

Rethinking Antiretroviral Neurotoxicity

Scott Letendre, M.D.

University of California, San Diego



Disclosures

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

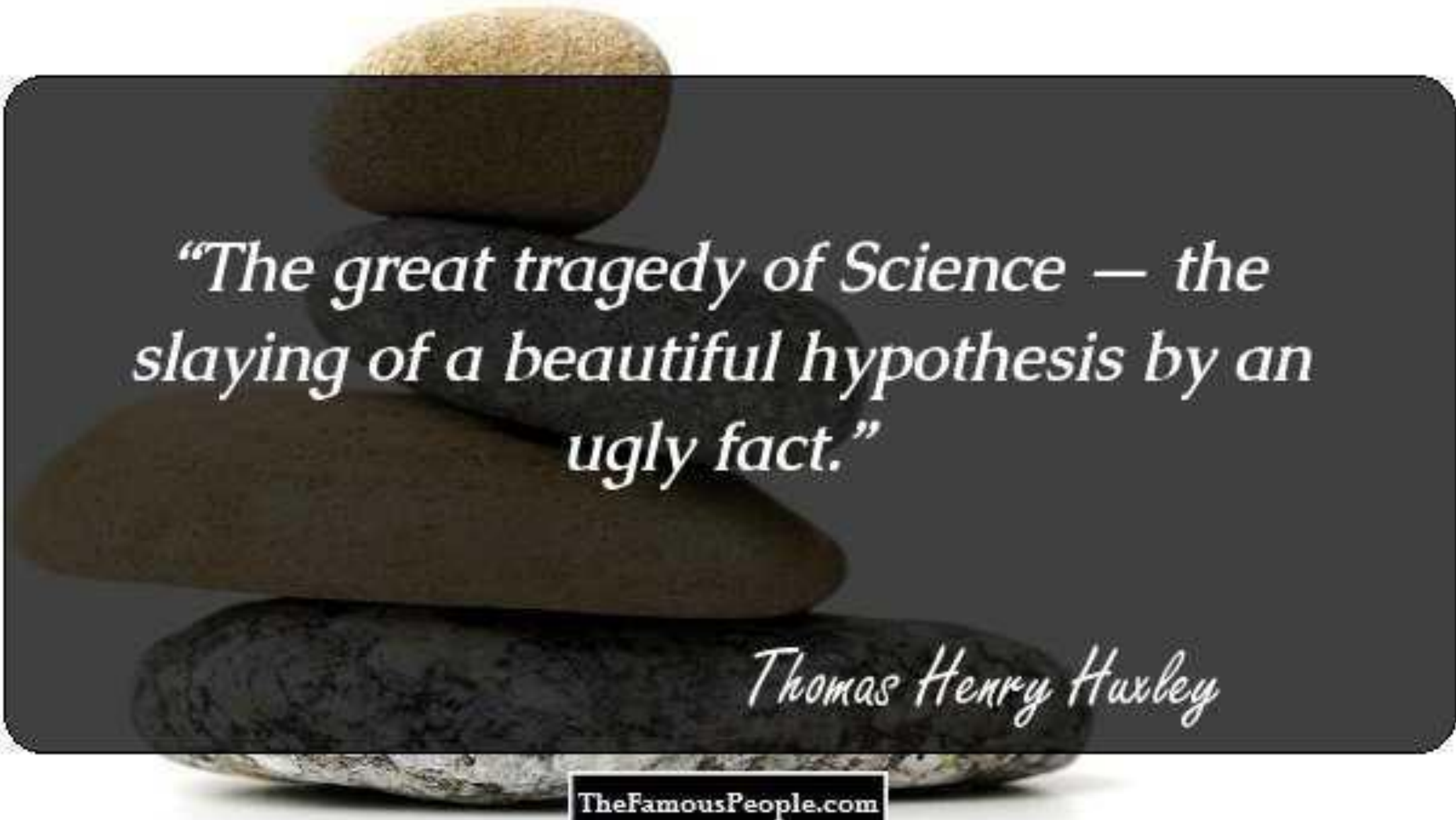
- National Institutes of Health
- Gilead Sciences

Travel expenses were paid for Dr. Letendre:

- ViiV Healthcare

Dr. Letendre was paid for a lecture:

- None



*“The great tragedy of Science — the
slaying of a beautiful hypothesis by an
ugly fact.”*

Thomas Henry Huxley

ART-Mediated Neuropsychiatric Adverse Events (NP AEs)

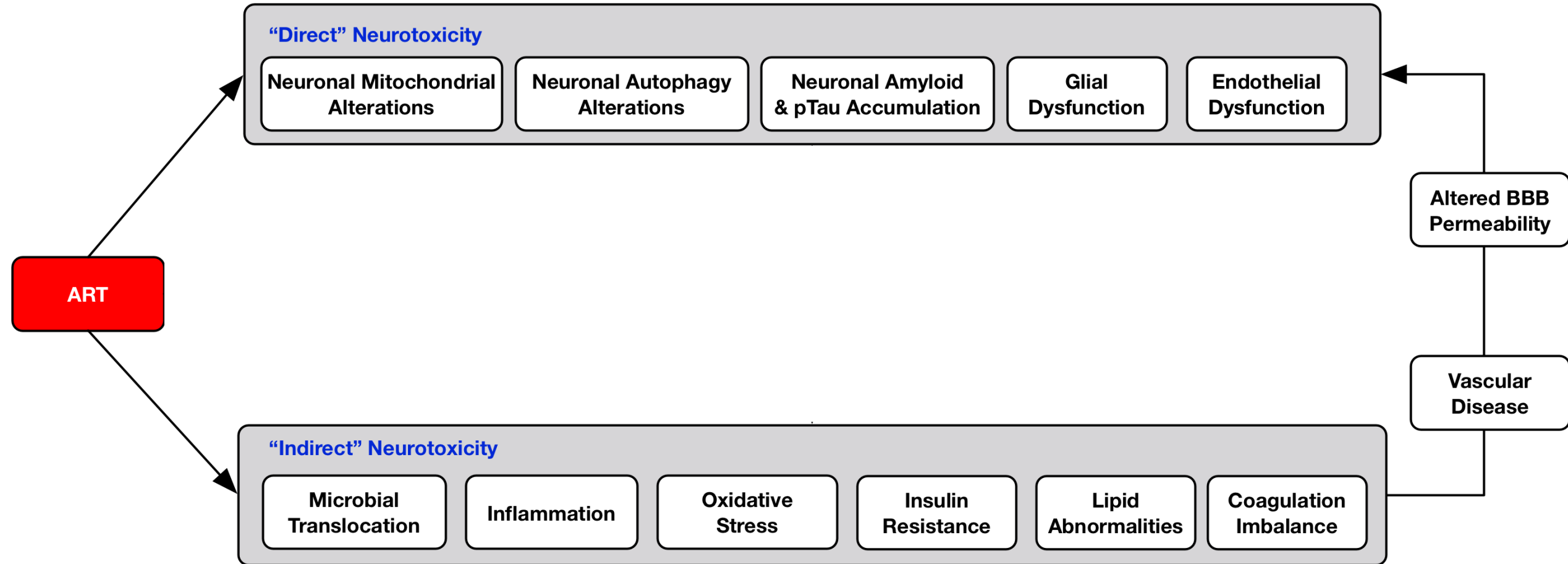
What We Know

- **Drugs have off-target effects**
 - ART drugs are no exception
- **Multiple factors worsen vulnerability of PLWH to NP AEs**
 - Psychiatric & Medical Comorbidities
 - Aging & Polypharmacy
 - Genetic variation
- **Mechanisms include mitochondrial, protein processing, and amyloid effects**

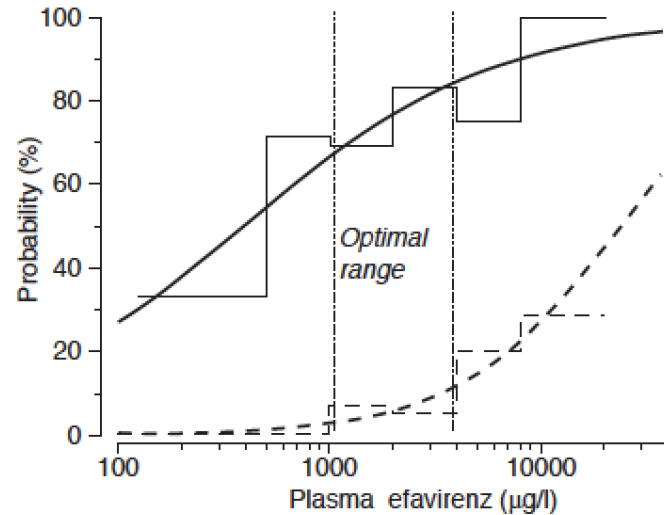
What We Don't Know

- **All the mechanisms by which ART drugs affect neurons and glia**
 - Drug-drug interactions
- **Approach to identifying patients at risk for developing NP AEs**
 - Dose-dependence
 - Effects of time: Cumulative effects, Aging vulnerability
- **How to diagnose NP AEs**
- **How to manage NP AEs**
 - Dose reduce or switch
 - Reversibility

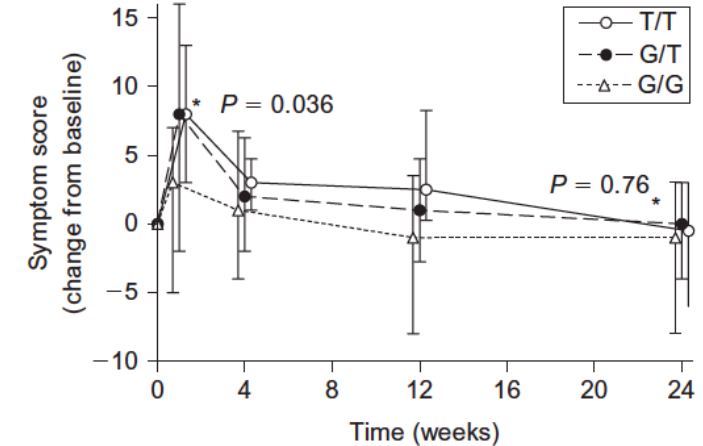
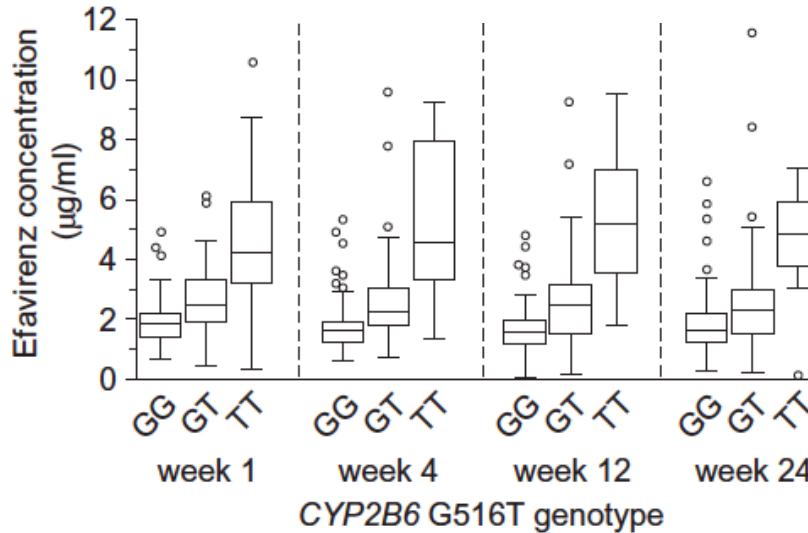
Direct and Indirect Neurotoxicity Can Occur



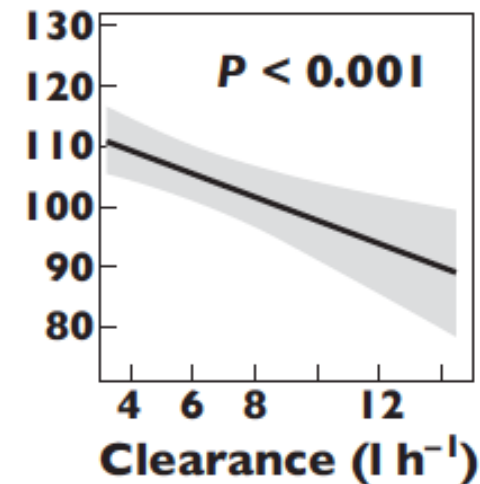
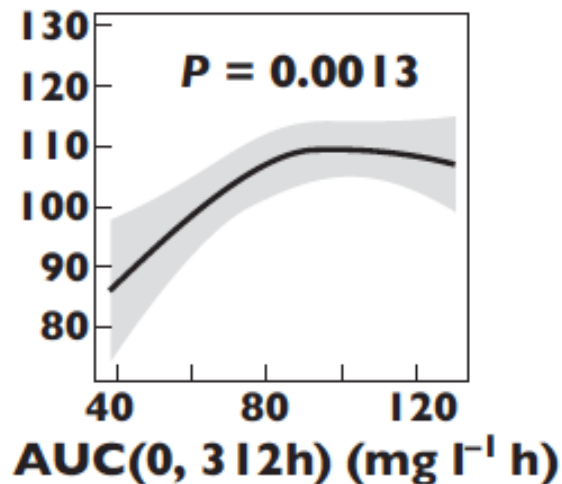
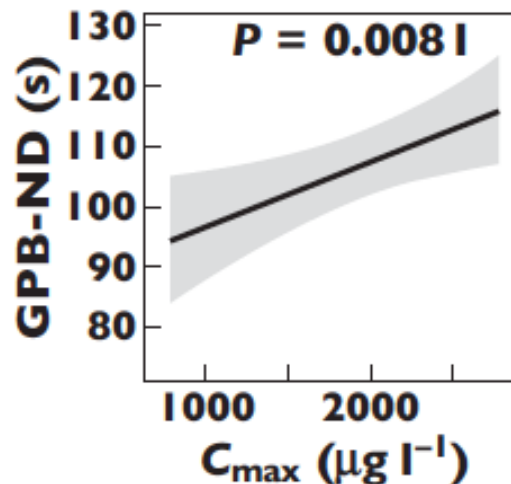
Greater Efavirenz Exposure is Associated with NP AEs



Marzolini et al, AIDS 2001, 15:71-75



Haas et al, AIDS 2004, 18:2391-2400

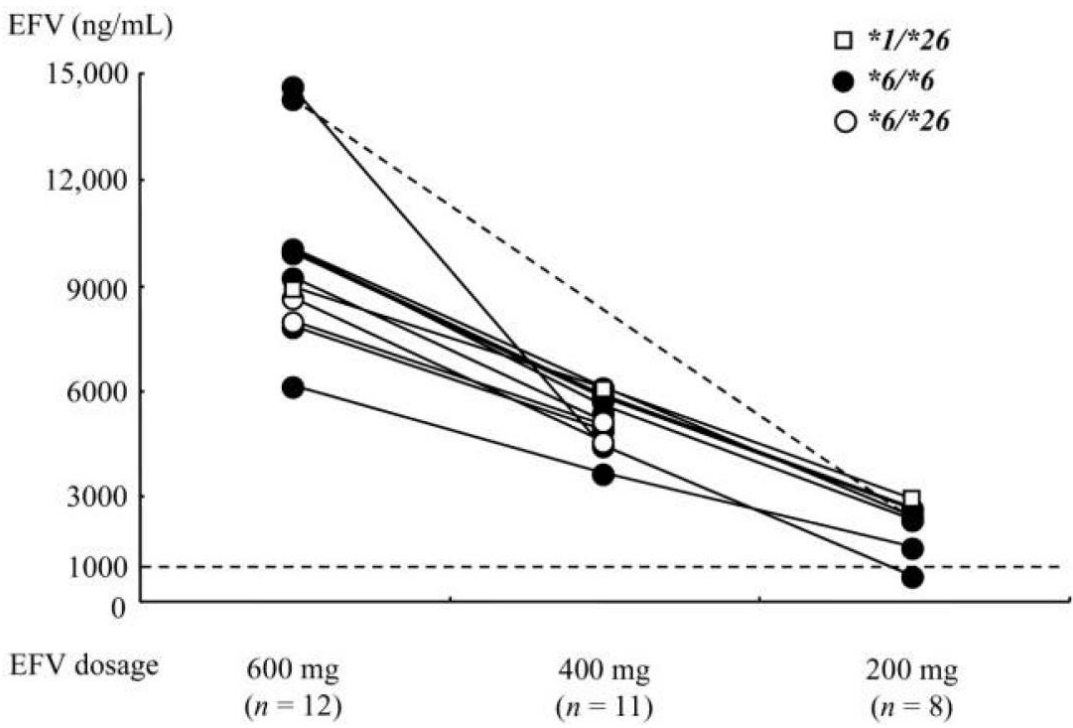


Johnson et al, Br J Clin Pharmacol 2012, 75: 997-1006

Longer Term Efavirenz Use is Associated with Risk of NC Impairment & Reducing Dose Improves Symptoms

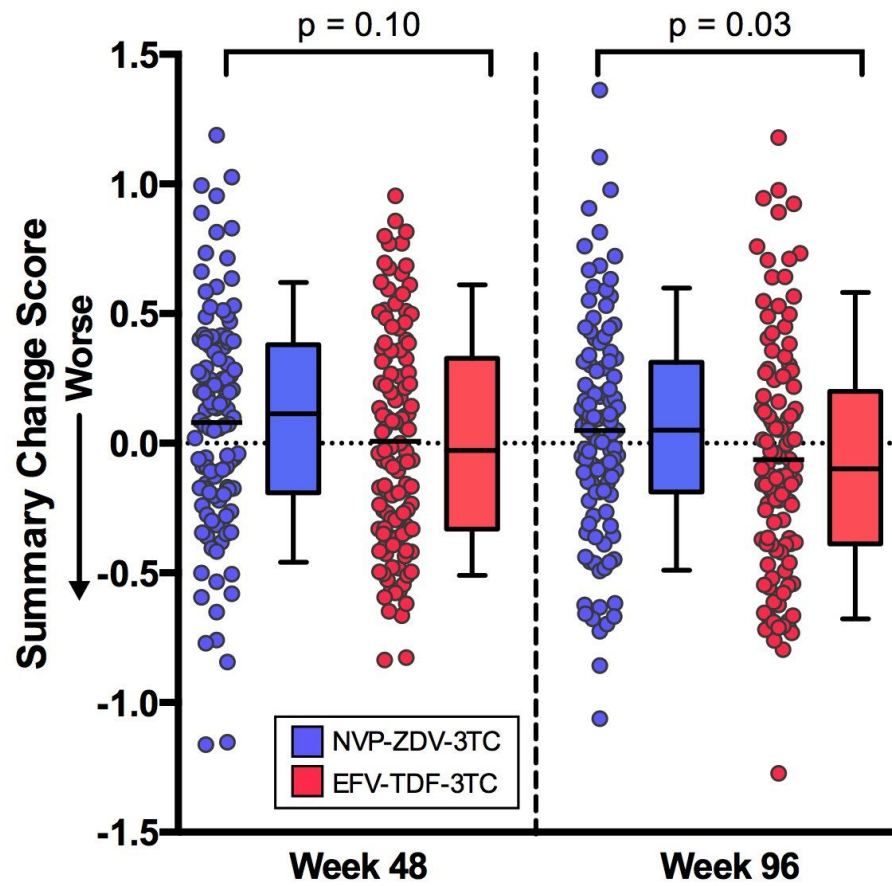
Risk Factor	Odds Ratio	P Value
Age (per 10 years)	0.83	0.29
Education (per 1 year)	0.85	0.002
Non-Italian Born	3.5	0.056
Efavirenz use	4.0	0.008

Ciccarelli et al, Neurology
2011, 76: 1403



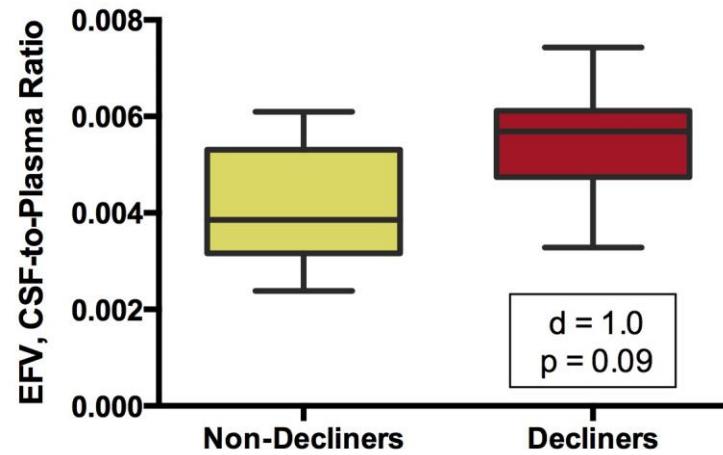
Gatanaga et al, Clinical Infectious Diseases 2007; 45:1230–7

Cognitive Decline May Be Linked to Higher Drug Concentrations in the CNS

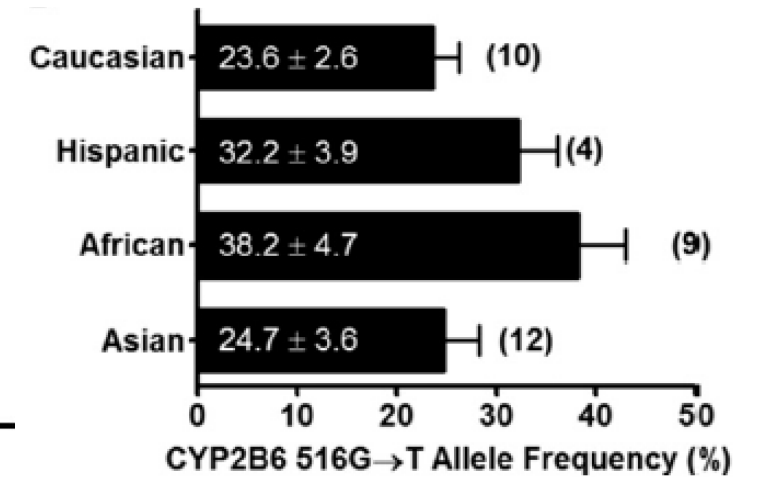


ITT Analysis, N = 233

Zhang, et al, CROI 2015, Abstract 56



Ma et al, CROI 2015, Abstract 444



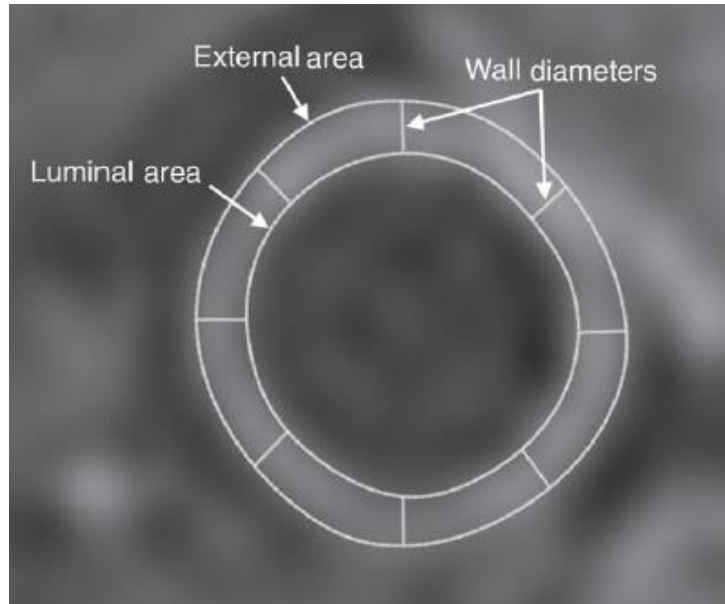
Dalwadi et al, Pharm Reviews 2018

	Plasma	CSF
GG	2209 (1697-3230)	8.77 (5.30-18.9)
GT	2445 (1740-3850)	14.7 (5.93-17.7)
TT	2429 (1869-5383)	27.2 (12.6-33.6)
p	0.582	0.045
CYP2B6 516G>T, Kruskal-Wallis Test		

Ma et al, CROI 2016, Abstract 446

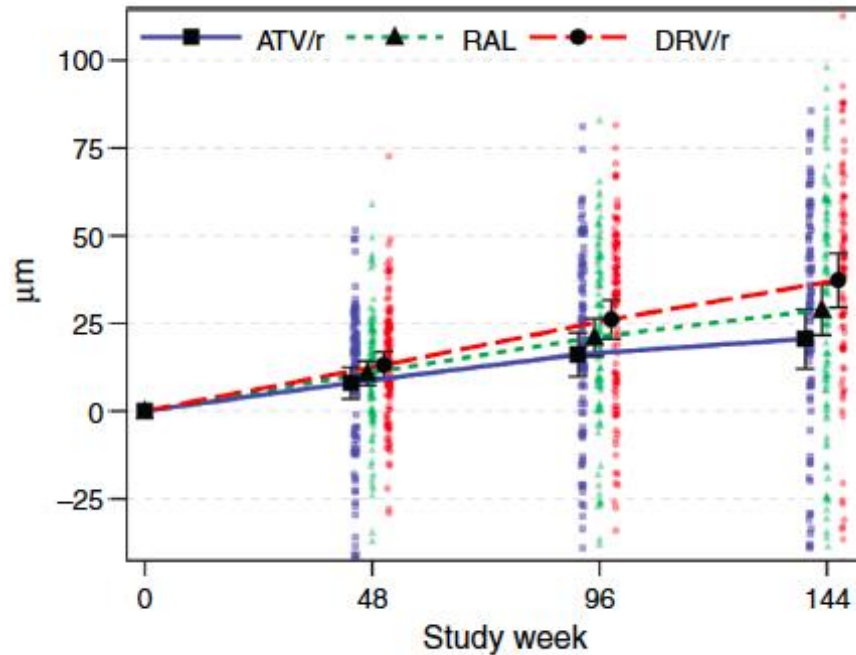
	Total (n)	NCI (n)
GG	27	9 (30%)
GT	26	8 (31%)
TT	6	5 (83%)
p		0.02
CYP2B6 516G>T, Fisher Exact Test		

Protease Inhibitors are Associated with Vascular Disease



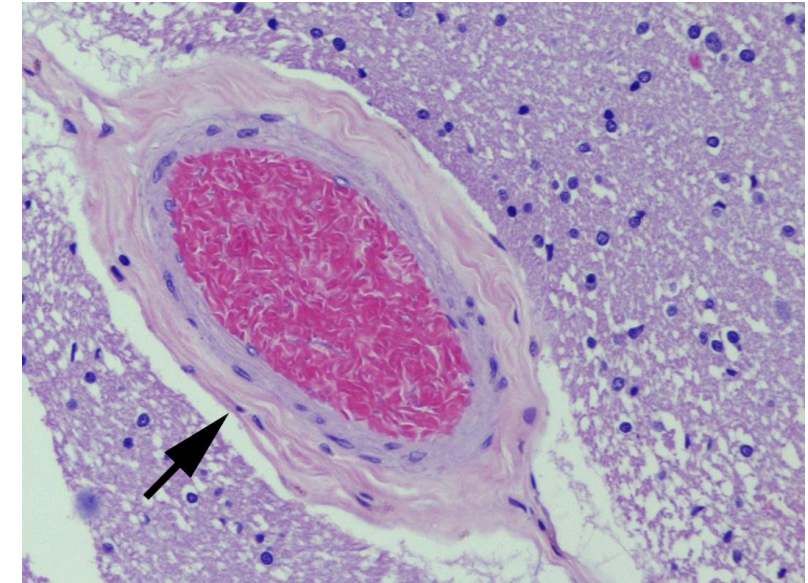
- Carotid artery wall thickness measured by 3.0 Tesla MRI
- **Longer duration of protease inhibitor therapy associated with thicker carotid wall**

LaBounty et al, HIV Medicine (2015)
DOI: 10.1111/hiv.12351



- Carotid intima media thickness measured by ultrasound
- **DRV/r was associated with faster progression than ATV/r**

Stein et al, AIDS 2015, 29:1775–1783



- Protease inhibitor use associated with cerebral small vessel disease (OR 2.8)
- **Mild cerebral small vessel disease associated with HAND (OR 4.8)**

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

N(t)RTI Toxicity

May Also Influence Neurocognition

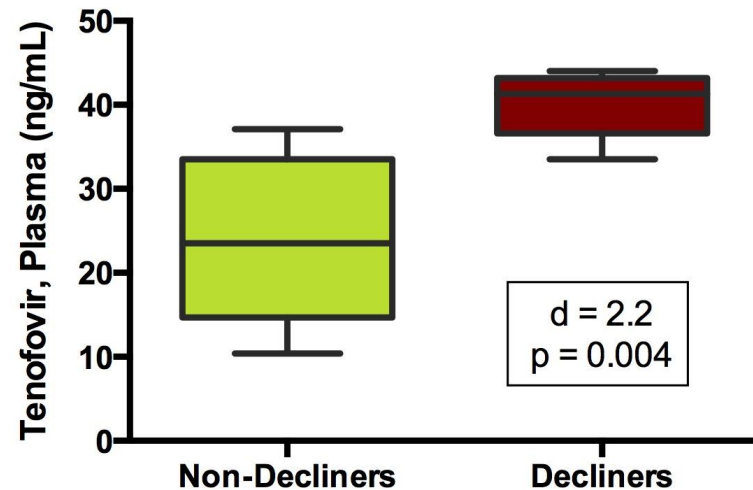
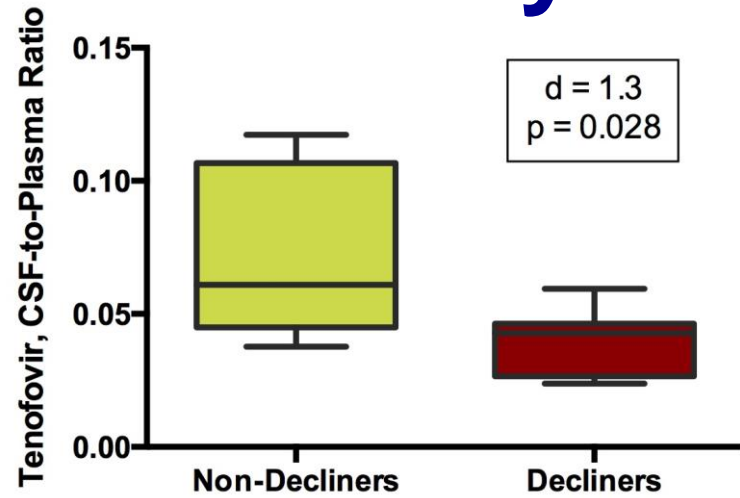
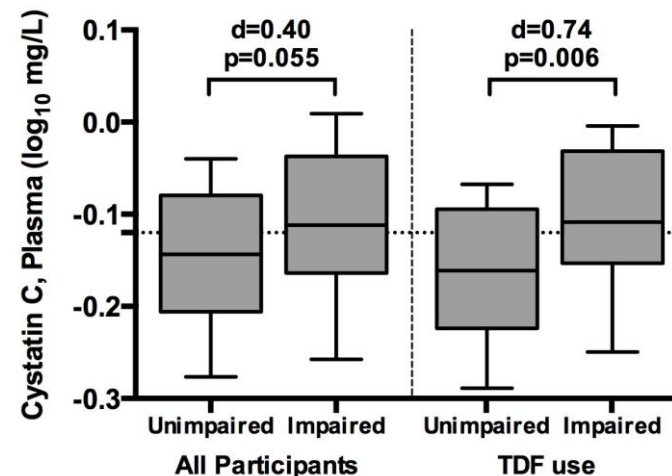


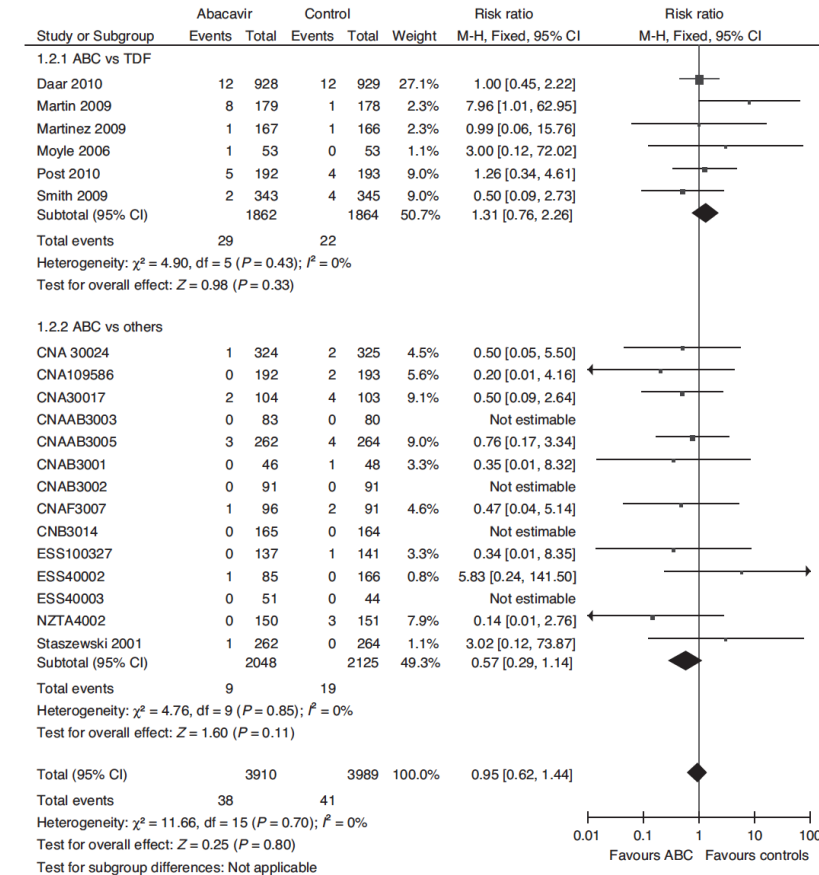
Table 2: Factors predicting NC decline over 36 months in Aviremic HIV+ individuals in CHARTER

Risk Factor [Reference level]	Odds Ratio	95% Confidence interval
eGFR ≤ 50 mL/min [> 50]	6.80	1.35, 34.23
HIV infection ≥ 15 years [$0-<5$]	5.45	1.19, 25.02
Education ≤ 12 years [> 12]	4.25	1.45, 12.42
CSF protein >45 mg/dL [≤ 45]	3.25	1.13, 9.35

Brouillette et al, CROI 2015, Abstract 469



Sakoda et al, CROI 2015, Abstract 484

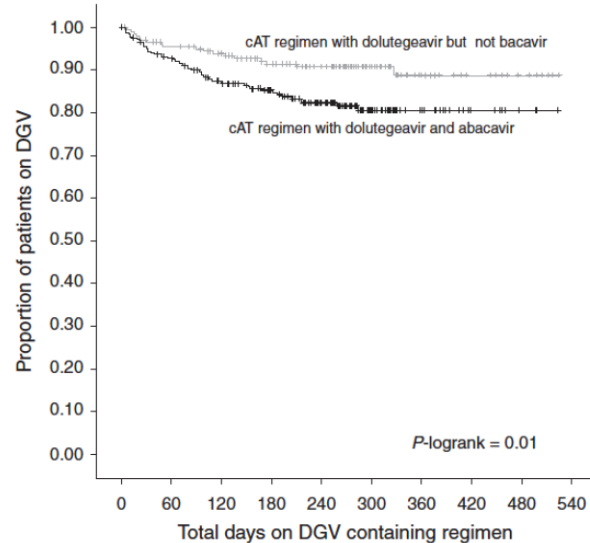


Cruciani et al, AIDS 2011, 25:1993–2004

Ma et al, CROI 2015, Abstract 444

Dolutegravir, NP AEs, & Discontinuation

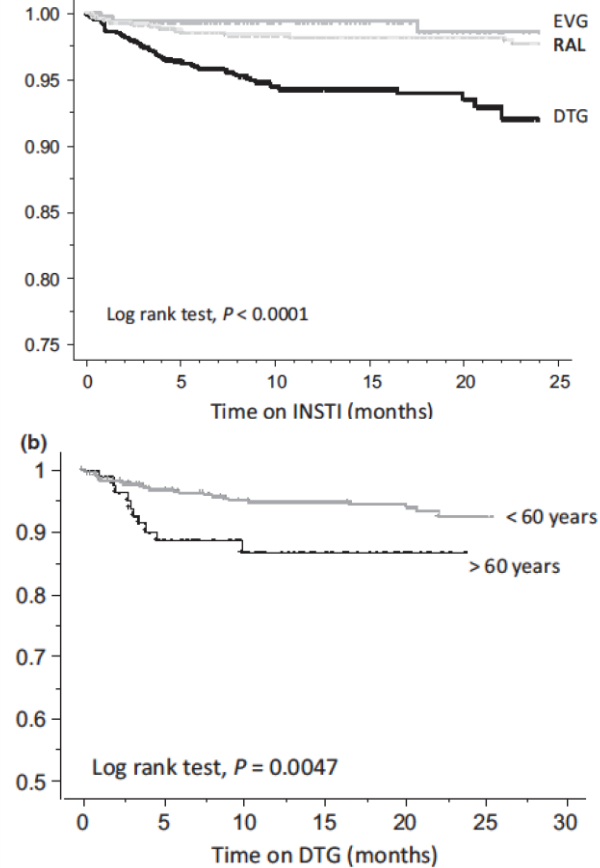
N=565 DTG Only



Adverse drug reaction	n (%)
Sleep disturbance, insomnia	31 (5.6)
Gastrointestinal complaints	21 (3.8)
Joint, tendon and/or muscle pain	11 (2.0)
Psychological/psychiatric symptoms ^b	14 (2.5)
Neurologic symptoms	10 (1.8)
General malaise (headache and severe fatigue)	24 (4.3)
Respiratory tract complaints	5 (0.9)
Other	9 (1.6)

de Boer et al, AIDS
2016, 30:2831–2834

N=1,950 InSTIs Only



Hoffmann et al, HIV Medicine
2017, 18, 56–63

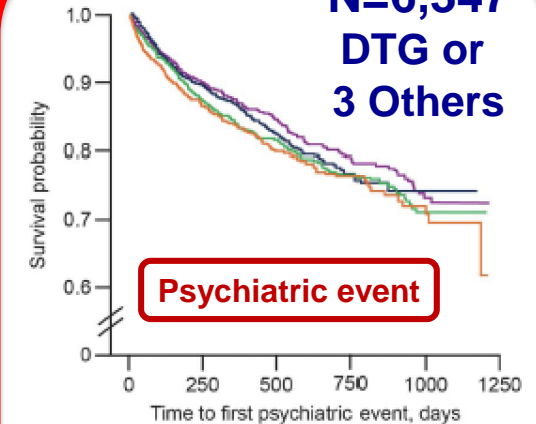
N=4,041 DTG vs. RAL

Variable	HR ^a	P value
Female	1.98	<0.001
Age, per 10 years older	0.93	0.319
Nonwhite ethnicity	0.75	0.172
Prior AIDS-defining condition	0.89	0.513
HCV-coinfection	0.80	0.221
CD4 ⁺ cells per μ l		
<350		
350–500	0.98	0.880
>500	1.07	0.735
HIV RNA >100 000 copies per ml	1.53	0.149
Treatment naive	1.05	0.858
Backbone		
Abacavir–lamivudine		
Tenofovir–emtricitabine	0.91	0.626
Other	0.97	0.902
Raltegravir versus dolutegravir	1.30	0.140

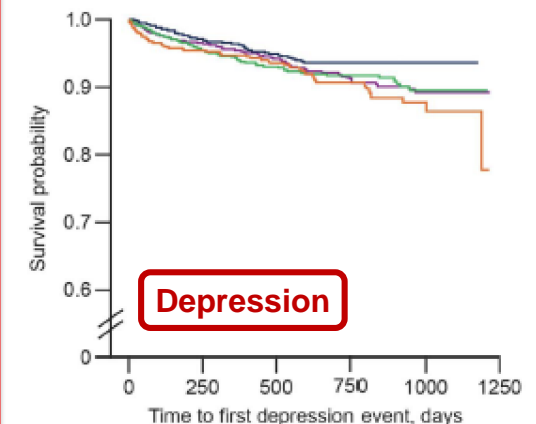
Toxicity:
RAL 4.3%
DTG 3.6%

Elzi et al, AIDS 2017,
31:1853–1858

N=6,347 DTG or 3 Others

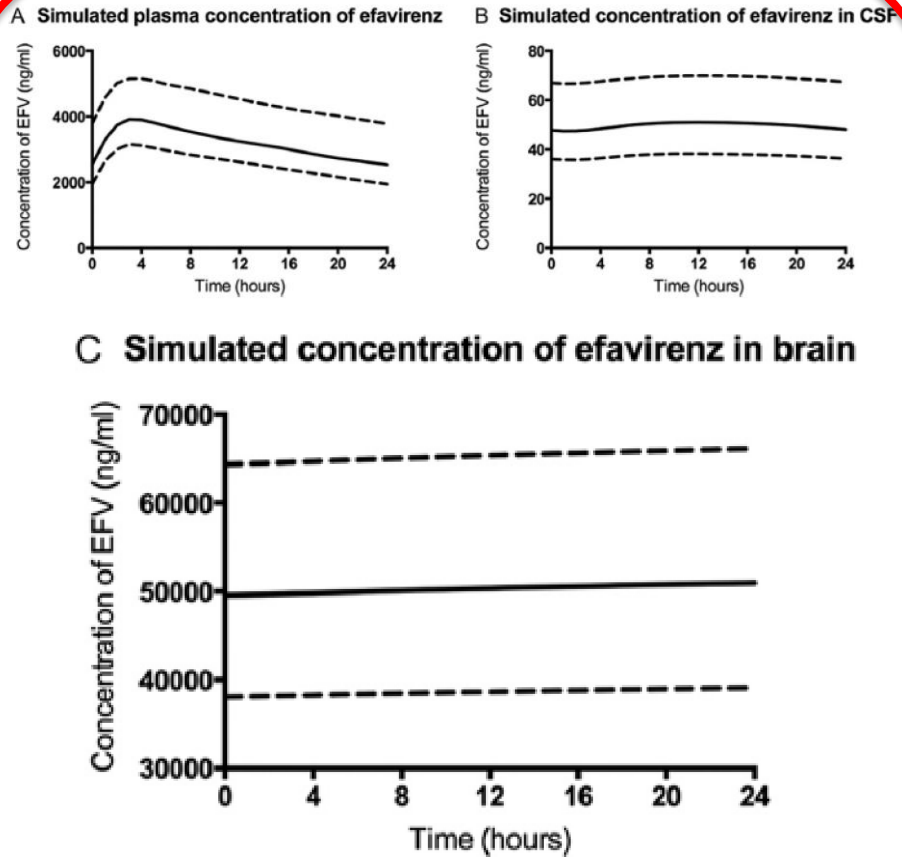


DRV	1747	1258	702	354	128	0
DTG	2029	1609	751	197	3	0
EFV	1607	1104	619	311	112	0
RAL	963	637	335	170	59	0

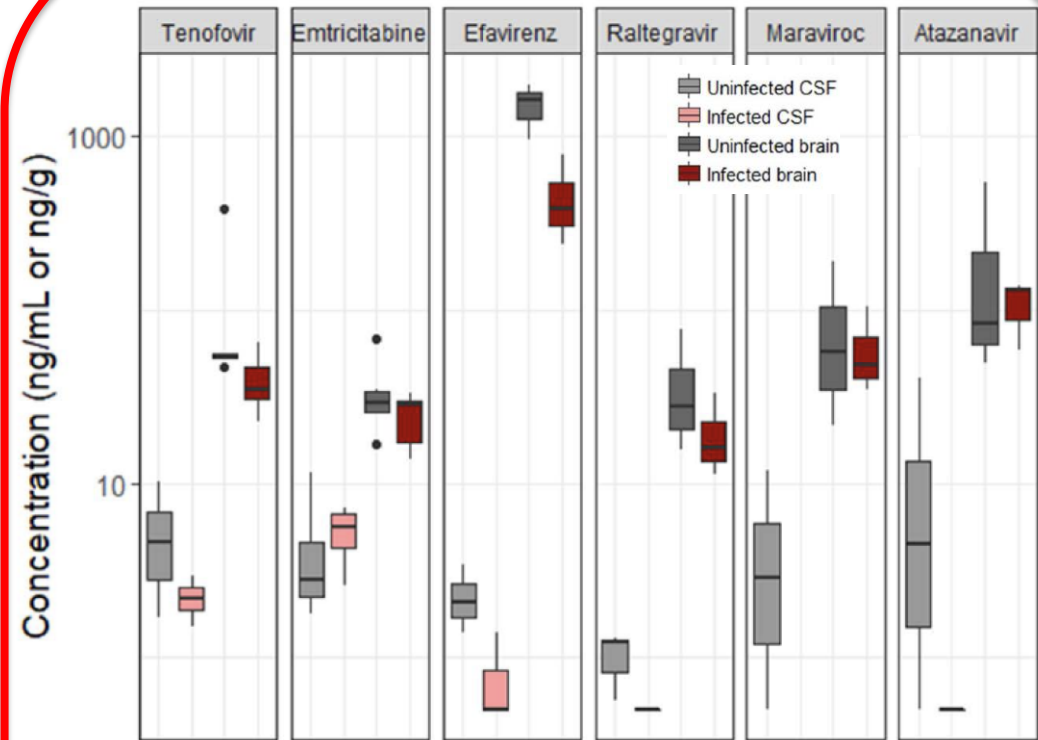


Fettiplace et al, J AIDS
2017;74:423–431

Animal Models Support That ART Concentrations in Brain Are Much Higher Than in CSF

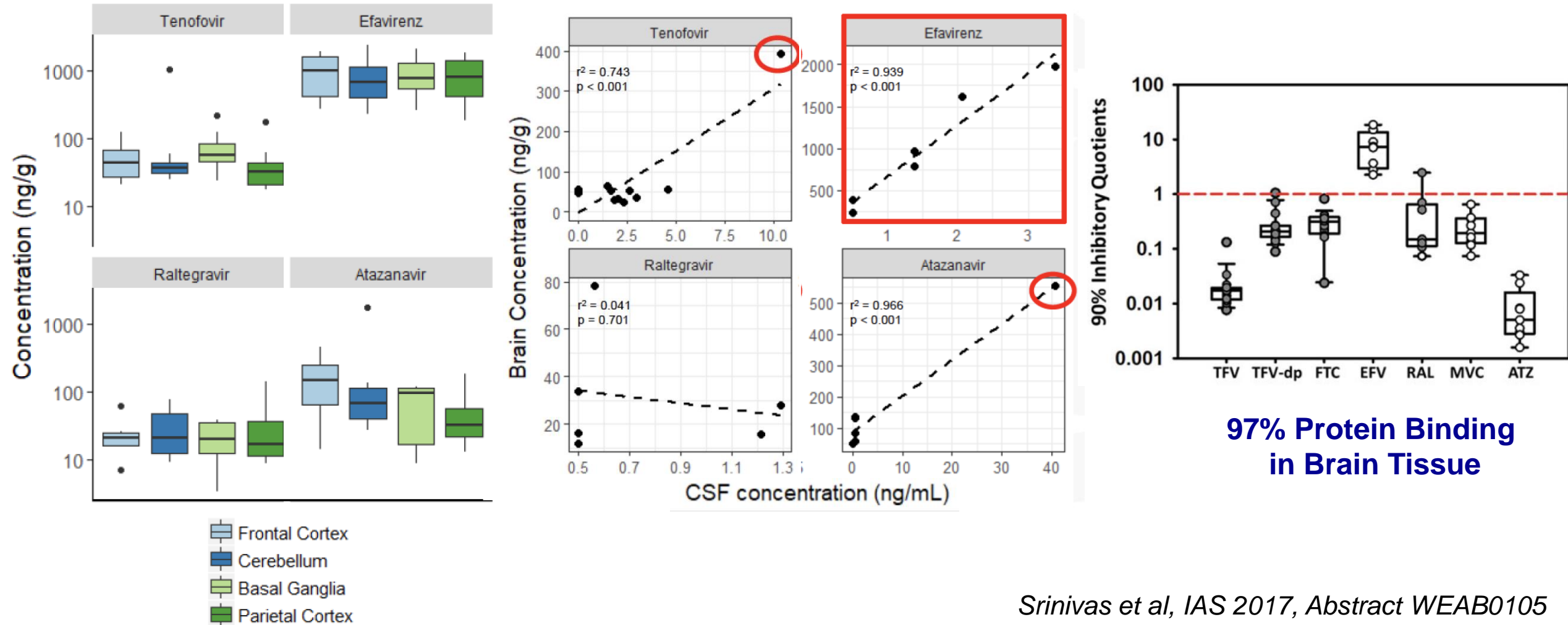


Curley et al, AAC
2017, 61(1): e01841-16

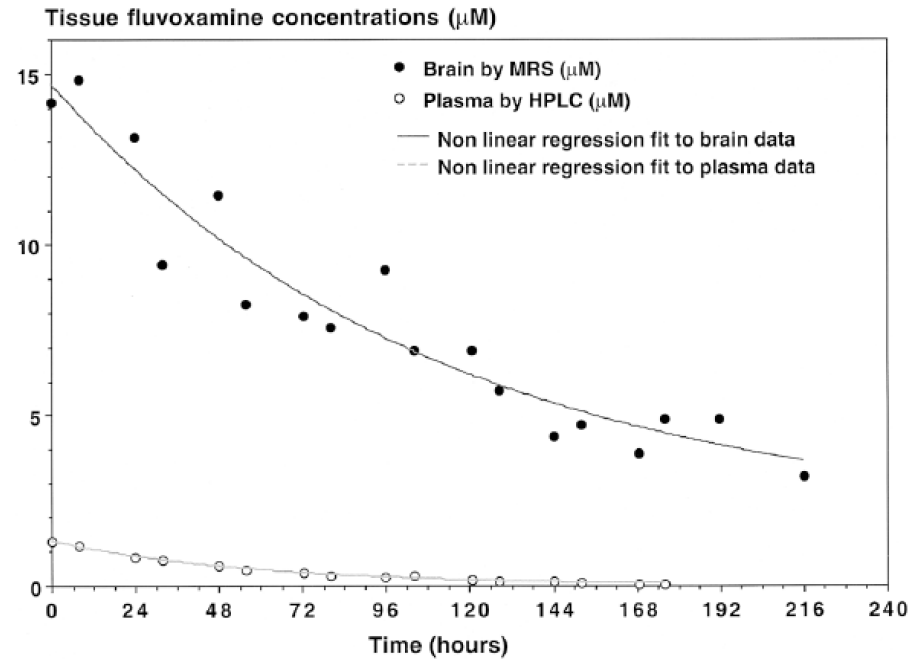
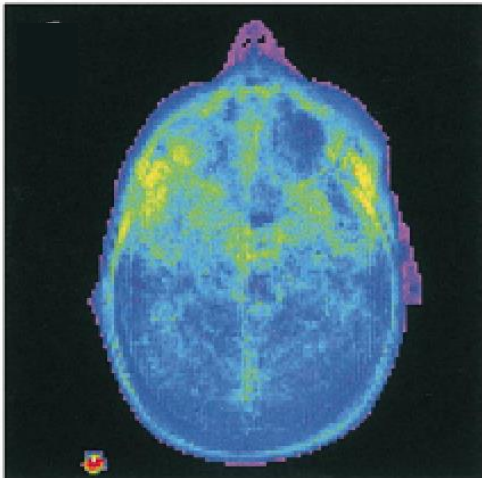
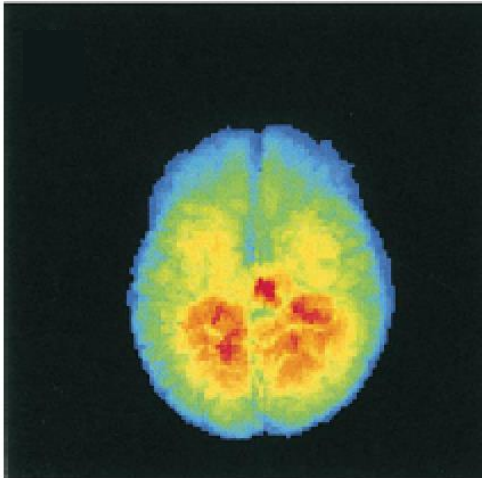


Srinivas et al, IAS 2017,
Abstract WEAB0105

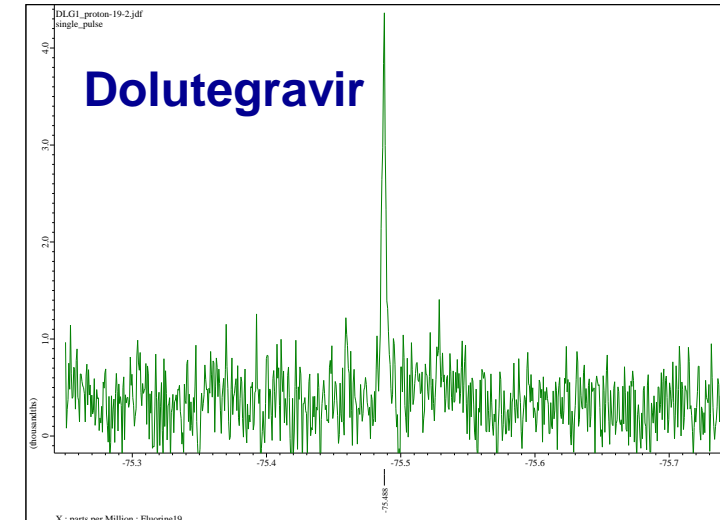
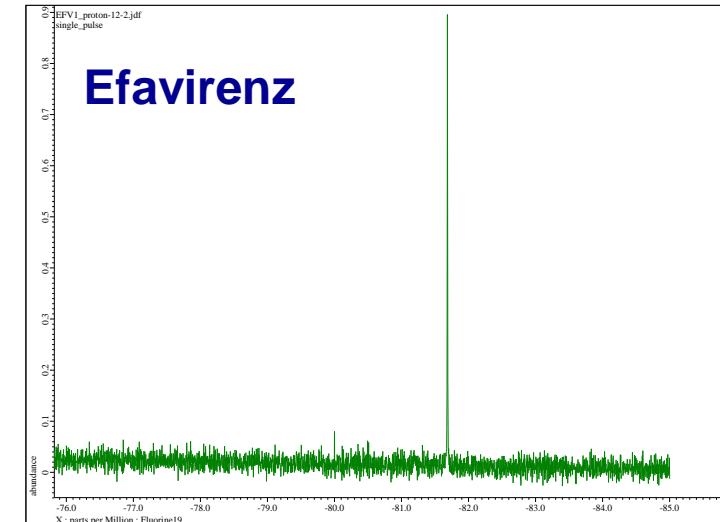
ART Concentrations in Brain Do Not Clearly Vary by Region & Correlate with CSF



In Vivo Measurement of Fluorinated Drugs with ^{19}F -MRSI

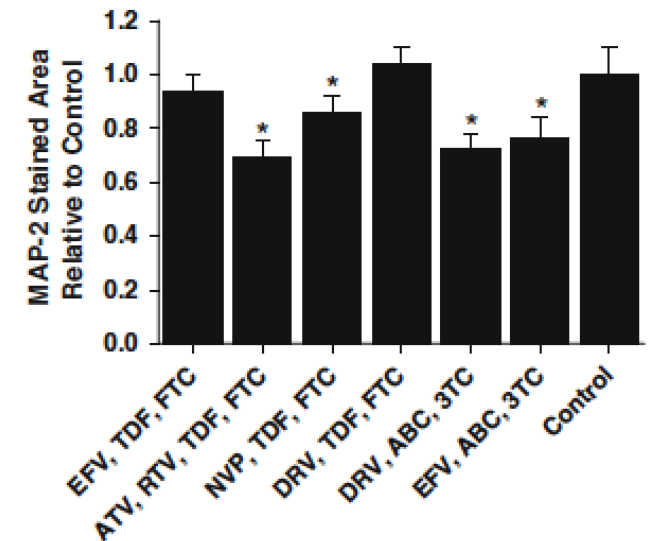
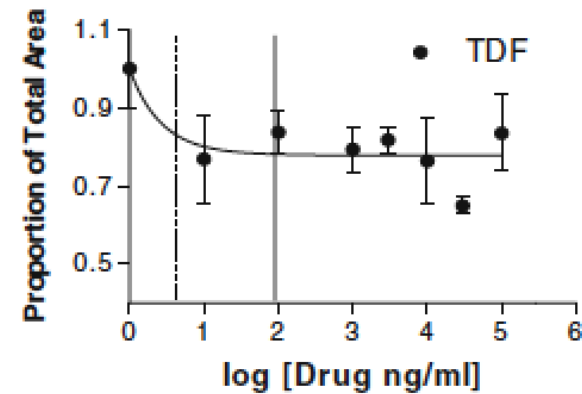
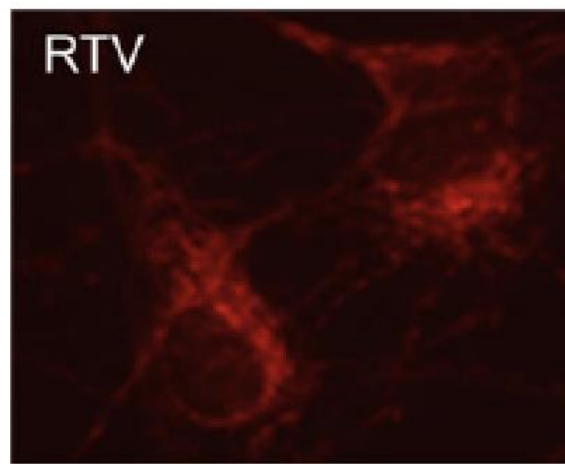
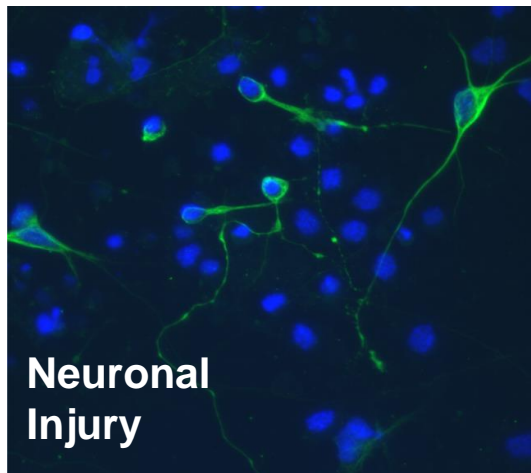
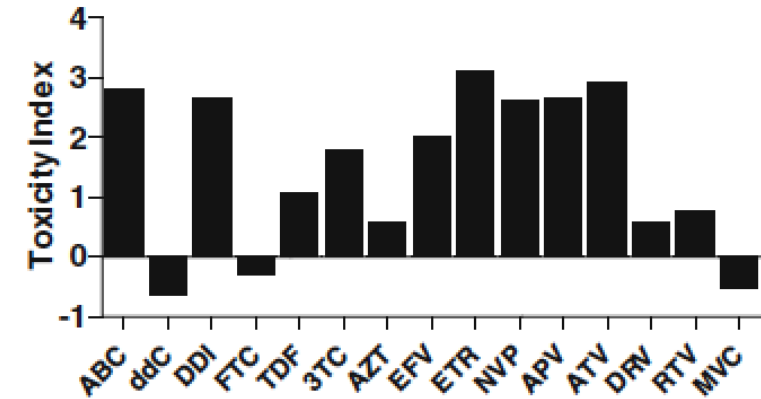
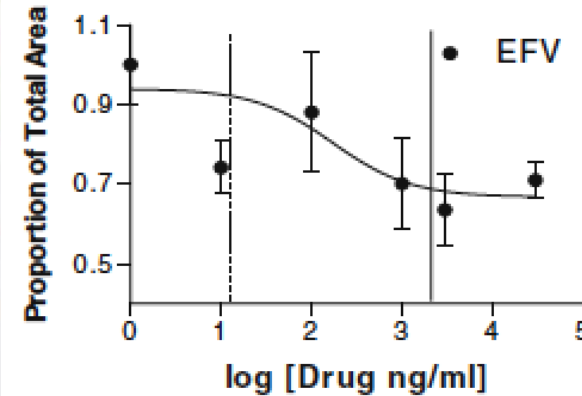
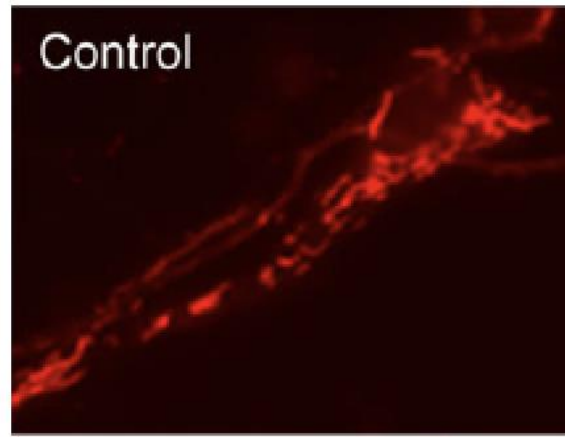
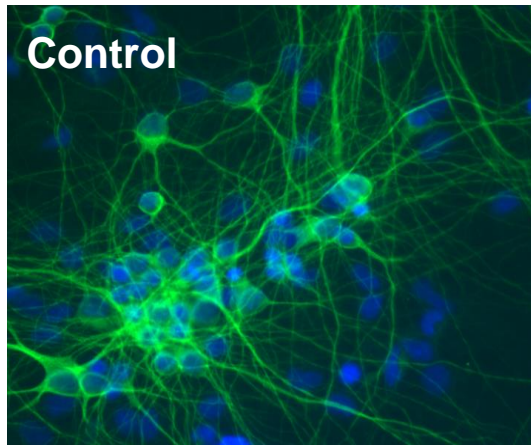


*Bolo et al, Neuropsychopharmacology
23:428–438, 2000*

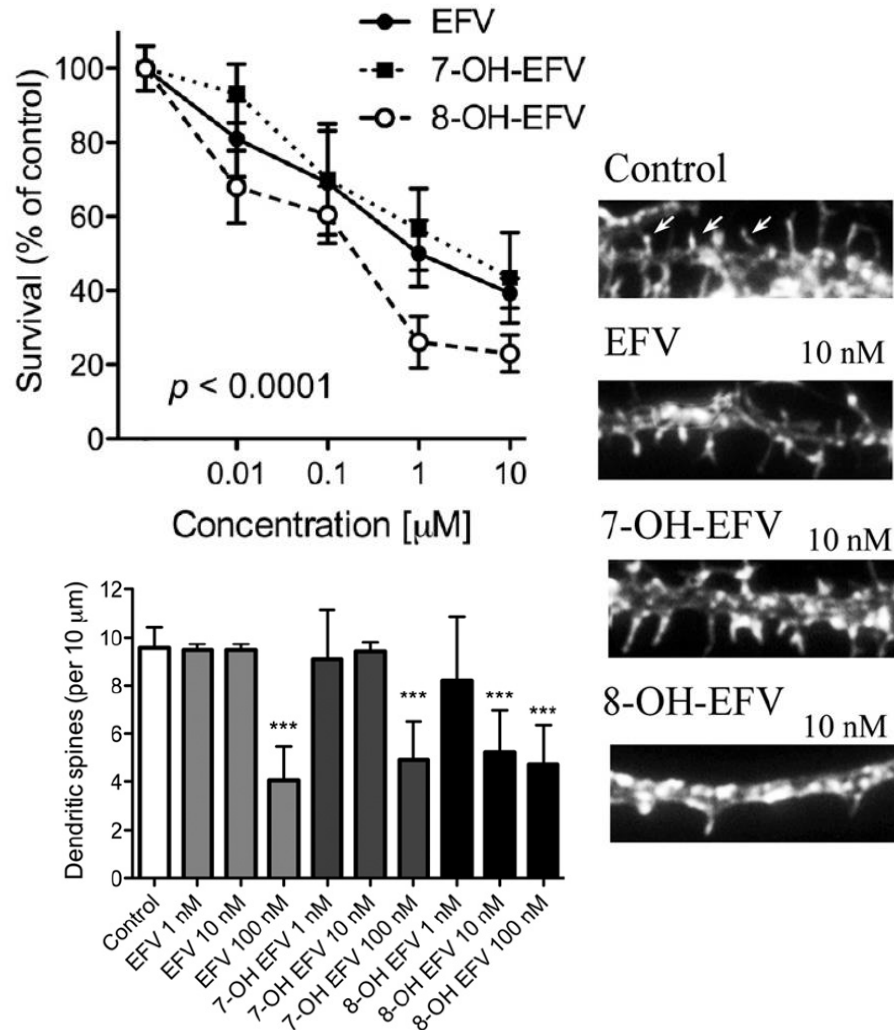


Bussell, Brown, & Letendre, Unpublished Data

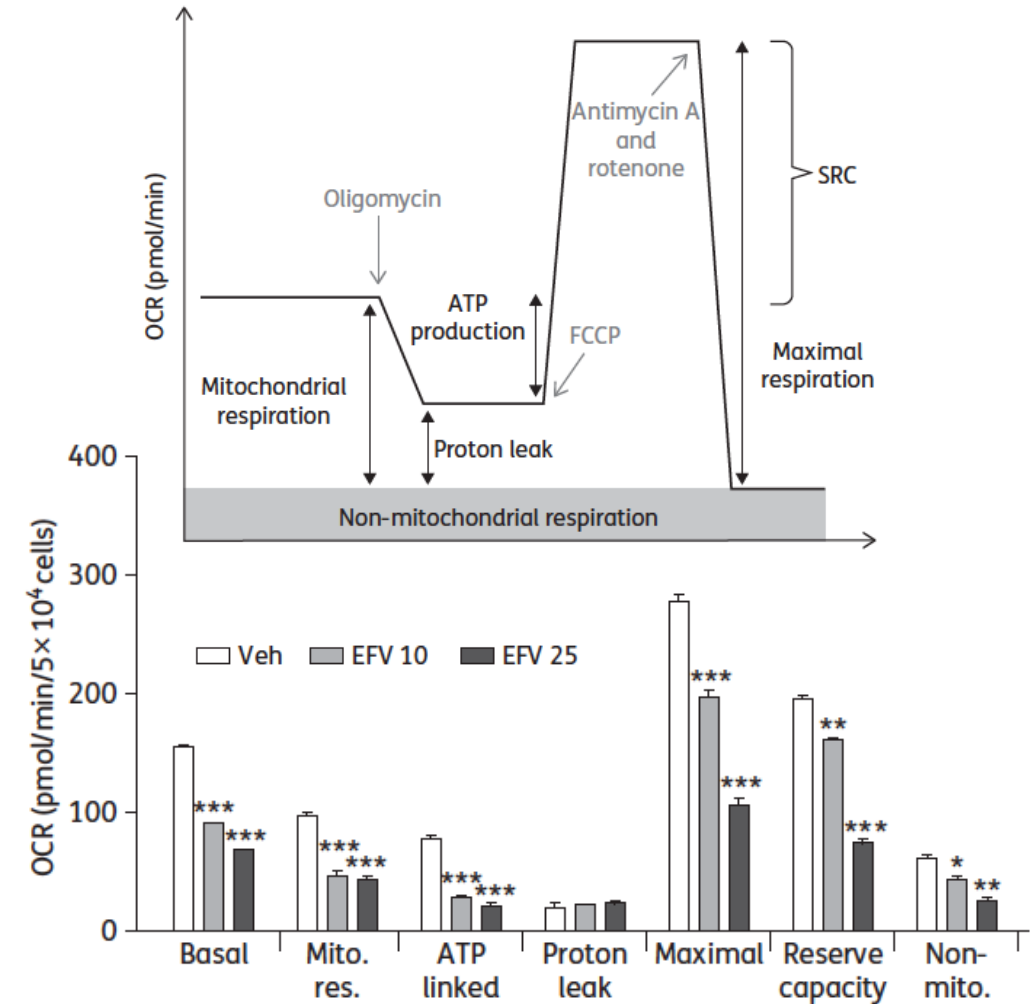
In Vitro Analyses of ART Toxicity in Fetal Rat Cortical Neurons



Efavirenz, Neurotoxic Metabolites, and Mitochondrial Respiration

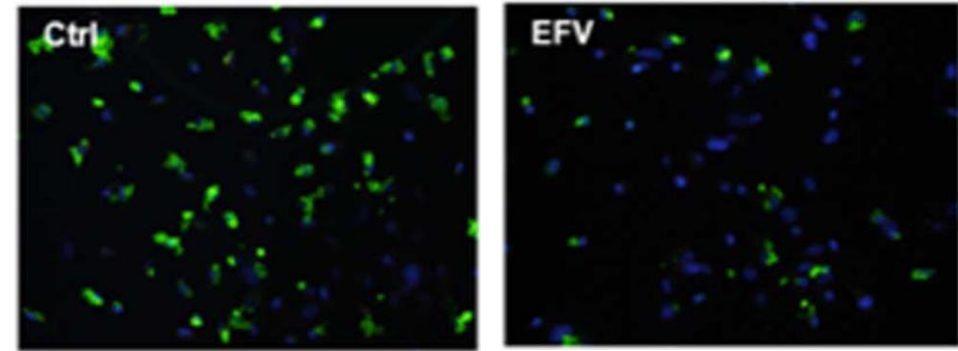
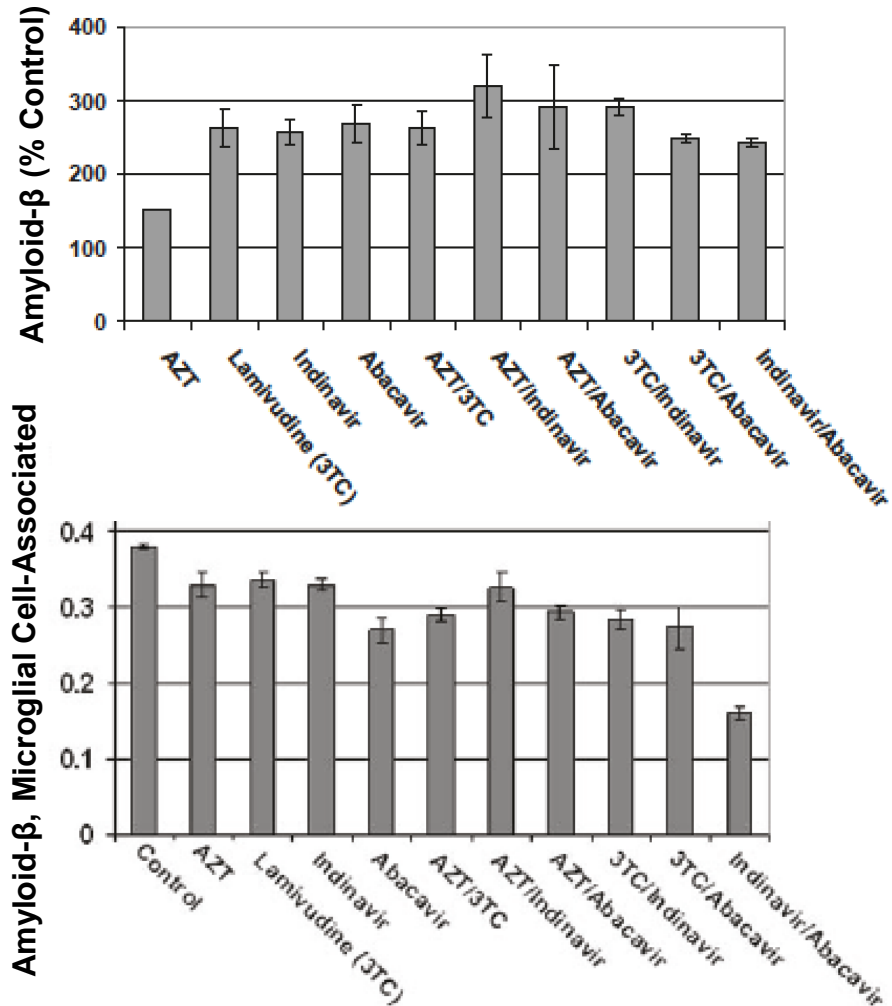


Tovar-y-Romo et al,
JPET 2012, 343(2): 696-703

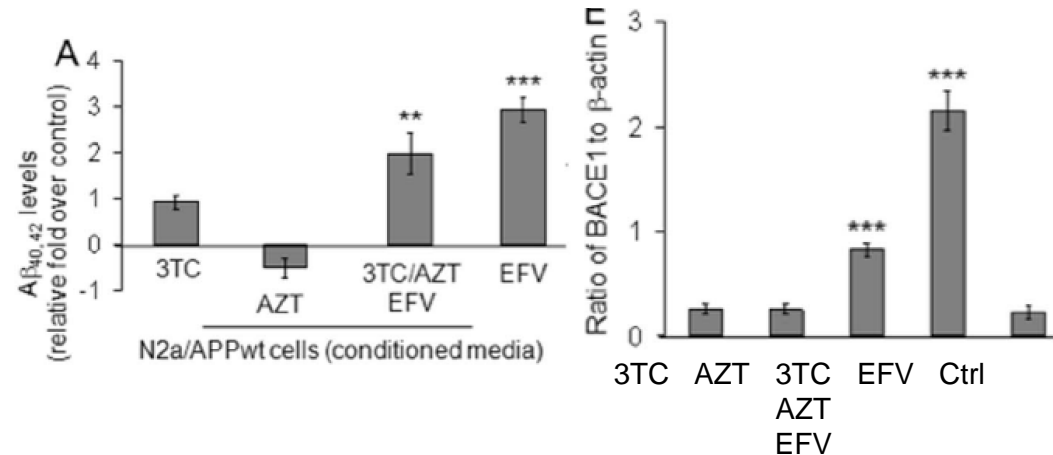


Funes et al, JAC 2015; 70: 2249-2254

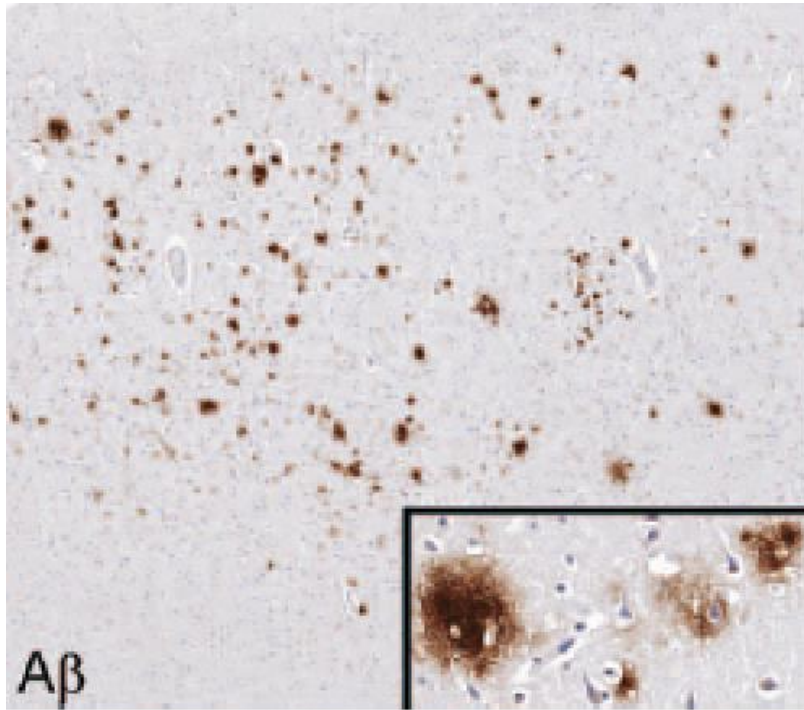
ART Drugs Can Increase Amyloid- β & Reduce Microglial Phagocytosis



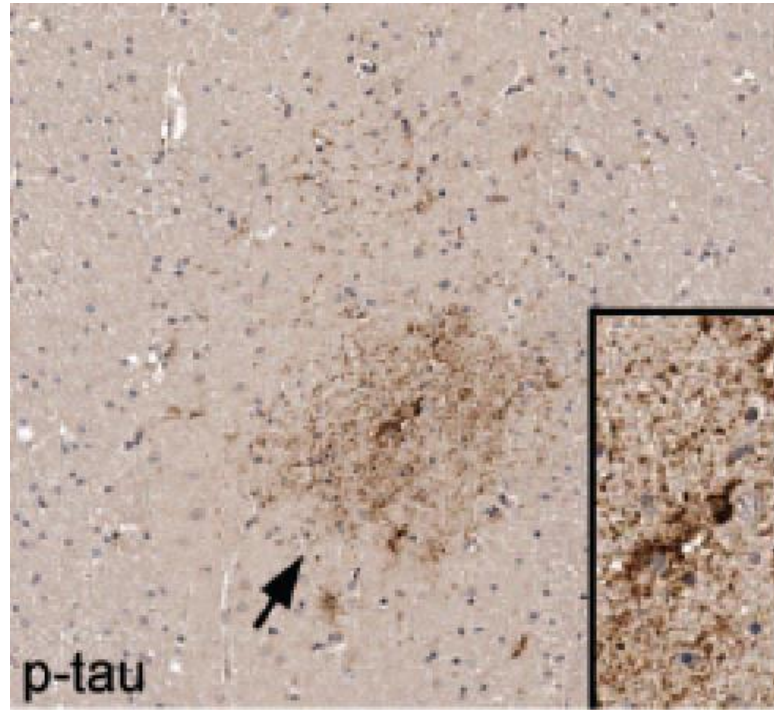
EFV Reduces Microglial Phagocytosis of A β ₁₋₄₂



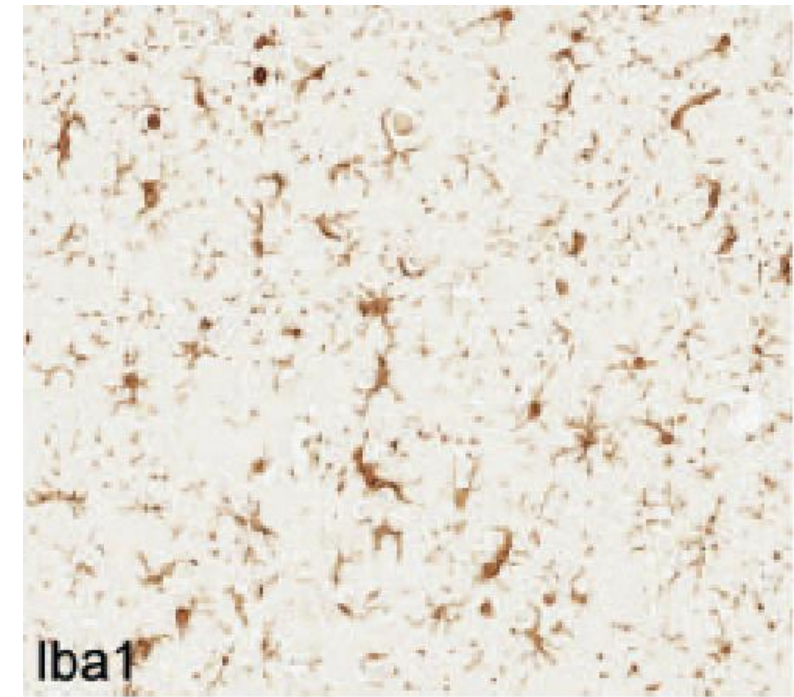
Amyloid and Phospho-Tau Neuropathology May be Influenced by Antiretrovirals



Tenofovir use prior to death
associated with lower odds of
amyloid β plaque deposition
(OR 0.13, $p=0.012$)



Darunavir use prior to death
associated with higher odds of
phospho-tau deposition in neurons
(OR 15.3, $p=0.0005$)

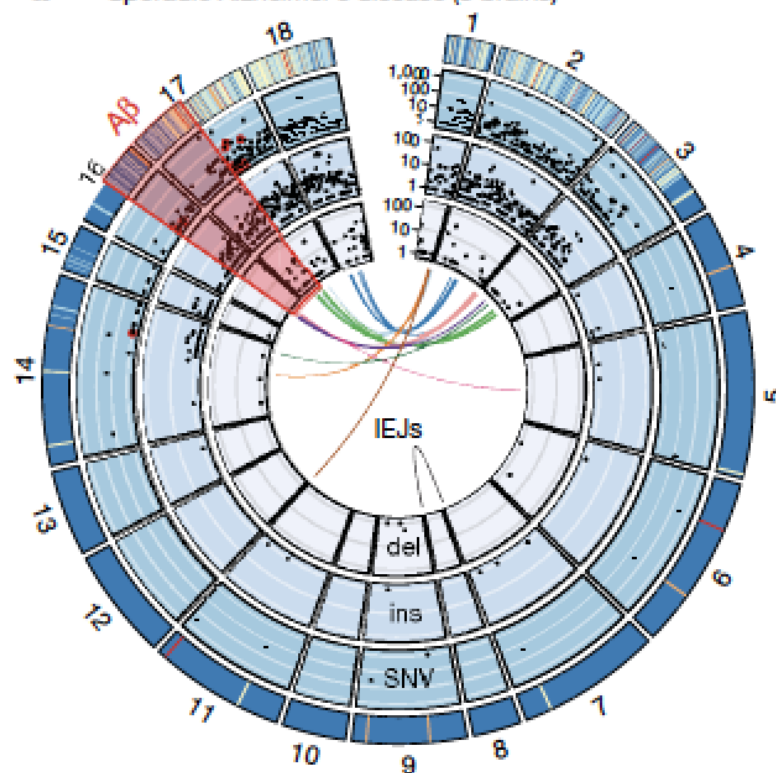


Ritonavir use prior to death
associated with higher odds of
microgliosis
(OR 4.96, $p=0.023$)

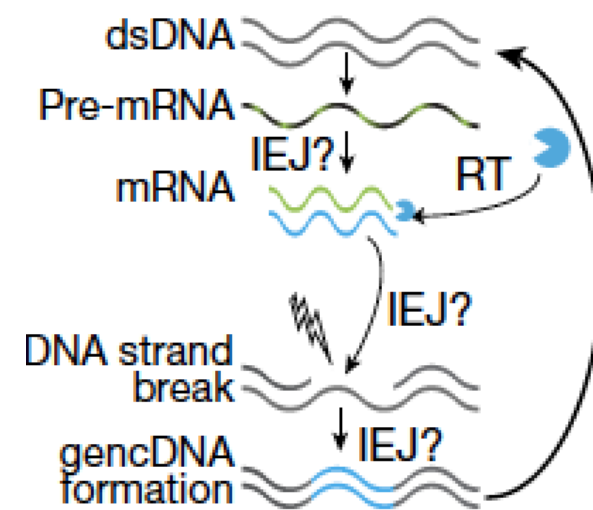
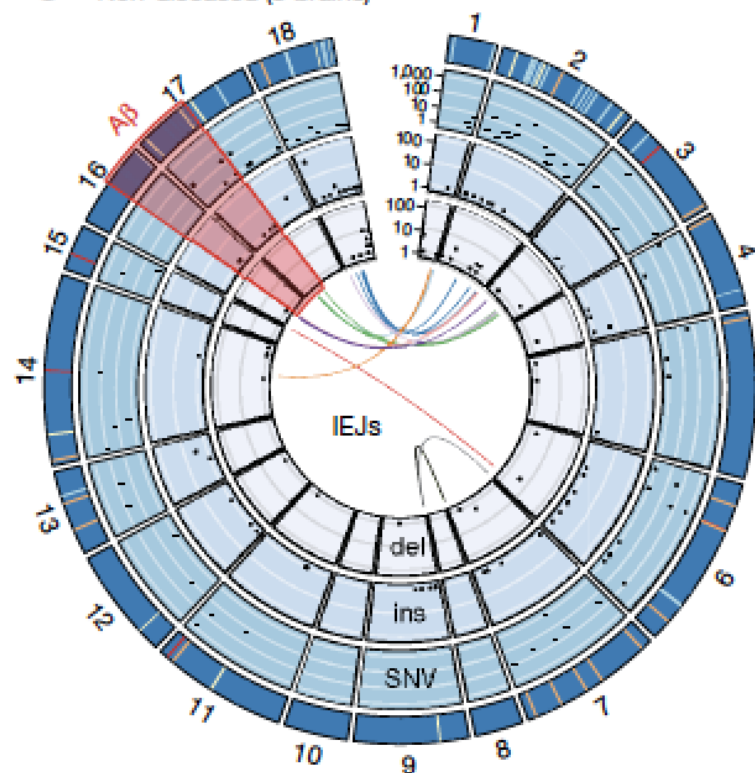
Somatic *APP* gene recombination in Alzheimer's disease and normal neurons

Ming-Hsiang Lee¹, Benjamin Siddoway^{1,3}, Gwendolyn E. Kaeser^{1,2,3}, Igor Segota^{1,3}, Richard Rivera¹, William J. Romanow¹, Christine S. Liu^{1,2}, Chris Park^{1,2}, Grace Kennedy¹, Tao Long¹ & Jerold Chun^{1*}

d Sporadic Alzheimer's disease (5 brains)



e Non-diseased (5 brains)

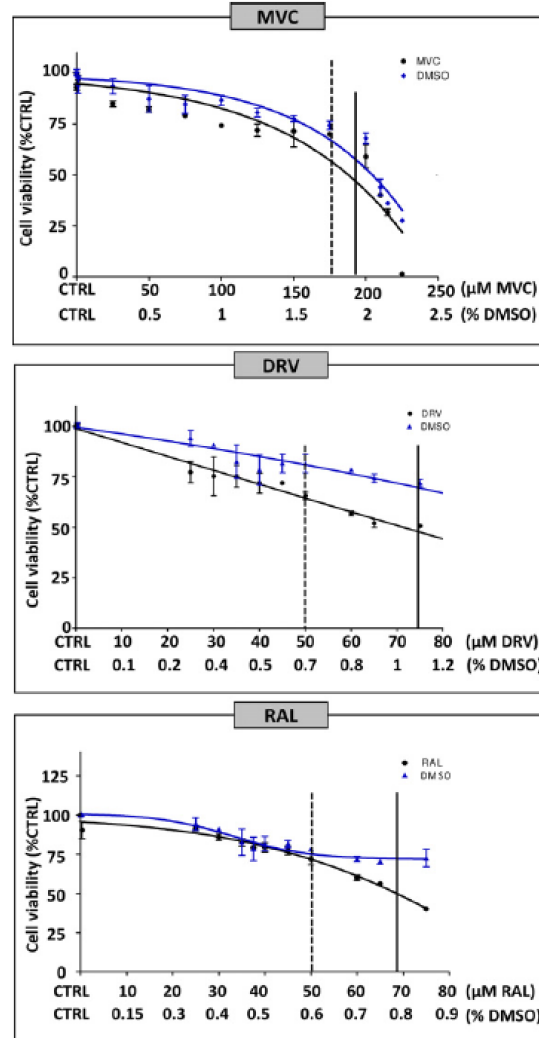


nature
International journal of science

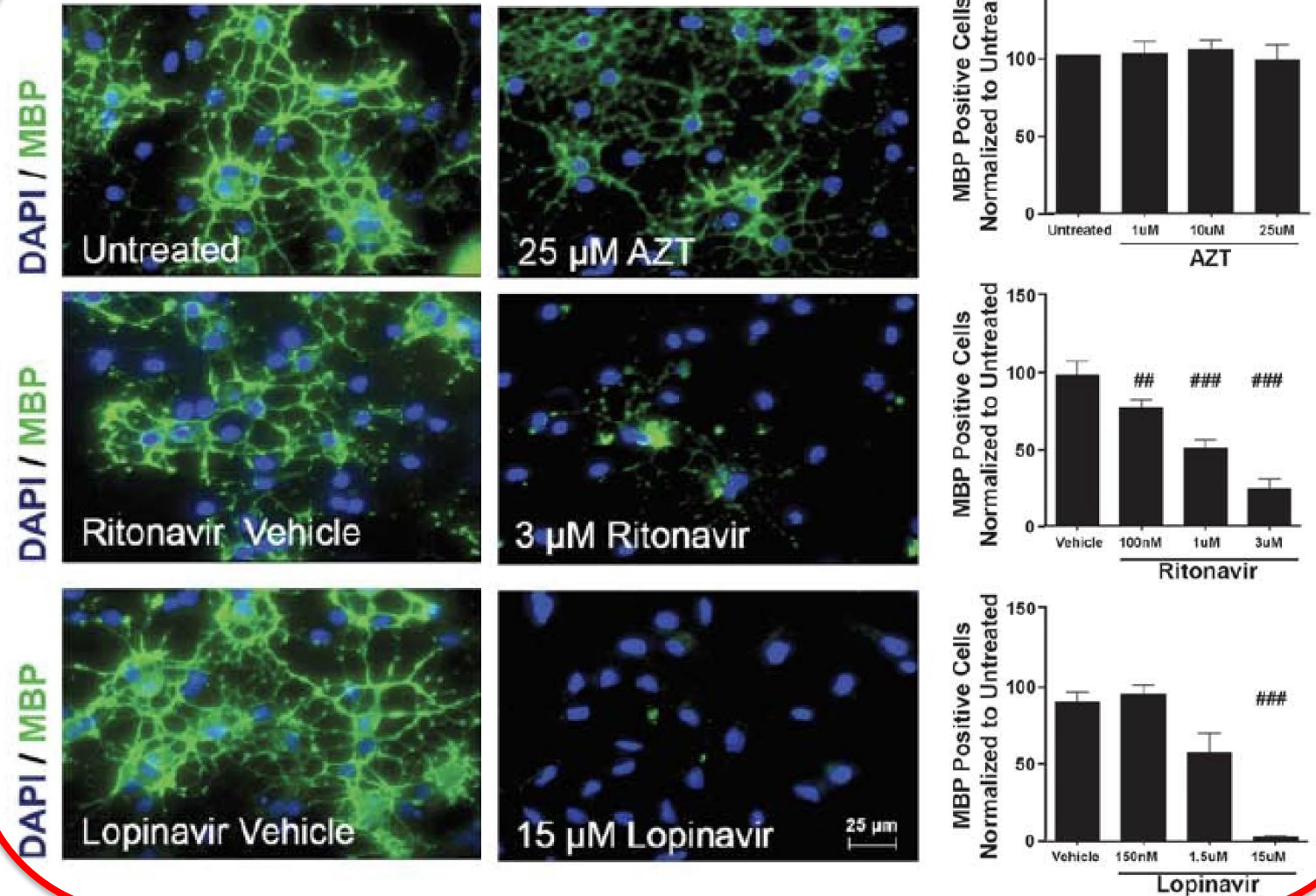
<https://doi.org/10.1038/s41586-018-0718-6>

ART Toxicity in Other Glial Cells

Astrocytes



Oligodendrocytes

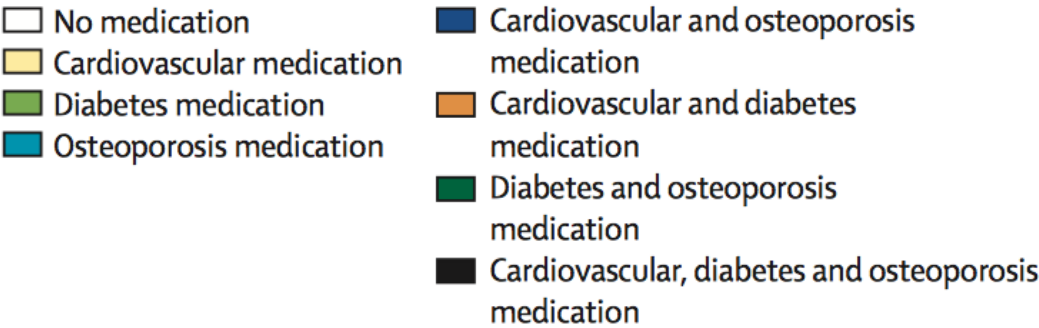
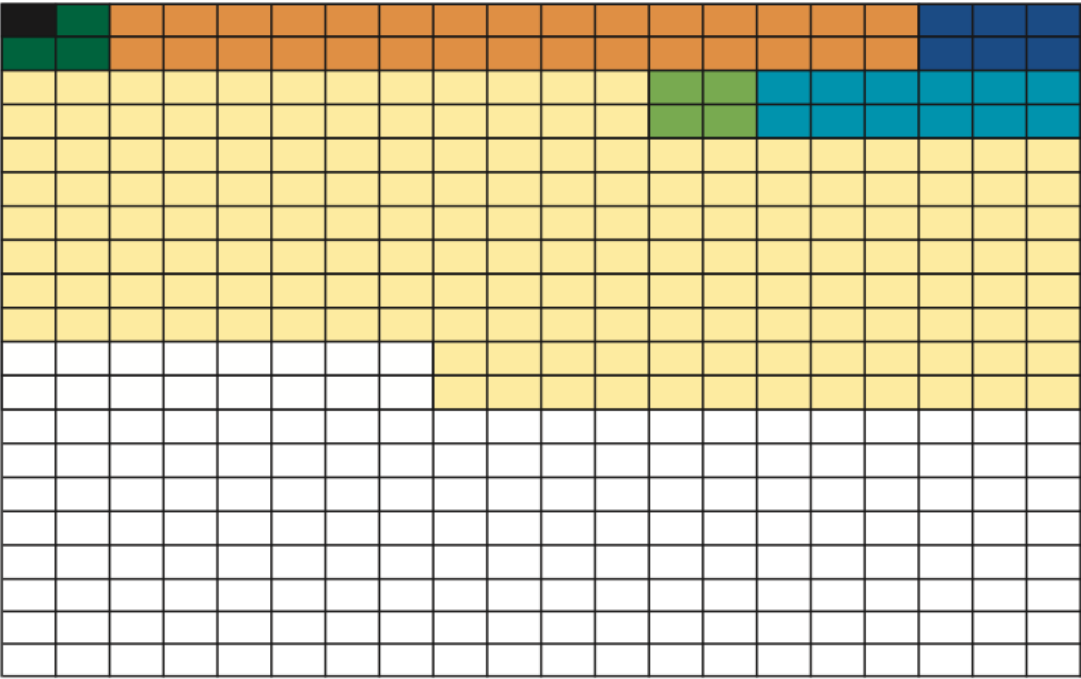
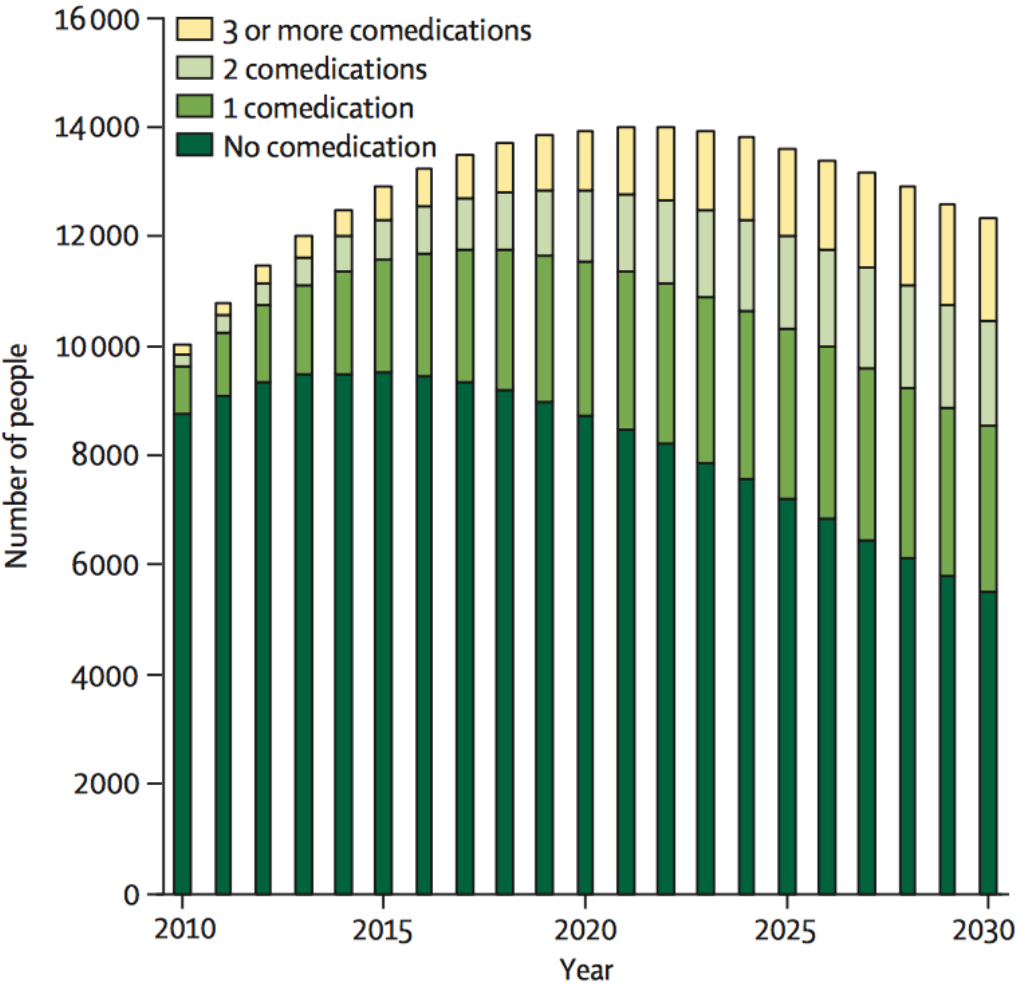


Summary of *in vitro* Evidence of Mechanisms of Neurotoxicity

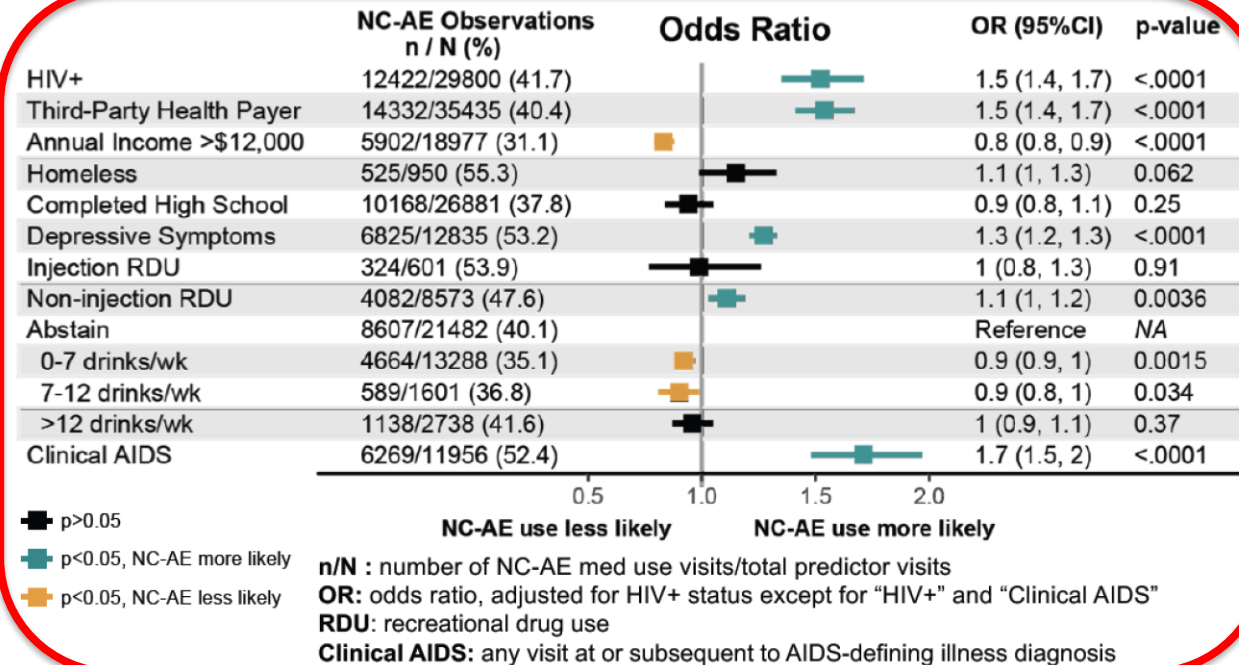
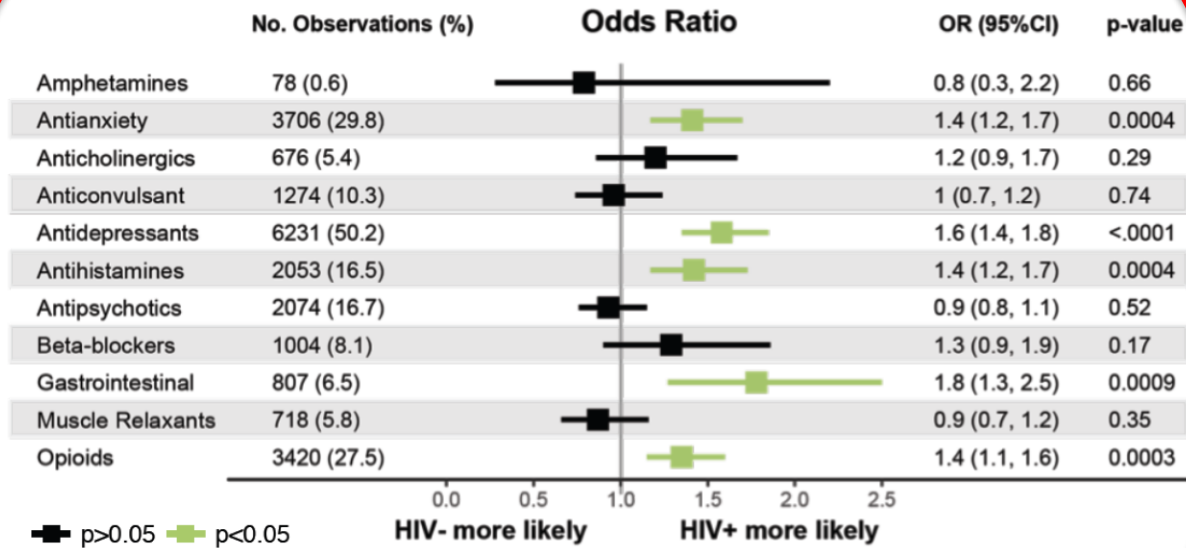
Drug	Effect
Maraviroc	↑ Microglial activation
Raltegravir	↑ IL-8 in brain macrophages
Efavirenz	↑ TNF- α and IL-1 β
	Dendritic spine injury
	Mitochondrial alterations
	↑ Autophagy
	↑ β -Secretase expression, ↑ amyloid beta, ↑ ROS
	↑ Endoplasmic reticulum stress
	↓ ATP stores; ↓ neural stem cell proliferation
Etravirine	↓ MAP-2 density in rat neurons

Drug	Effect
Zidovudine	↓ Mitochondrial DNA in cortical neurons
	↑ Amyloid- β production
Lamivudine	↓ Mitochondrial DNA in cortical neurons
	↑ Amyloid- β production
Abacavir	↑ Amyloid- β production
Indinavir	↑ Amyloid- β production
Lopinavir	↓ Myelin basic protein, ↓ galactocerebroside in oligodendrocytes
	↑ Oxidative stress, ↑ ER stress, ↑ IL-6 and TNF- α in macrophages
	↓ Tight junction proteins, ↓ synaptic proteins, ↑ TNF- α , IL-6 and IL-1 β
Atazanavir	↑ Oxidative stress, ↓ MAP-2, ↓ synaptophysin

Increasing Polypharmacy in Aging HIV+ Adults



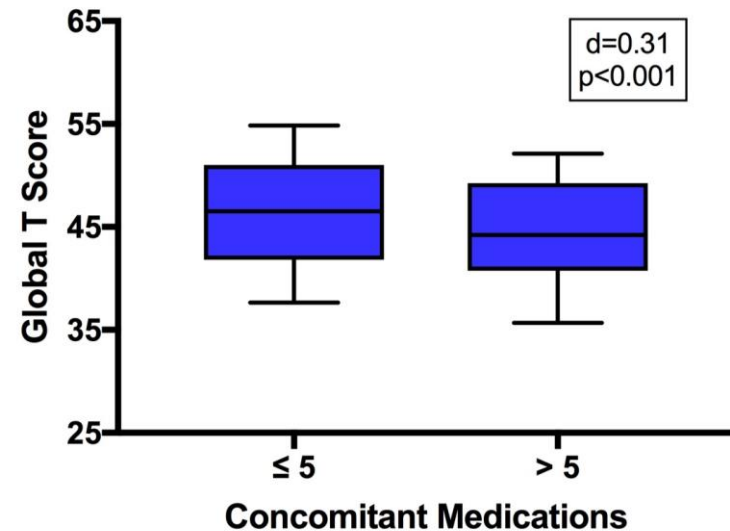
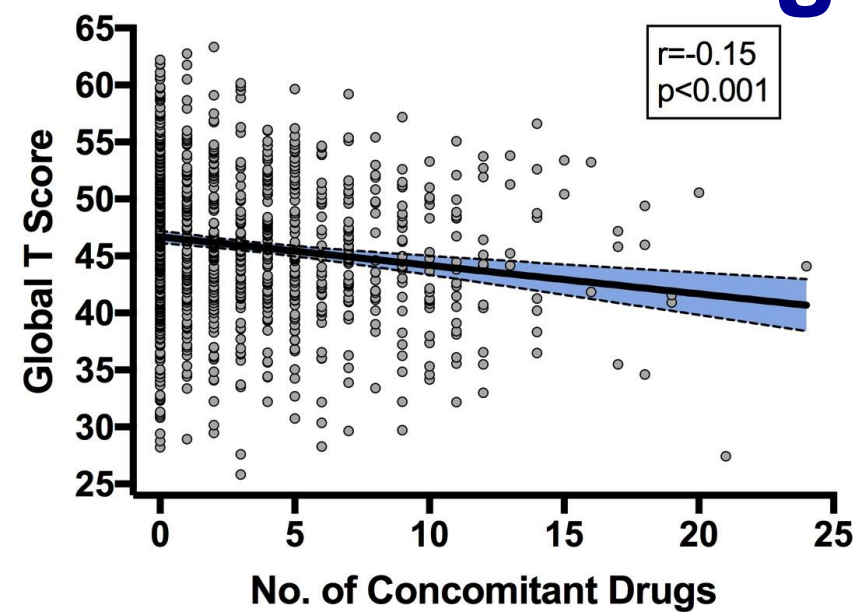
Women with HIV are More Likely to Use Other Medications Associated with NP-AEs



NP-AE Drug Use and ART

Outcome	OR (95% CI)	p-value
cART use	1.46 (1.35-1.57)	<0.0001
cART adherence	1.03 (0.95-1.12)	0.45
Undetectable viral load	1.12 (1.05-1.19)	0.0008

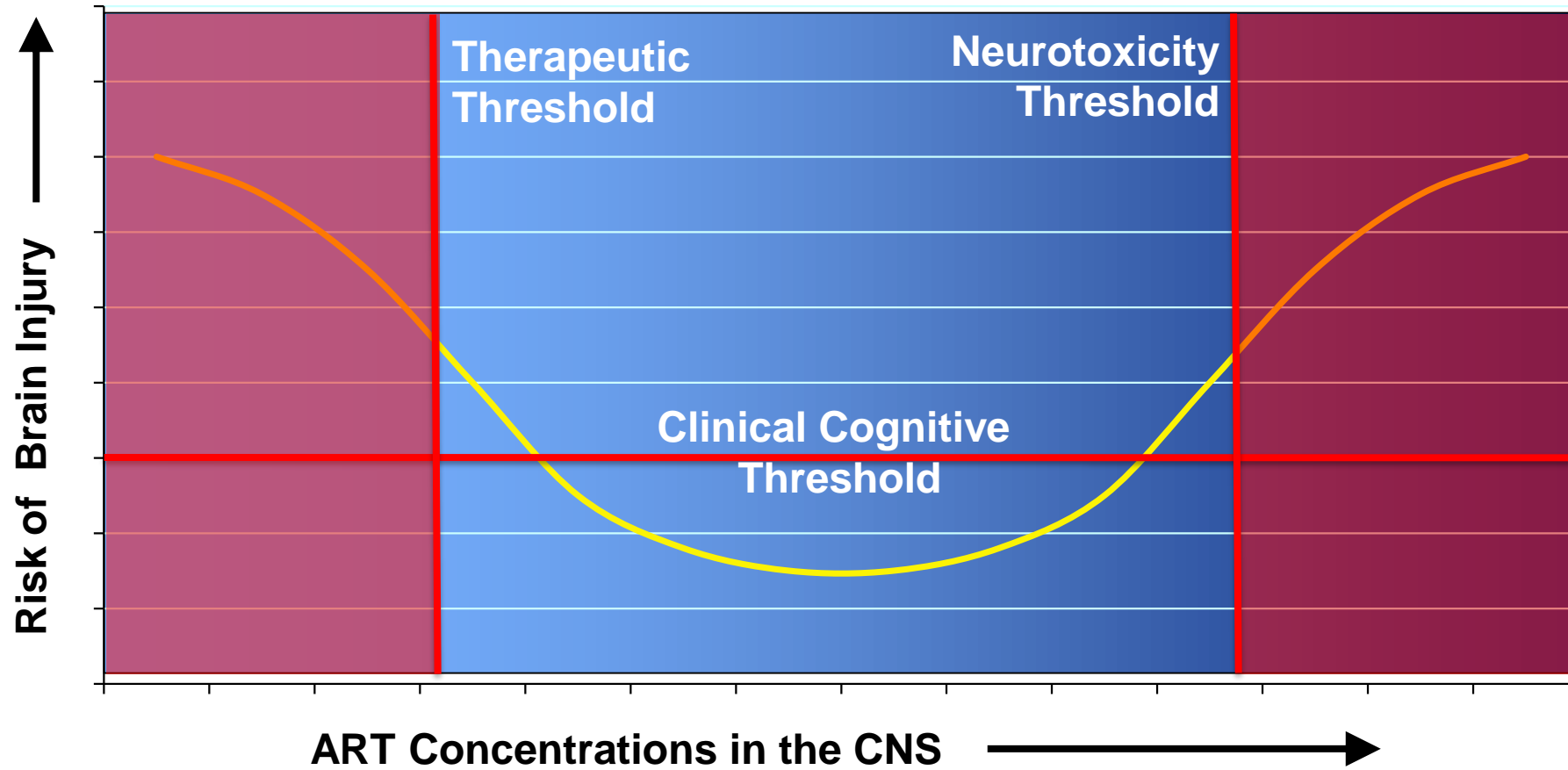
Polypharmacy Is Associated with Worse Neurocognitive Performance



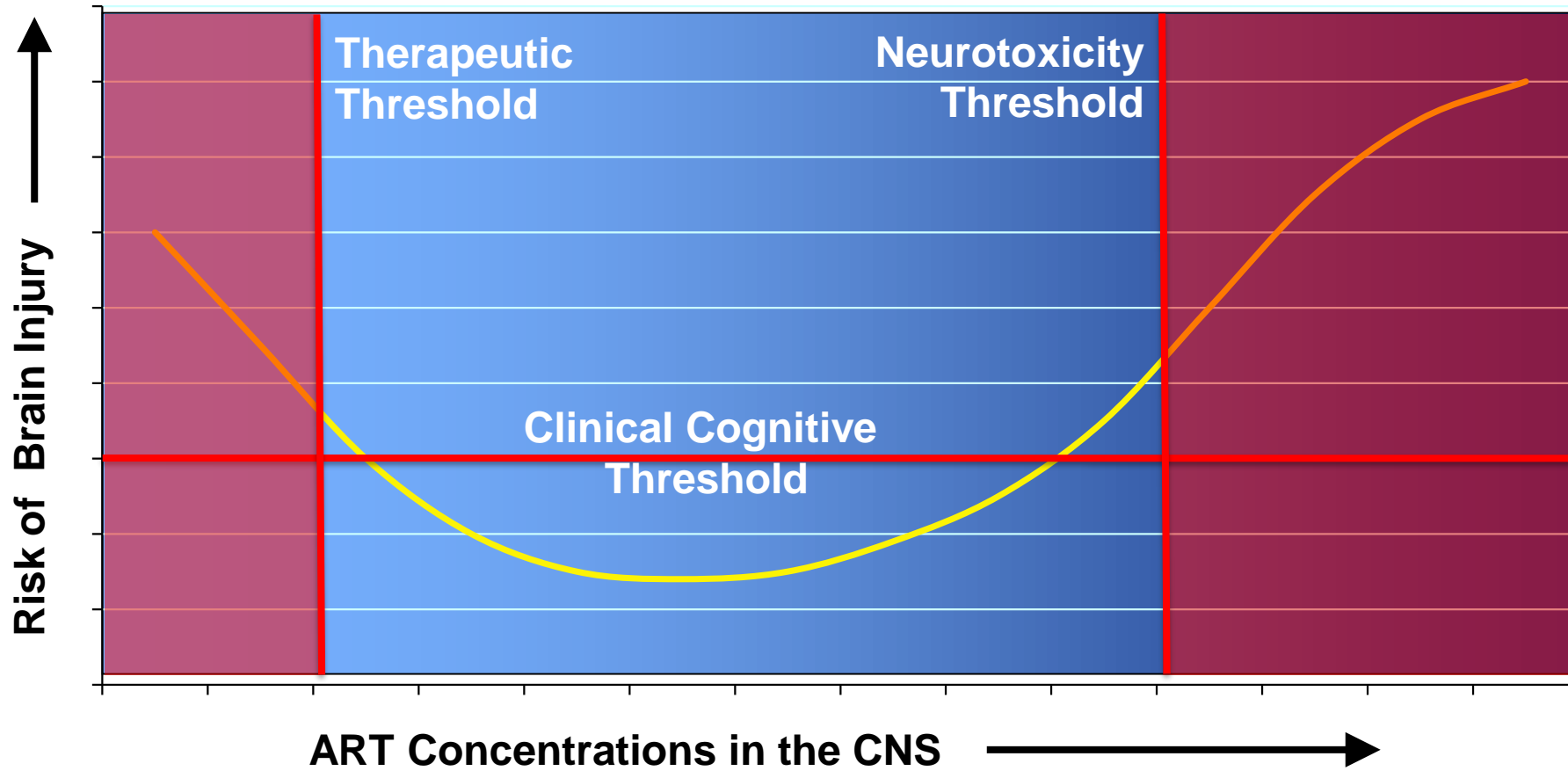
	Executive Function	Learning	Working Memory	Recall	Information Processing	Motor Function	Verbal Fluency
Anxiolytics	***	***	***	***	***	-	**
Antipsychotics	***	***	***	***	-	**	***
Opioids	***	***	***	**	***	**	-
Antimicrobials	***	***	-	***	**	-	-
Protease Inhibitors	**	-	**	-	**	***	*

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$, - $p > 0.10$

CNS Therapeutic Window



CNS Therapeutic Window



Reduce the Risk of
Virologic Failure

Increase the Risk of
Neurotoxicity

More Potent ART, Fewer Drug Resistance Mutations
Earlier ART Initiation, Higher CD4+ T-Cell Count
Older Age, Polypharmacy, Women,
Drug-Drug Interactions



Neurotoxicity Intervention

Table 1 Risk factors (and the degree of association) for HIV-associated neurocognitive disorders and published beneficial interventions

Variable	Degree of association with HAND	Degree of association with ARVs' choice	Other relevant factors	Beneficial interventions
Low CD4 nadir	High	–	–	None
High HIV DNA	Moderate	Low	Duration of viral suppression	None
Plasma HIV RNA	High	High	Several	Genotype-based, adherence
CSF HIV RNA	Moderate	High	Several	Unclear
Symptomatic CSF escape	High (neurological symptoms)	High	Low nadir CD4, resistant-associated mutations	Genotype-based, CNS-targeted
Asymptomatic CSF escape	Low	Moderate	Plasma HIV RNA	Unclear
Residual CSF HIV RNA	Unclear	Unclear	Duration of viral suppression	None
Macrophage-derived cell infection	Low	Moderate	Viral tropism	None
Compartmental immune activation/inflammation	Moderate	Unclear	Low nadir CD4	None
Neurotoxicity	Moderate	High	Host genetics	Unclear
Cardiovascular risk profile	High	Moderate	Several	None

Acknowledgements

Study Volunteers

UC San Diego

- Igor Grant
- Ronald J. Ellis
- Robert Heaton
- J. Allen McCutchan
- Brookie Best
- Edmund Capparelli
- Cris Achim
- David Moore
- Davey Smith
- Sara Gianella
- Sanjay Mehta
- Greg Brown
- Bob Bussell
- Connie Benson
- Chip Schooley
- Doug Richman

CHARTER/NNTC

- Todd Hulan
- Asha Kallianpur
- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier
- Ann Collier
- Christina Marra
- Susan Morgello
- David Simpson
- Ben Gelman
- Howard Fox

NIH

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

Trainees

- Qing Ma (Buffalo)
- Bert Anderson (Emory)
- Jenny Iudicello
- Micol Ferrara
- Kemi Okwuegbuna
- Raeanne Moore
- Josue Perez Santiago

