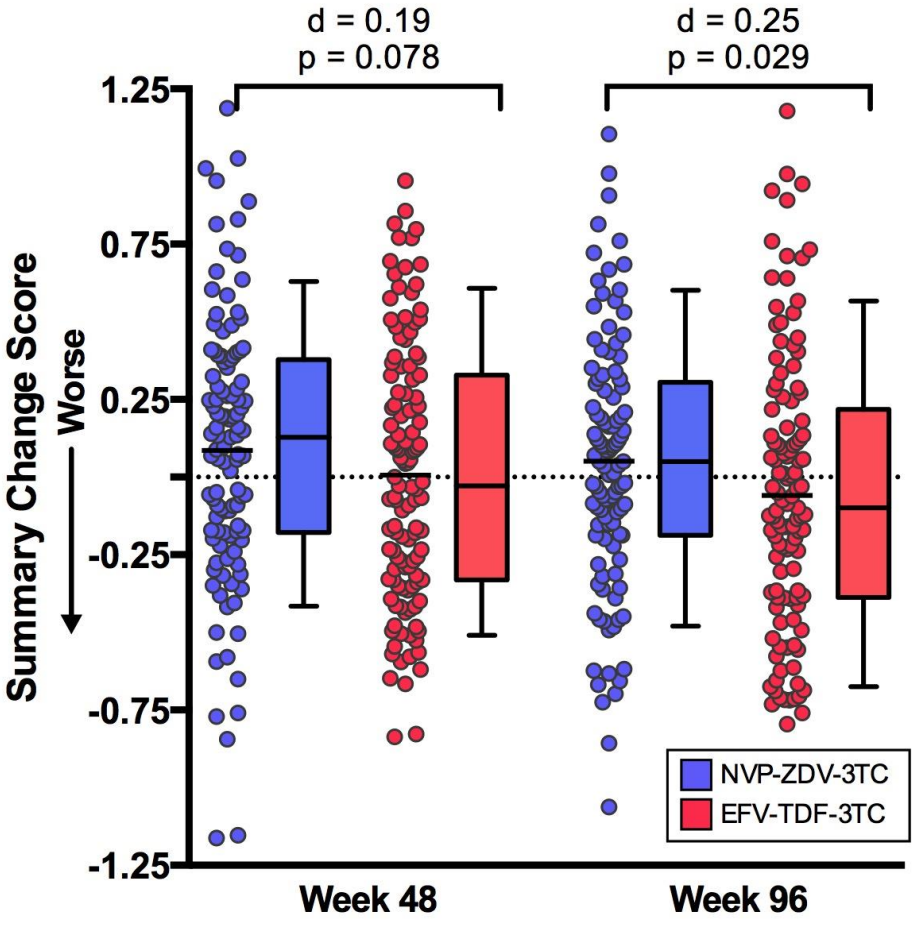
Baseline

	ZDV-3TC-NVP	TDF-3TC-EFV	P Value
Sample Size	128	122	-
Age (Years)	32.9 (7.7)	31.9 (8.3)	0.19
Sex (Number (%) Men)	124 (97%)	122 (100%)	0.12
Ethnicity (Number (%) Han)	121 (94.5%)	116 (95.1%)	0.84
AIDS Diagnosis	83 (66%)	81 (68%)	0.89
HIV RNA, Plasma (log_{10} c/mL)	4.2 (0.8)	4.2 (0.9)	0.95
CD4+ T-cells (/mm^3)	235.1 (89.8)	222.1 (83.6)	0.32
HCV Seropositive	3 (2%)	3 (2%)	1.00
Global Deficit Score	0.12 (0.15)	0.14 (0.14)	0.15

Week 48

	ZDV-3TC-NVP	TDF-3TC-EFV	P Value
Sample Size	112	121	-
HIV RNA, Plasma (≤ 50 c/mL)	108 (92%)	111 (92%)	0.65
CD4+ T-cells (/mm^3)	396 (157)	400 (161)	0.78
100% Adherence	117 (99%)	121 (100%)	0.49

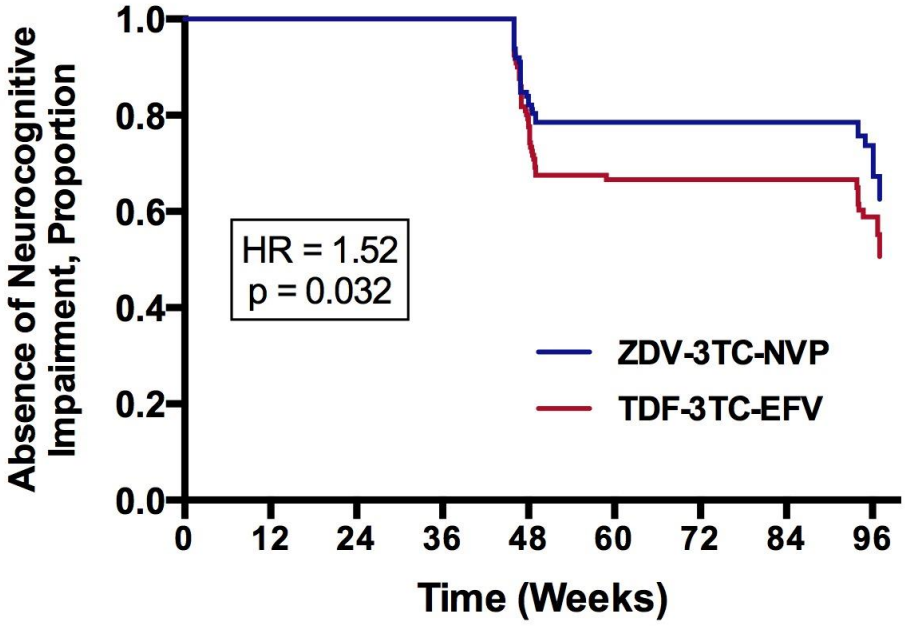
The Primary Outcome, Summary Change Score, Differed after 96 Weeks

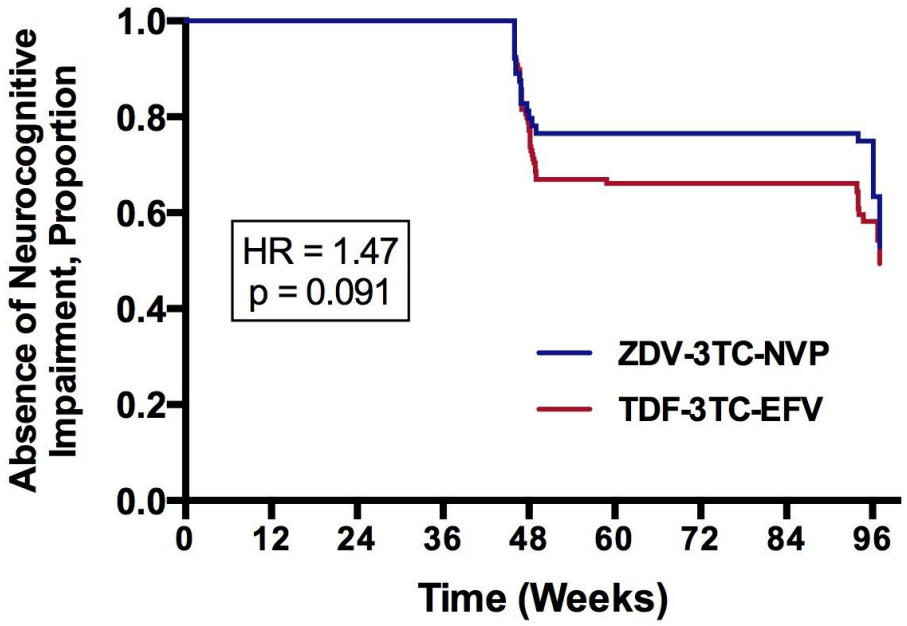


Per Protocol Analysis, N = 233

Zhang et al, CROI, 2015, Accepted

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





Per Protocol Analysis, N = 233

As Treated Analysis, N = 183

<u>Proportional Hazards multivariable analysis</u>: difference between arms was not substantially affected by including demographic (age, education, gender) or disease (HIV RNA, CD4+ count, AIDS) characteristics in multivariable models

Zhang et al, CROI, 2015, Accepted

Supplemental Project of 30 Subjects Was Performed

- **15 Neurocognitive Decliners were matched to 15 Non-Decliners for age, education, ethnicity, and baseline NC performance**
  - Decline determined at Week 48
- **23 successfully underwent lumbar puncture**
  - ART drug concentrations were measured in matched blood and CSF specimens

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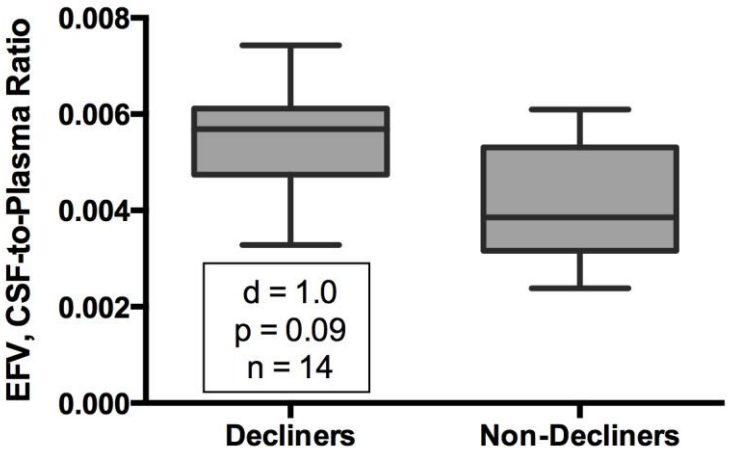
Cases & Controls were Comparable

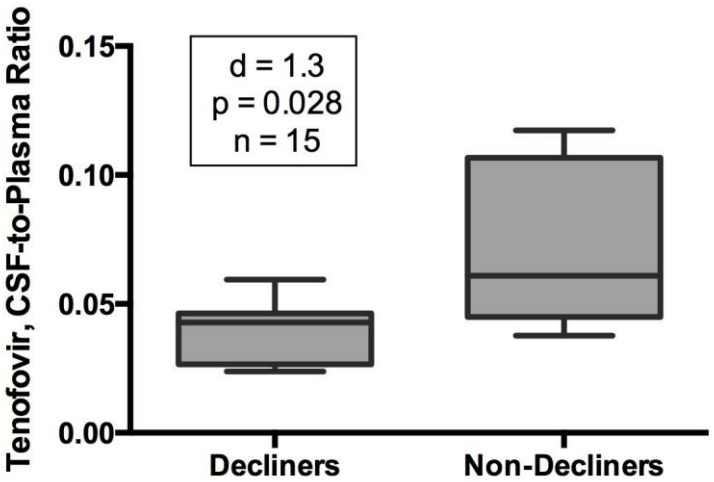
	Non-Decliners	Decliners	P Value
Sample Size	11	12	-
Global Deficit Score	0.11 (0.15)	0.76 (0.25)	< 0.0001
Age (years)	32.8 (6.3)	33.0 (8.8)	0.95
Sex (men)	11 (100%)	12 (100%)	1.00
Randomized Regimen			0.54
- EFV-TDF-3TC	5 (45.5%)	7 (58.3%)	
- NVP-ZDV-3TC	6 (54.5%)	5 (41.7%)	
Post-Dose Sampling Time	12.9 (5.4)	10.6 (4.7)	0.28
Baseline HIV RNA, Plasma (log_{10} c/mL)	4.5 (0.6)	4.3 (0.9)	0.51
Current HIV RNA, Plasma (Number (%) ≤ 50 c/mL)	10 (90.9%)	11 (91.7%)	0.95
Current CD4+ T-cells (/mm^3)	360.1 (92.5)	418.0 (136.8)	0.24
Nadir CD4+ T-cells	229.9 (59.3)	256.3 (49.5)	0.26

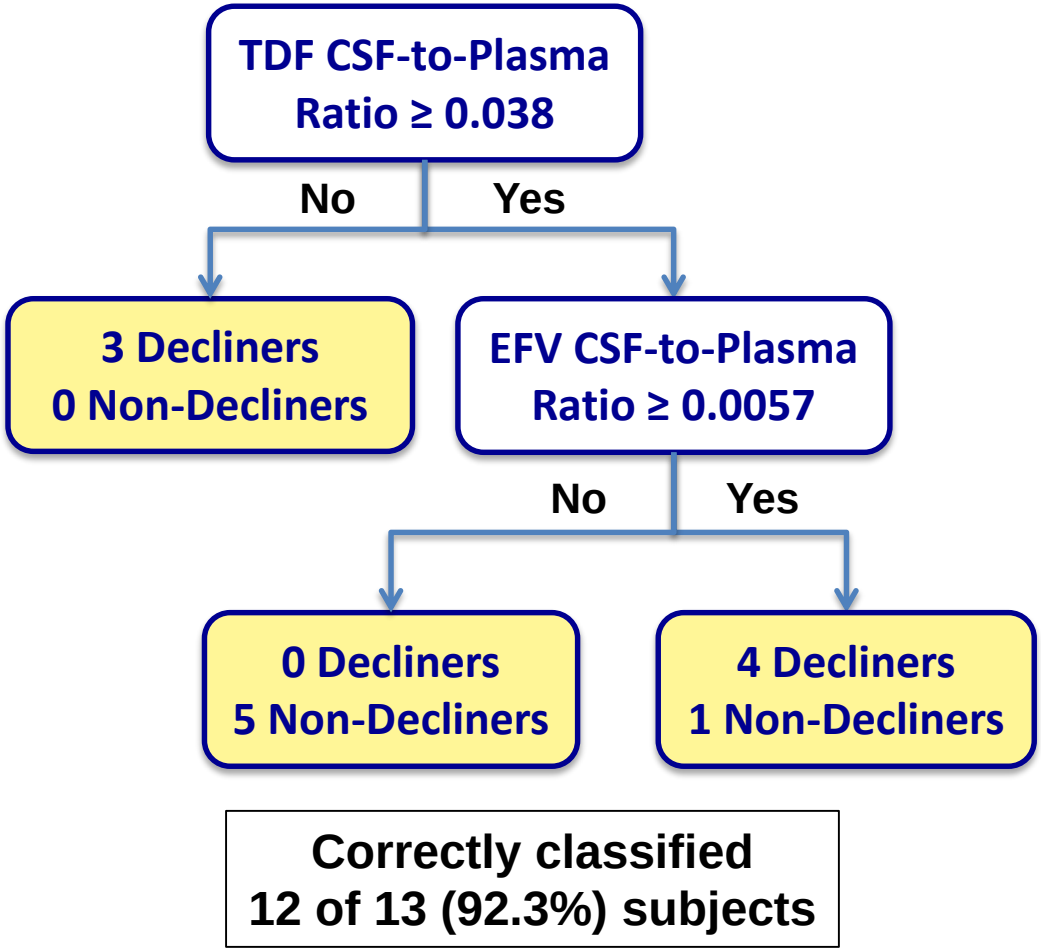
Funded by NIH R01 MH92225 (PI: Letendre)

Ma et al, CROI, 2015, Accepted

Cases & Controls Differed by CSF-Plasma Ratios of EFV & TDF







Ma et al, CROI, 2015, Accepted

ART Drug Concentrations in Brain: Regional Variation, CSF Comparability

	n	Overall Mean	WM (mean)	GP (mean)	CGM (mean)
Concentrations Similar to Historical CSF Concentrations					
Atazanavir (ATV)	2	< 25	< 25	< 25	< 25
Efavirenz (EFV)	2	38.6	45.2	34.8	35.9
Emtricitabine (FTC)	4	181.3	230.4	173.2	140.3
Lamivudine (3TC)	3	196.9	205.5	209.8	175.4
Concentrations in White Matter Higher than Historical CSF Concentrations					
Lopinavir (LPV)	4	153.3	410.6	< 25	< 25
Concentrations Higher than Historical CSF Concentrations					
Tenofovir (TDF)	6	206.0	220.0	212.1	185.8

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

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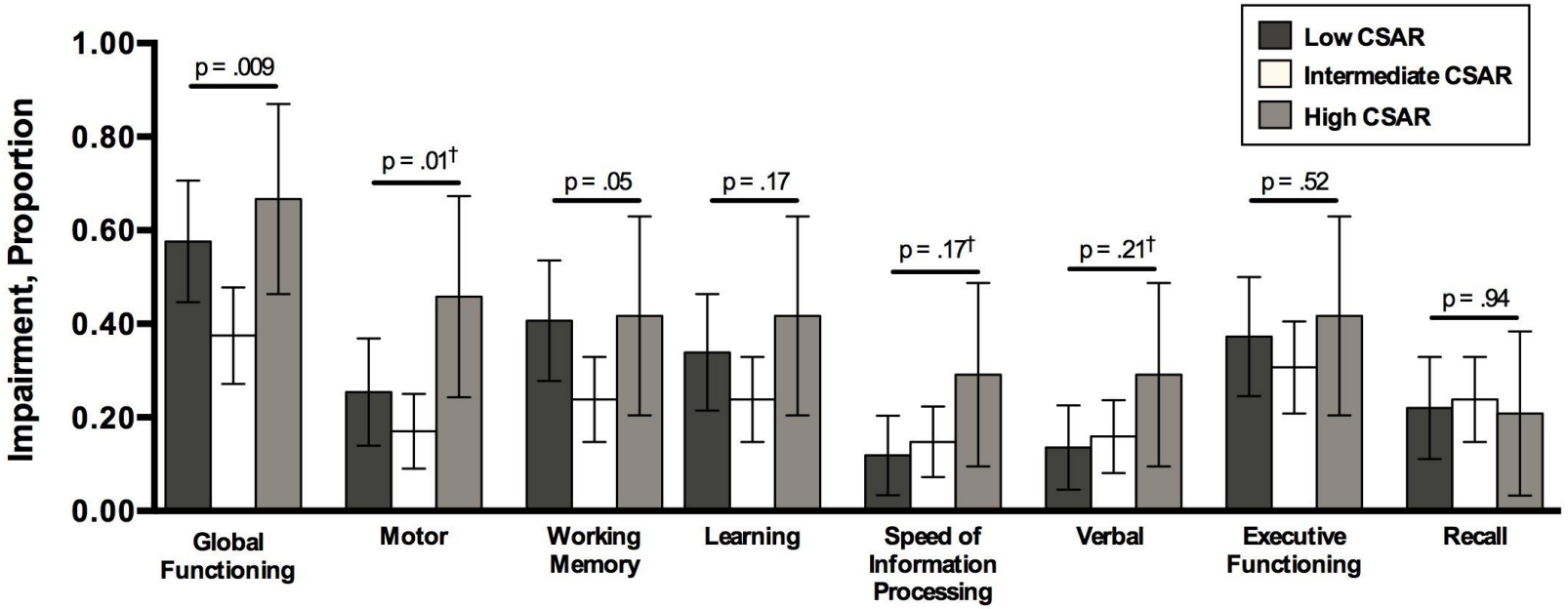
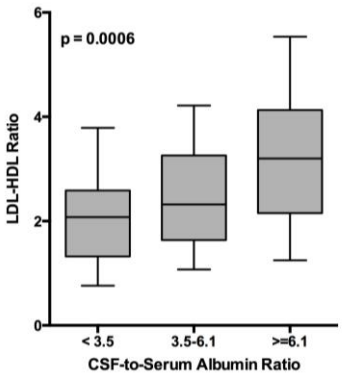
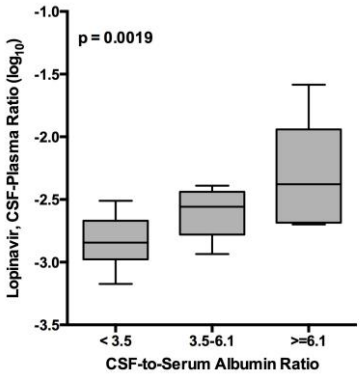
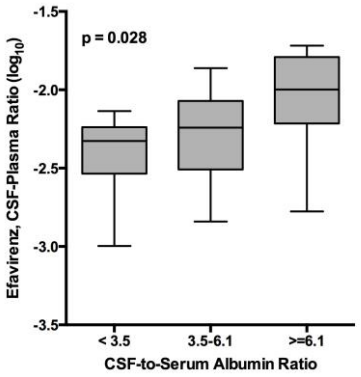
Bumpus et al, CROI, 2015, Accepted

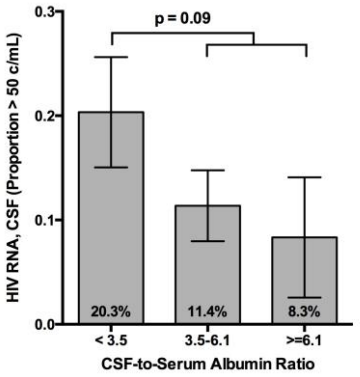
BBB Permeability During ART May Define Different HAND Phenotypes

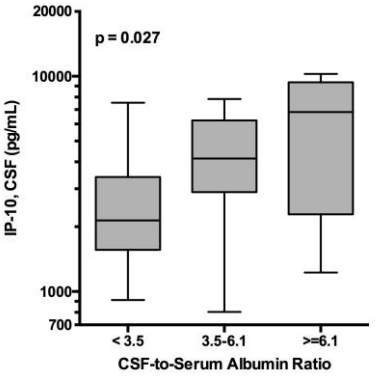












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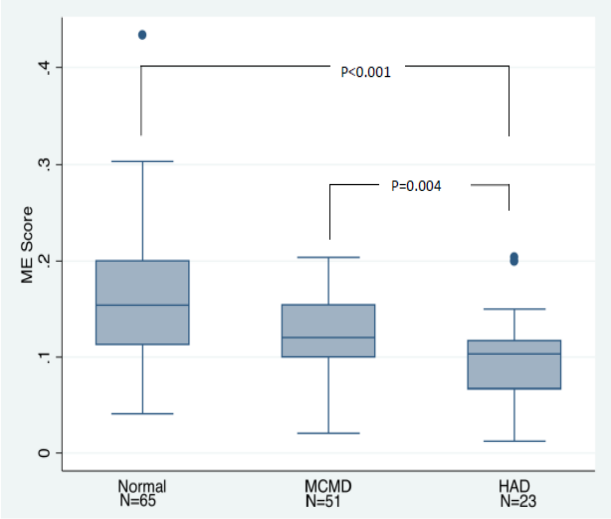
CHARTER Data, Manuscript in Preparation

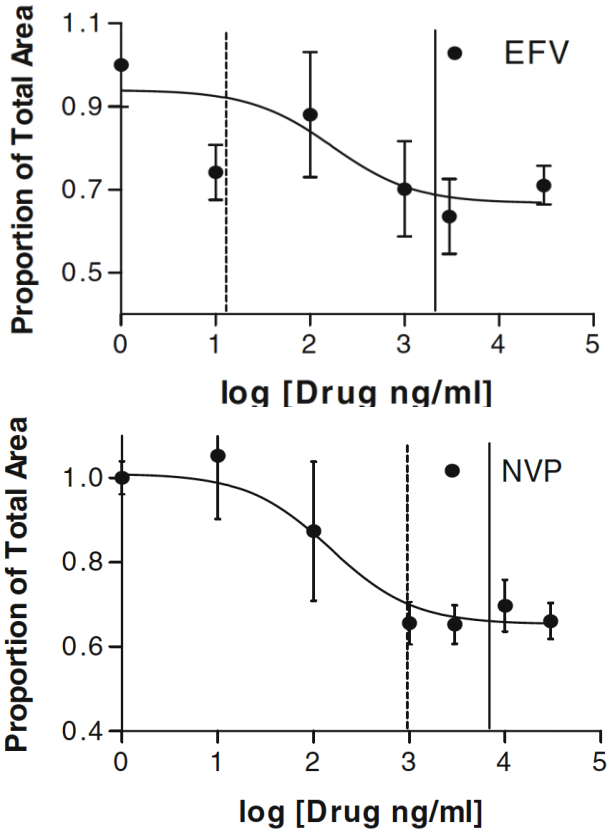
Other Characteristics May Influence the ART Efficacy & Safety in the CNS

Monocyte Efficacy



Shikuma et al, Antiviral Therapy 2012, 17: 1233-42

Neuronal Toxicity



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

Combined Characteristics May Alter Estimates of CNS Effectiveness

	CPE (1-4) Higher is Better	ME (3-333) Higher is Better	Toxicity Index Lower is Better
Zidovudine	4	50	-0.75
Tenofovir	1	50	-0.25
Abacavir	3	3	+2.75
Lamivudine	2	50	+0.40
Emtricitabine	3	12.5	-0.75
Efavirenz	3	100	-0.10
Nevirapine	4	20	+1.75
Atazanavir	2	-	+0.75
Darunavir	3	-	-1.50
Lopinavir	3	-	-
Maraviroc	3	-	-1.90
Raltegravir	3	-	-

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Atazanavir	2	-	+0.75
Darunavir	3	-	-1.50
Lopinavir	3	-	-
Maraviroc	3	-	-1.90
Raltegravir	3	-	-

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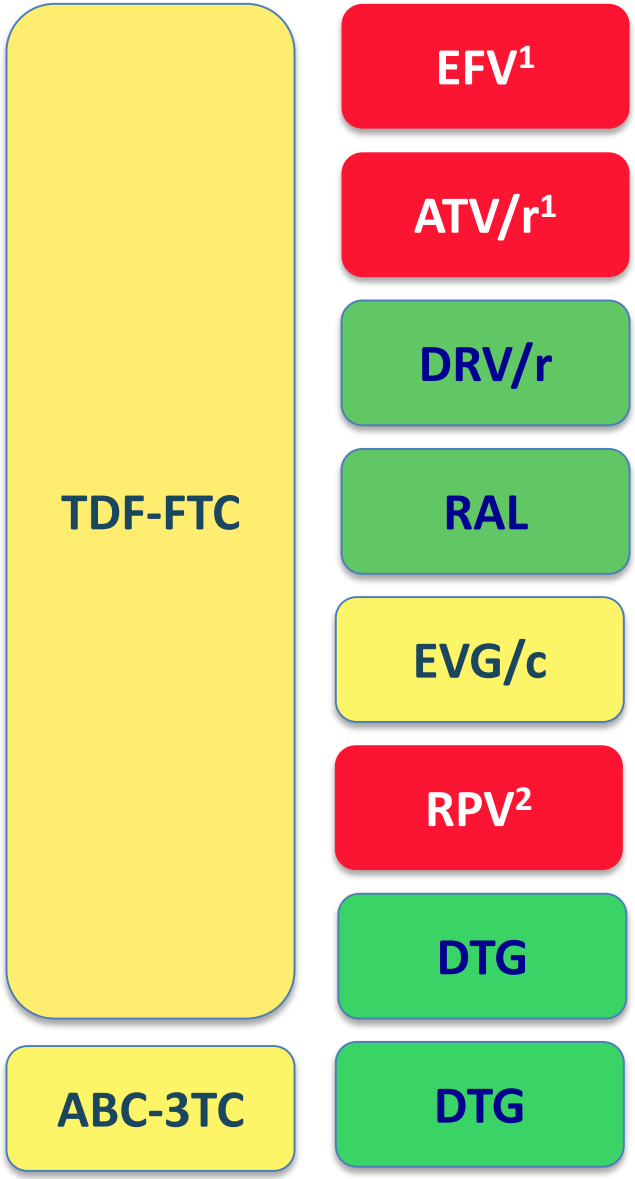
Atazanavir	2	-	+0.75
Darunavir	3	-	-1.50
Lopinavir	3	-	-
Maraviroc	3	-	-1.90
Raltegravir	3	-	-


NVP-ZDV-3TC
EFV-TDF-3TC
Per Protocol
N = 112
Per Protocol
N = 121
42 Discontinued Due to Adverse Events 1
3 Discontinued Due to Virologic Failure 1
3 Started an Alternative Regimen 0
As Treated
N = 64
As Treated
N = 119

DHHS Preferred Regimens (ART Naive)



- **Short- and long-term neurotoxicity**
- **CSF concentrations do not consistently exceed inhibitory concentrations**
- **Associated with CSF viral escape**
- **CSF concentrations exceed 50% inhibitory concentrations in all**
- **CSF concentrations exceed 50% inhibitory concentrations in all**
- **No CSF pharmacokinetic data**
- **CSF concentrations do not consistently exceed inhibitory concentrations**
- **CSF concentrations exceed 50% inhibitory concentrations in all**
- **Fewer CNS side effects than EFV**
- **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

		DHHS	EACS	BHIVA	WHO
TDF-FTC	EFV[1]	✓	✓	✓	✓
	ATV/r[1]	✓	✓	✓	
	DRV/r	✓	✓	✓	
	RAL	✓	✓	✓	
	EVG/c	✓	✓	✓	
	RPV[2]	✓	✓		
	DTG	✓	✓		
ABC-3TC	DTG	✓	✓		

[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

Summary & Conclusions

- **Published reports of the cognitive effects of ART continue to have inconsistent findings**
  - Substantial variation in methods
  - Few studies use ideal methods or have sufficient power to address the questions
- **Randomized clinical trial in China supports differences in two ART regimens in preventing HAND**
  - Effect sizes are small to medium
  - May be due to both ineffectiveness and toxicity in the CNS
- **BBB permeability may define different HAND phenotypes that may inform clinical management**
  - Independent confirmation is needed
- **Selecting the "right" ART for the CNS should consider effectiveness and toxicity outside the CNS**

Acknowledgements & Conflicts

Study Volunteers

UC San Diego

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- Wu Hao
- Zhao Hongxin
- Wu Weiwei
- Shi Chuan
- Zhang Hongwei
- Han Ning
- Zeng Hui
- Liu Xia

National Institutes of Health

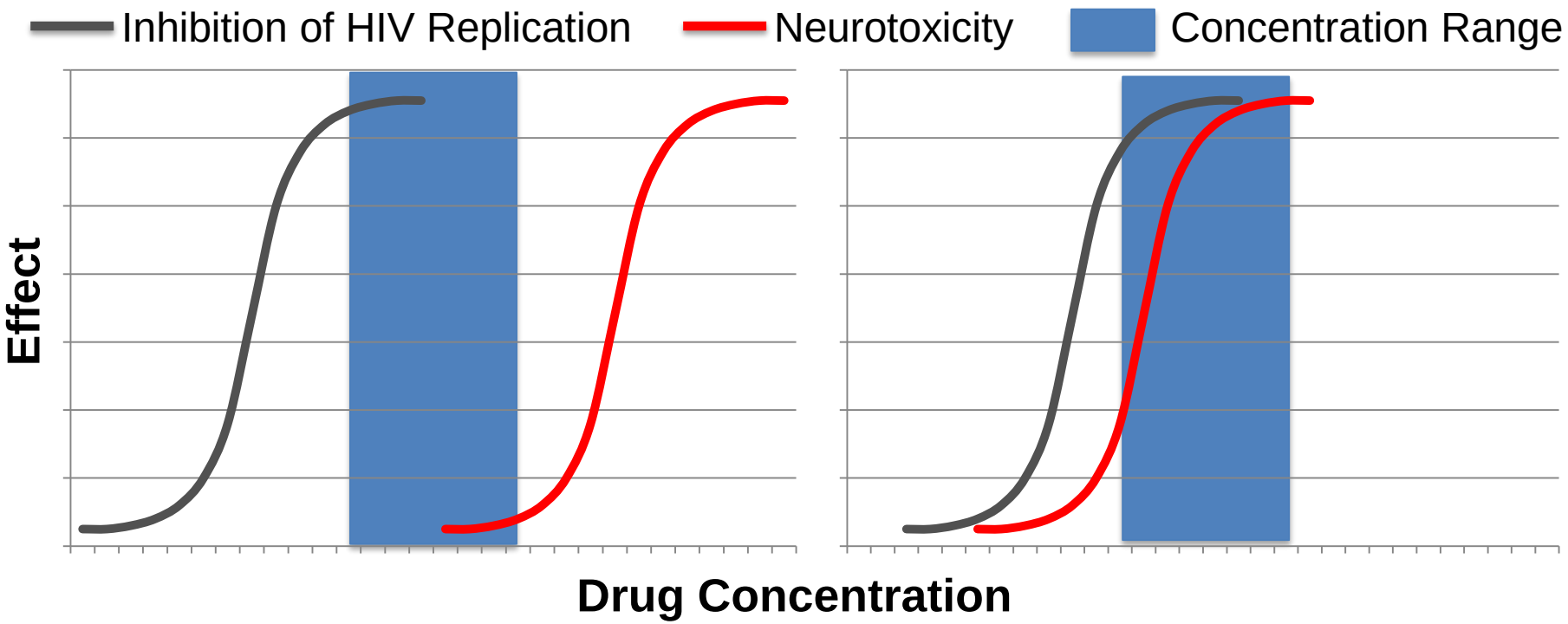
- …Mental Health
- …Drug Abuse
- …Allergy and Infectious Diseases

Industry

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

La Familiglia di Torino

Inhibitory, Toxic, and Pharmacologic Concentrations Vary By Drug



- **It does not necessarily follow that a drug that reaches more efficacious concentrations in the CNS will also reach more toxic concentrations**