Safety of Current Antiretroviral Therapy on the CNS

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Disclosures

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- Gilead Sciences
- Merck & Co., Inc.
- ViiV Healthcare

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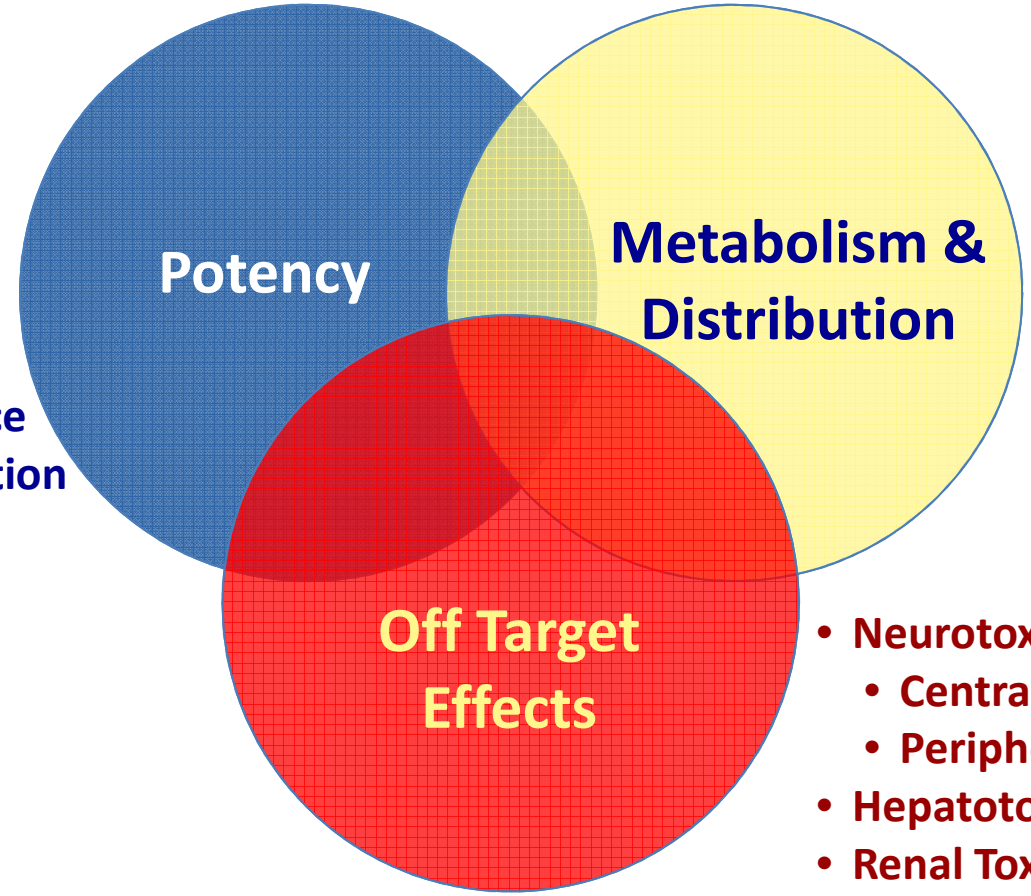
- Cipla
- Merck & Co., Inc.
- ViiV Healthcare

Dr. Letendre was paid for a lecture:

- Janssen

Several ART Drug Characteristics Can Influence CNS Effectiveness

- **Suppression of HIV Replication**
  - Lymphocytes
  - Monocytes & Macrophages
- **Barrier to Resistance**
- **Viral Protein Inhibition**
- **Immune Recovery**



- **Long Half-Life**
- **Protein Binding**
- **Lipophilicity**
- **Molecular Weight**
- **Molecular Transporters**

- **Neurotoxicity**
  - **Central NS**
  - **Peripheral NS**
- **Hepatotoxicity**
- **Renal Toxicity**
- **Metabolic & Vascular Disorders**

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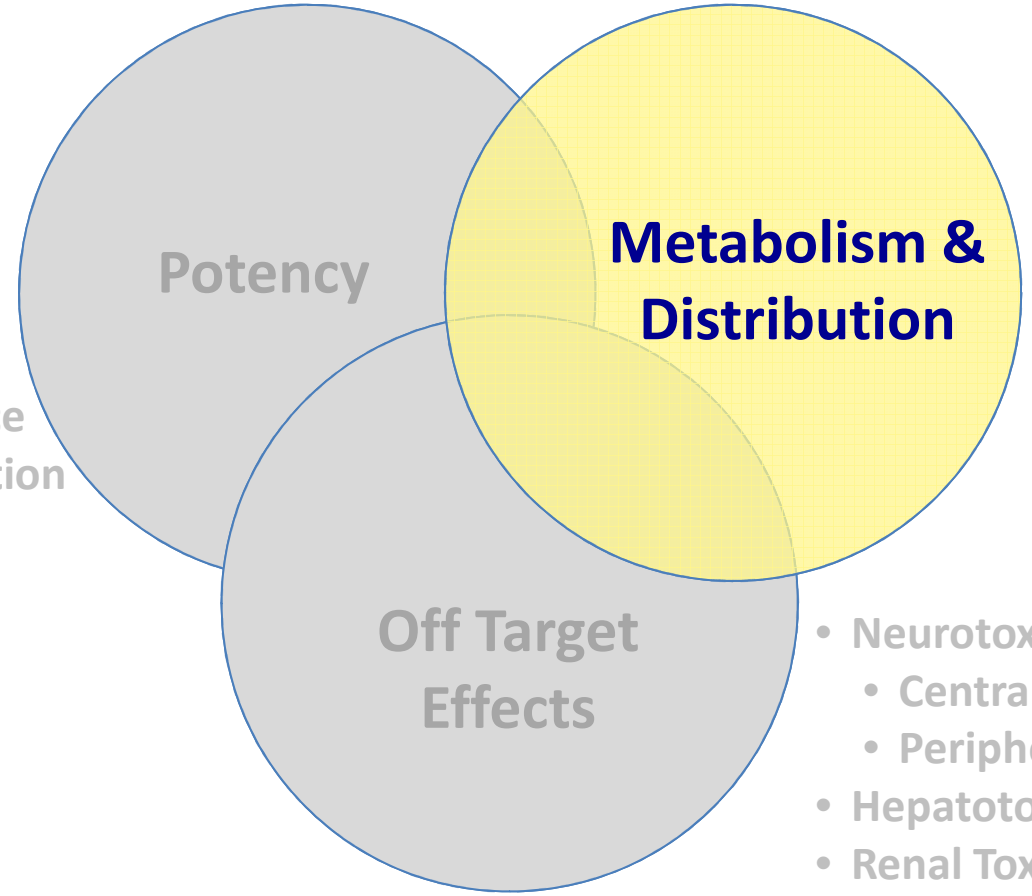

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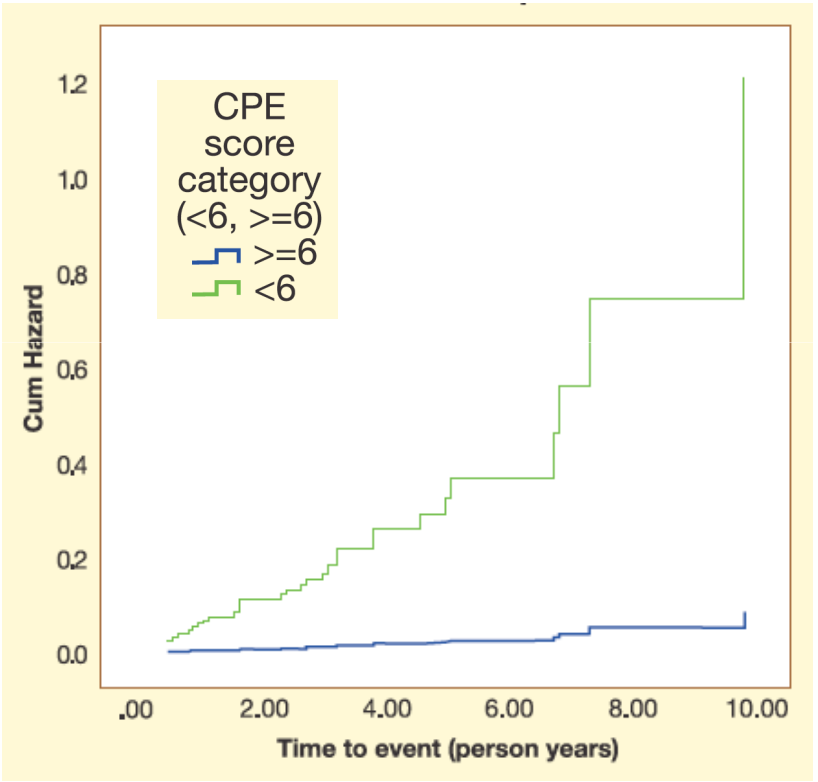
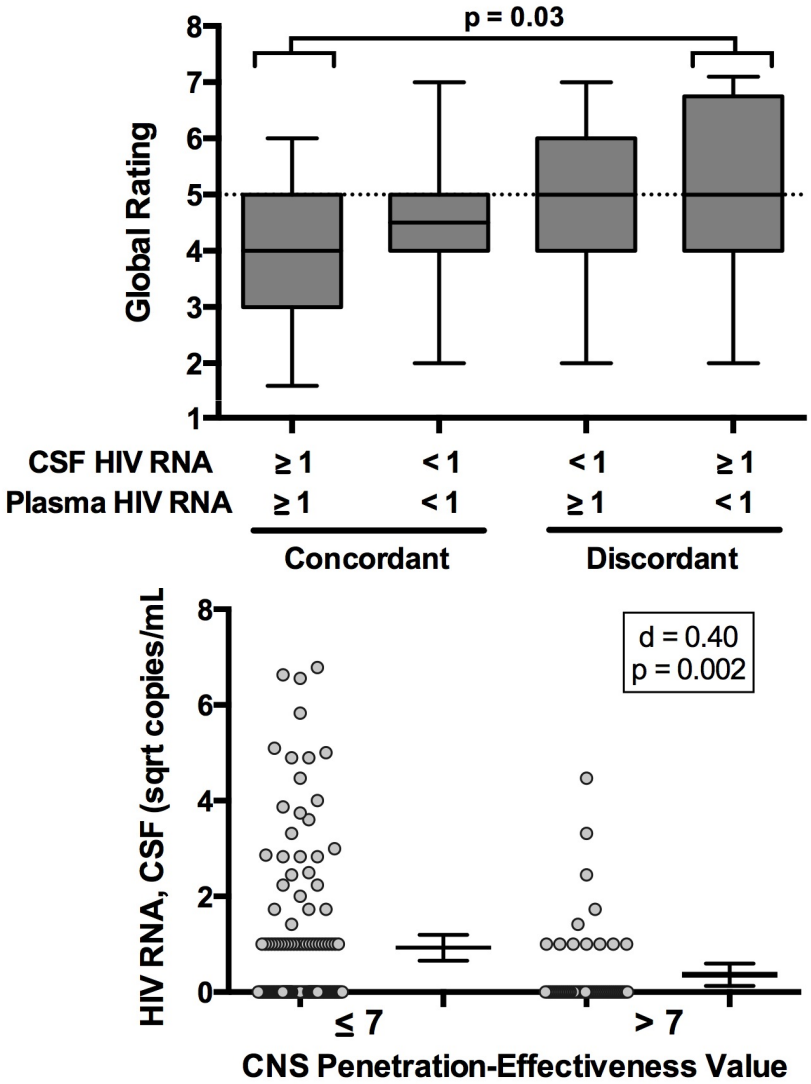
Continuing Reports of CSF Viral Escape

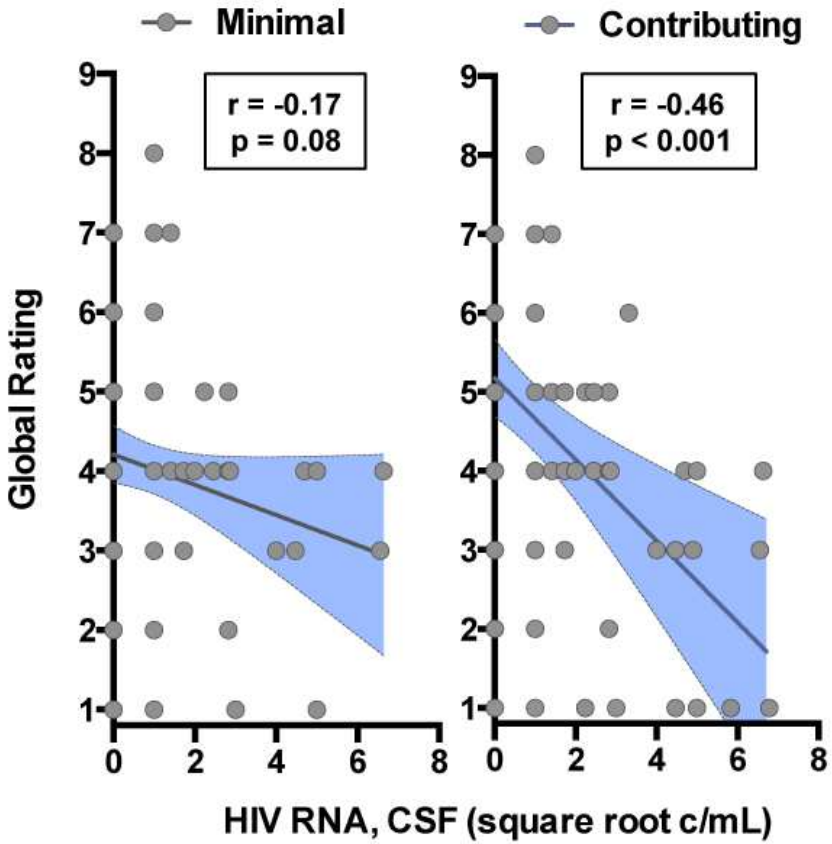
Patient No.	ART Regimen at the time of neuro-deterioration	CD4 count at baseline	CD4 count at the time of neuro-deterioration	Plasma viral load at neuro-deterioration	CSF HIV viral load at neuro-deterioration
1	TDF/FTC/NVP	83 cells/mm^3	108 cells/mm^3	0 copies/ml	12,000 copies/ml
2	TDF/FTC/ATV/r	32 cells/mm^3	187 cells/mm^3	210 copies/ml	16000 copies/ml
3	TDF/FTC/ATV/r	70 cells/mm^3	274 cells/mm^3	134 copies/ml	35200 copies/ml
4	ABC/3TC/LPV/r	108 cells/mm^3	367 cells/mm^3	110 copies/ml	3100 copies/ml
5	TDF/FTC/ATV/r	68 cells/mm^3	135 cells/mm^3	238 copies/ml	1900 copies/ml
6	TDF/3TC/ATV/r	8 cells/mm^3	521 cells/mm^3	340 copies/ml	1200 copies/ml
7	TDF/3TC/ATV/r	132 cells/mm^3	509 cells/mm^3	890 copies/ml	3320 copies/ml
8	TDF/3TC/ATV/r	65 cells/mm^3	562 cells/mm^3	500 copies/ml	4800 copies/ml
9	AZT/3TC/TDF/ATV/r	56 cells/mm^3	313 cells/mm^3	110 copies/ml	4400 copies/ml
10	TDF/FTC/ATV/r	28 cells/mm^3	153 cells/mm^3	720 copies/ml	2000 copies/ml
11	TDF/FTC/ATV/r	45 cells/mm^3	367 cells/mm^3	0 copies/ml	900 copies/ml
12	TDF/3TC/ATV/r	178 cells/mm^3	419 cells/mm^3	0 copies/ml	150 copies/ml
13	LPV/r/Raltegravir	189 cells/mm^3	367 cells/mm^3	256 copies/ml	2450 copies/ml



Dravid, et al, EACS Conference 2015

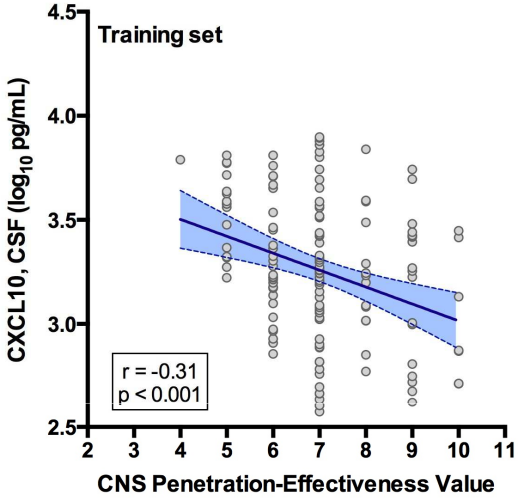
Low-Level HIV RNA in CSF is Associated with Higher CPE Values

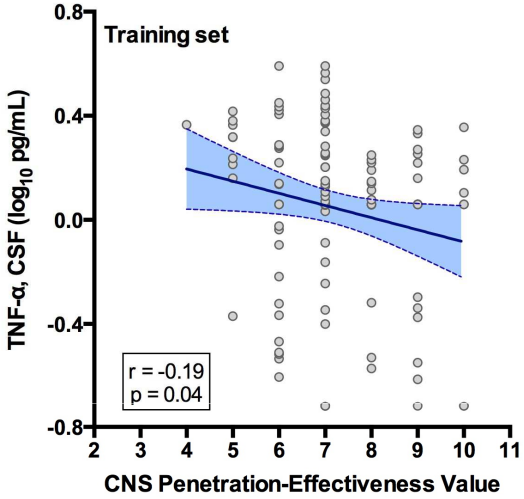


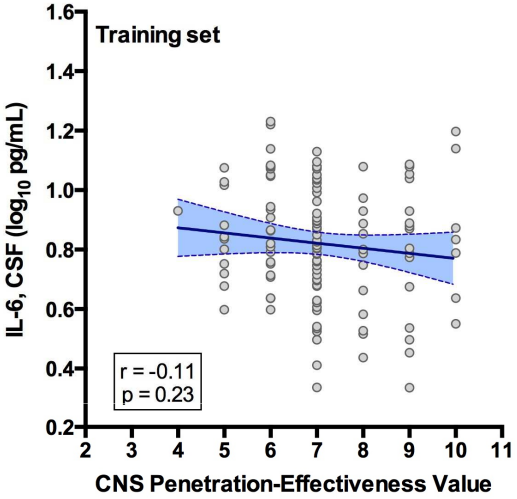


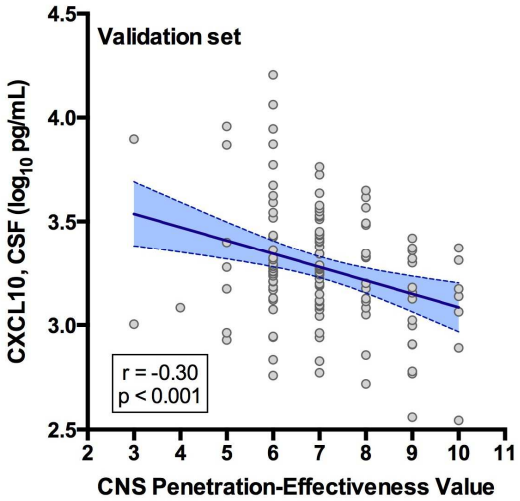
Anderson, et al, In Preparation

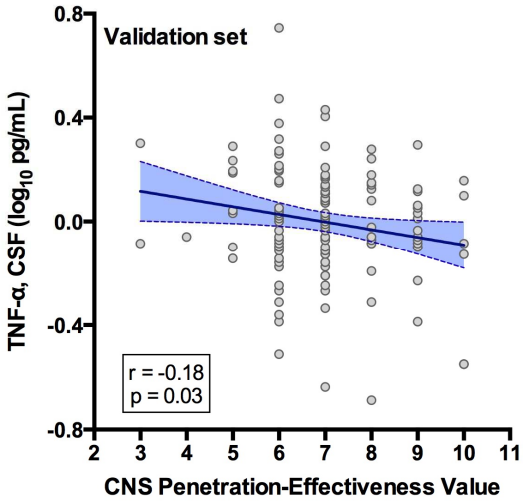
Higher CPE Values Associated with Lower Levels of Some Biomarkers

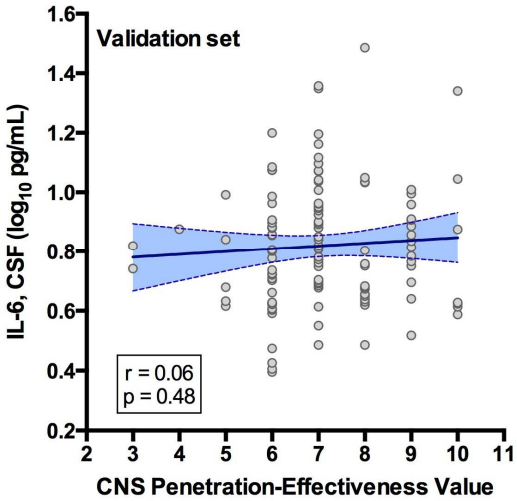






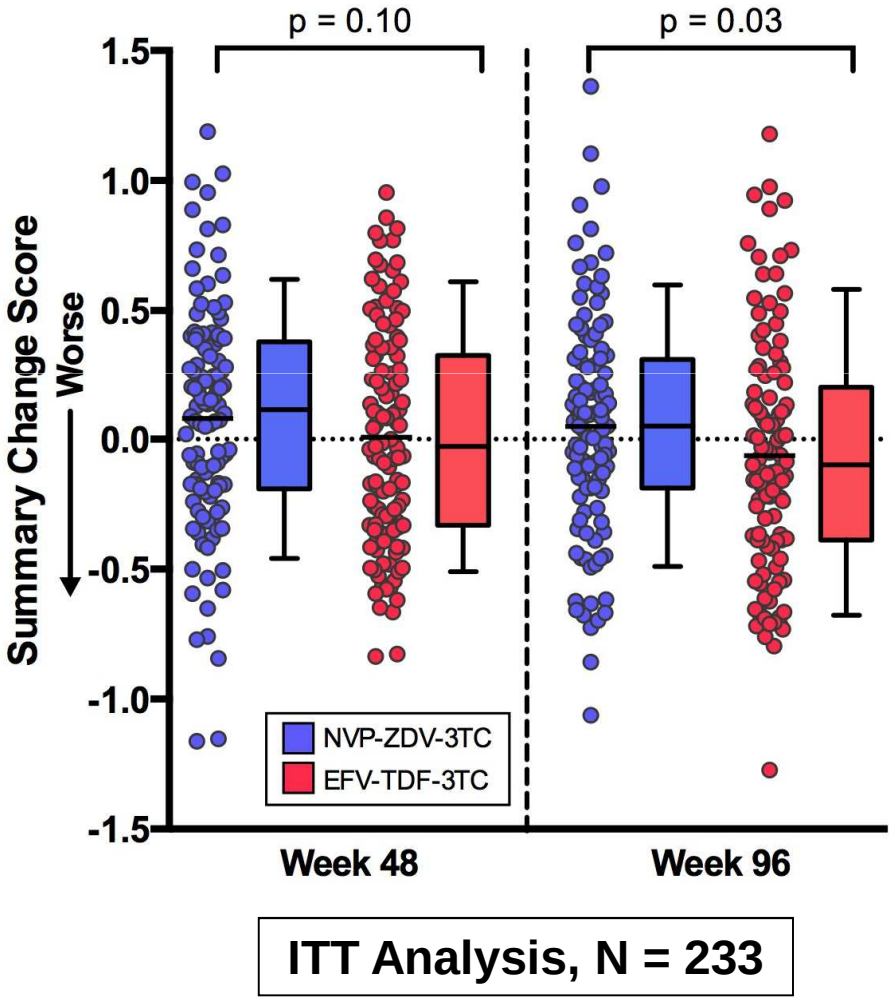






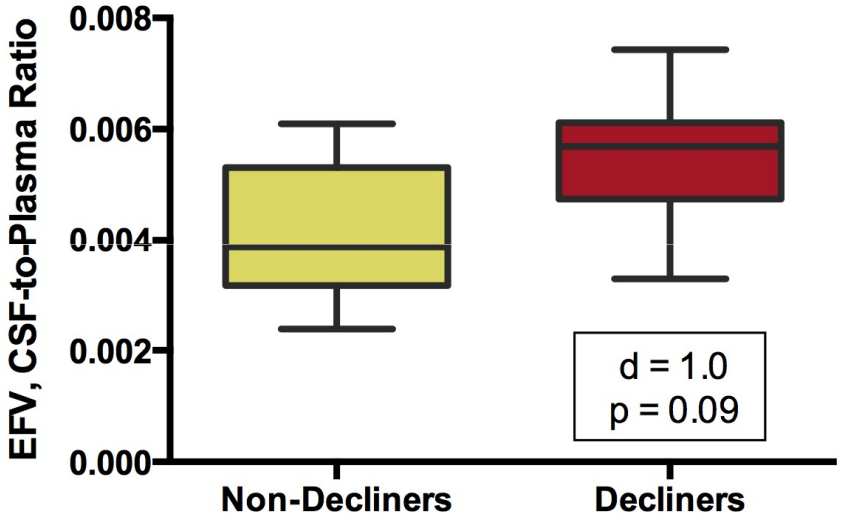
Anderson, et al, CROI 2016, Abstract 412

Cognitive Decline May Be Linked to Higher Drug Distribution into CSF



ITT Analysis, N = 233

Zhang, et al, CROI 2015, Abstract 56



Ma et al, CROI 2015, Abstract 444

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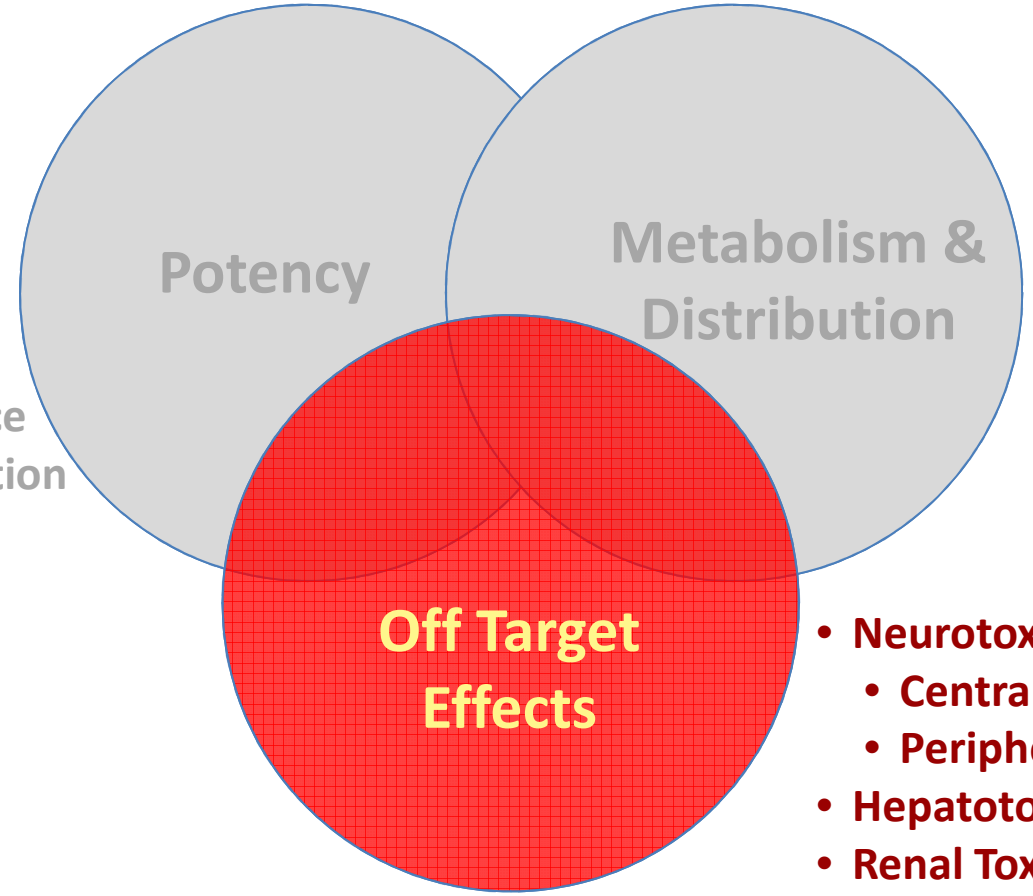

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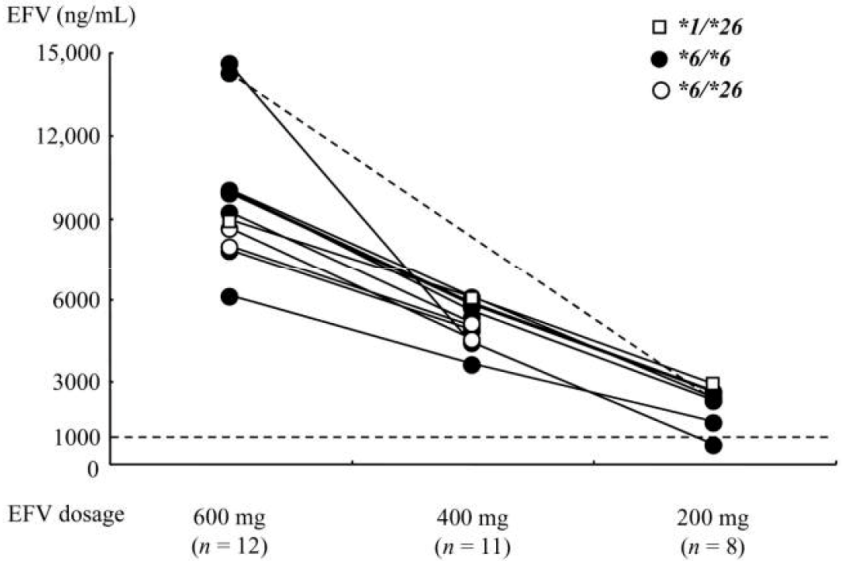
Longer Term Efavirenz Use is Associated with Increased Risk of NC Impairment and Reducing Dose May Improve NC Symptoms

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

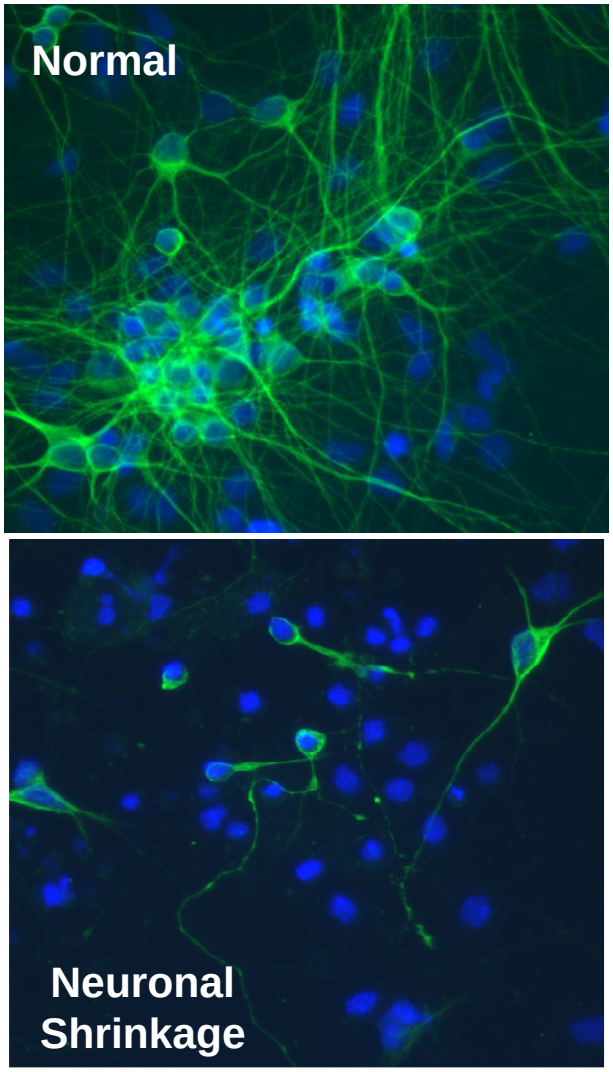


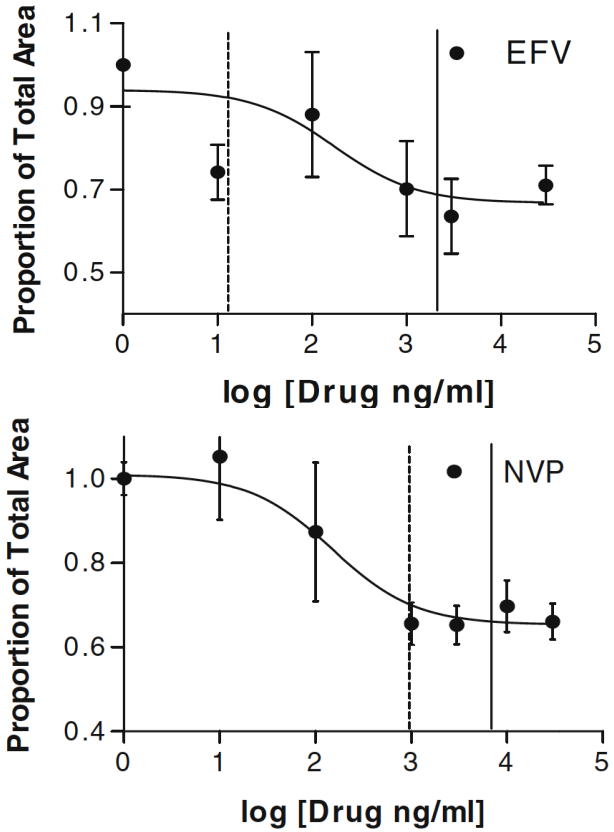
Gatanaga et al, Clinical Infectious Diseases 2007; 45:1230–7

If One Drug Causes Neurotoxicity, Might Others Do So Also?

Neurotoxicity in a Cell Culture System

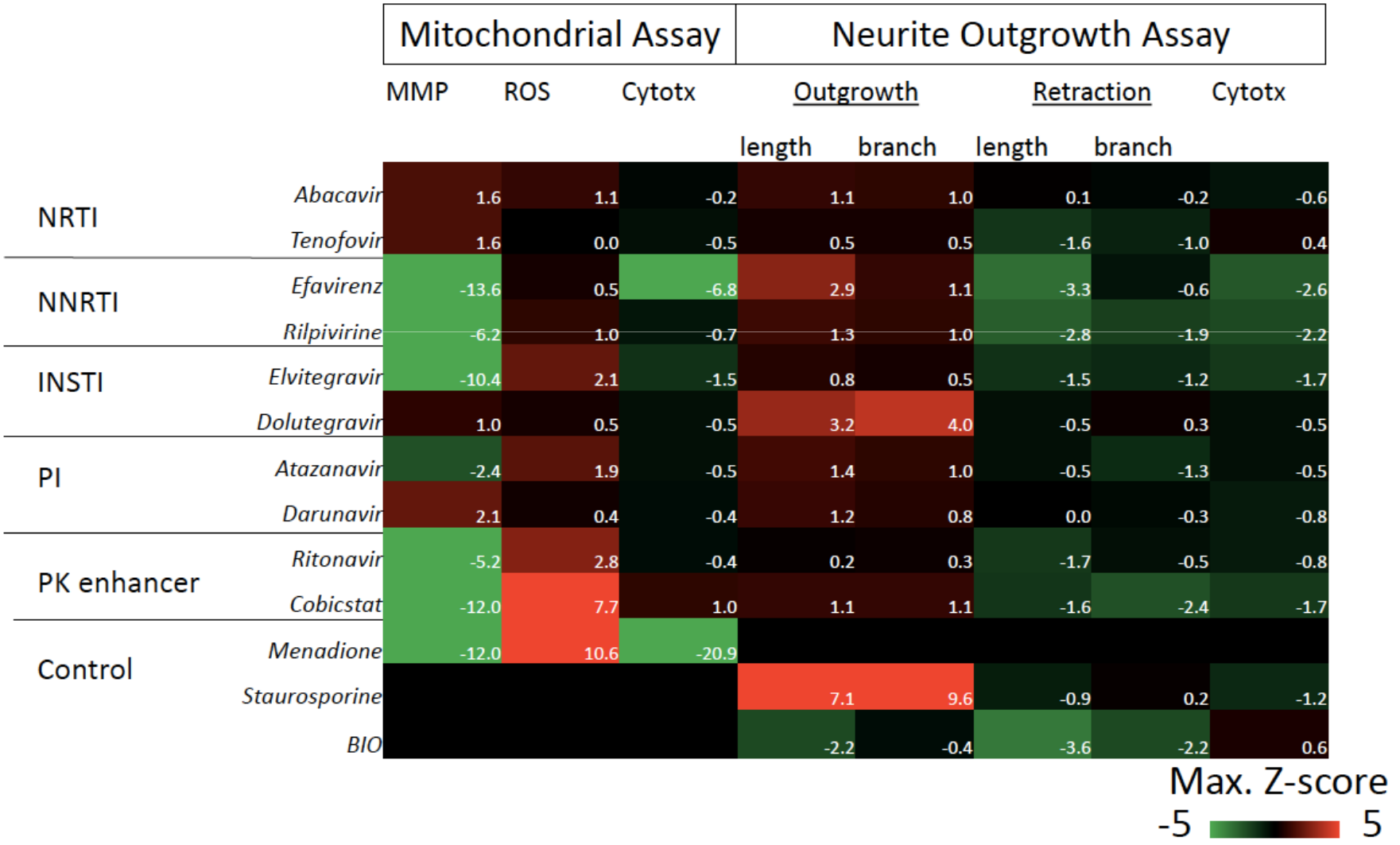
- Fetal rat cortical neuron cultures exposed to increasing ARV concentrations
- At least mild injury was seen with all drugs
- Constructed dose-effect curves and calculated toxicity indices





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

Neurotoxicity Screening of ART Drugs With Human iPSC-Derived Neurons



Hinckley et al, CROI 2016, Abstract 395

Vascular and Metabolic Disease Increase Risk for Neurocognitive Impairment

- **292 HIV+ adults in the START study**
- **Prior CVD was associated with NCI**

Wright et al. Neurology 2010; 75: 864

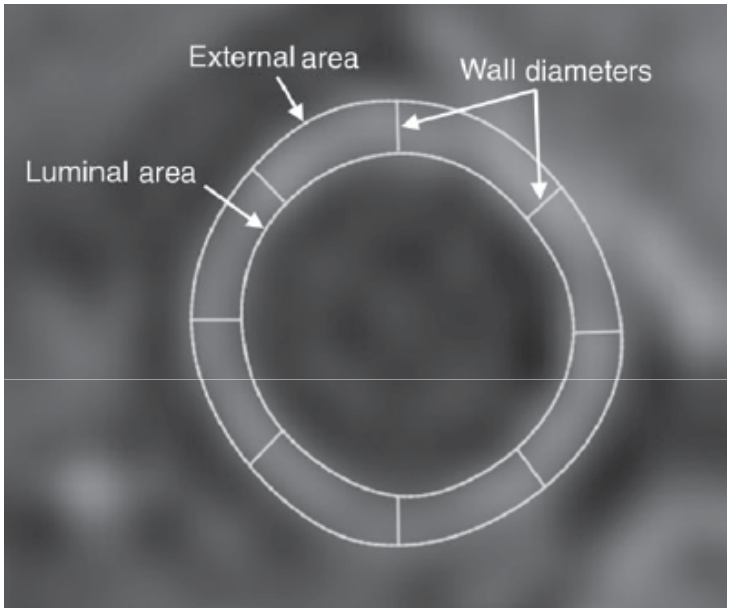
	Risk	OR	p
Prior CVD	Yes	6.2	0.01
Total cholesterol	Higher	1.1	0.06
AIDS	No	0.41	0.08
Race	Black	2.2	0.08

- **130 HIV+ adults in the CHARTER study**
- **Diabetes and waist circumference were associated with NCI**

McCutchan et al. Neurology 2012. 78: 485

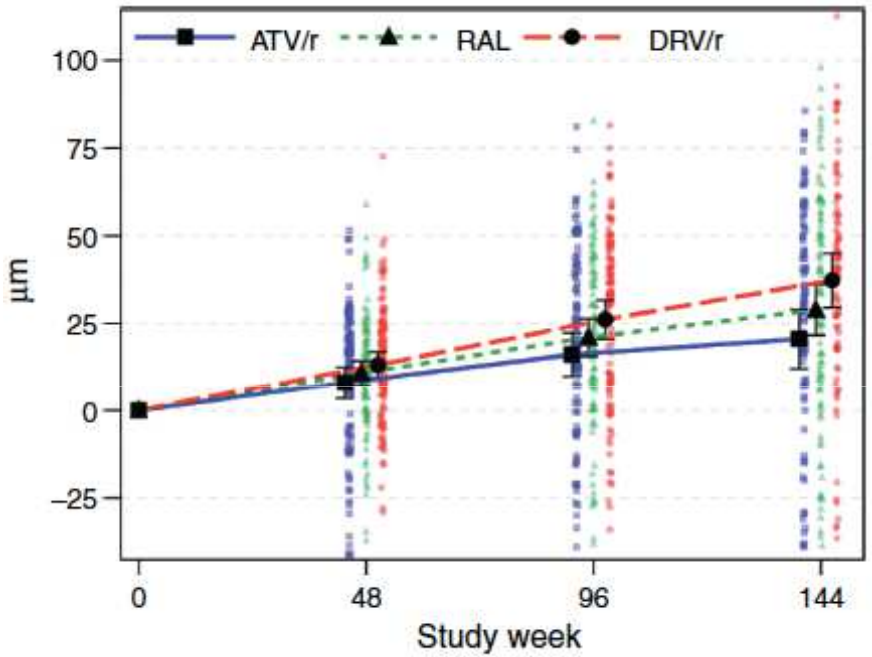
	Risk	OR	p
AIDS	Yes	49.6	0.01
Diabetes	Yes	17.6	0.07
Waist circumference	Larger	1.3	0.001
Triglycerides	Lower	0.32	0.09
BMI	Smaller	0.69	0.04

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**

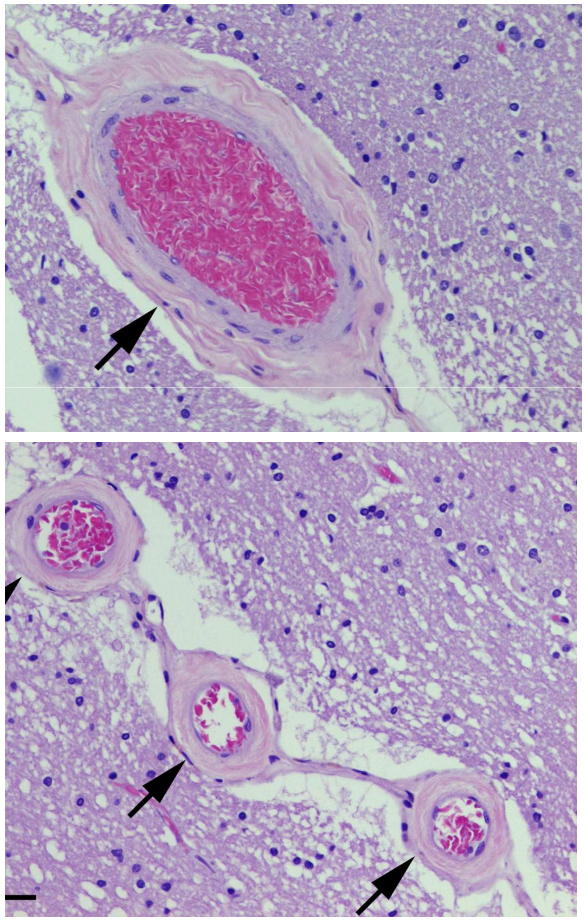
LaBounty et al, HIV Medicine (2015)
DOI: 10.1111/hiv.12351



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

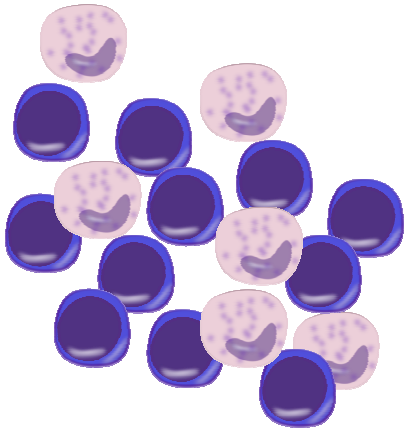
Stein et al, AIDS 2015, 29:1775–1783

Protease Inhibitor Use is Associated with Cerebral Small Vessel Disease

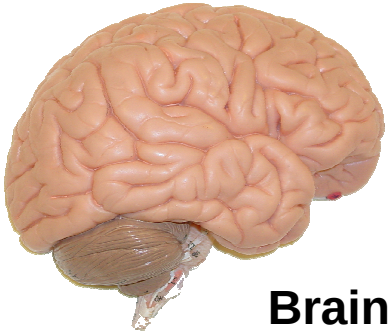


- **Protease inhibitor use was associated with cerebral small vessel disease**
  - Mild: **OR 2.8** (95% CI 1.03–7.9)
  - Moderate-severe: **OR 2.6** (95% CI 1.03–6.7)
- **Mild cerebral small vessel disease was associated with HAND**
  - **OR 4.8** (95% CI 1.1–21.2)

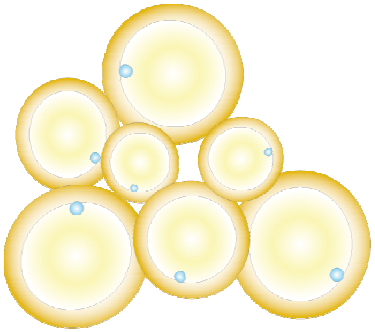
Soontornniyomkij et al, AIDS 2014, 28:1297–1306



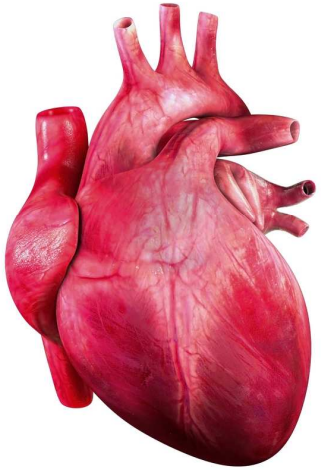
Persistent
Inflammation



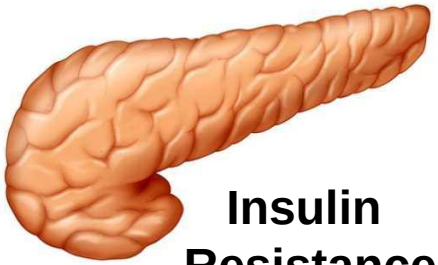
Brain
Disease



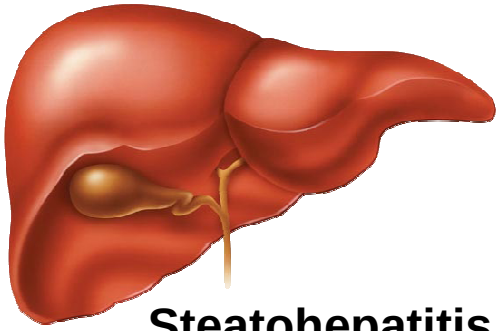
Dyslipidemia
Visceral Fat



Vascular
Disease

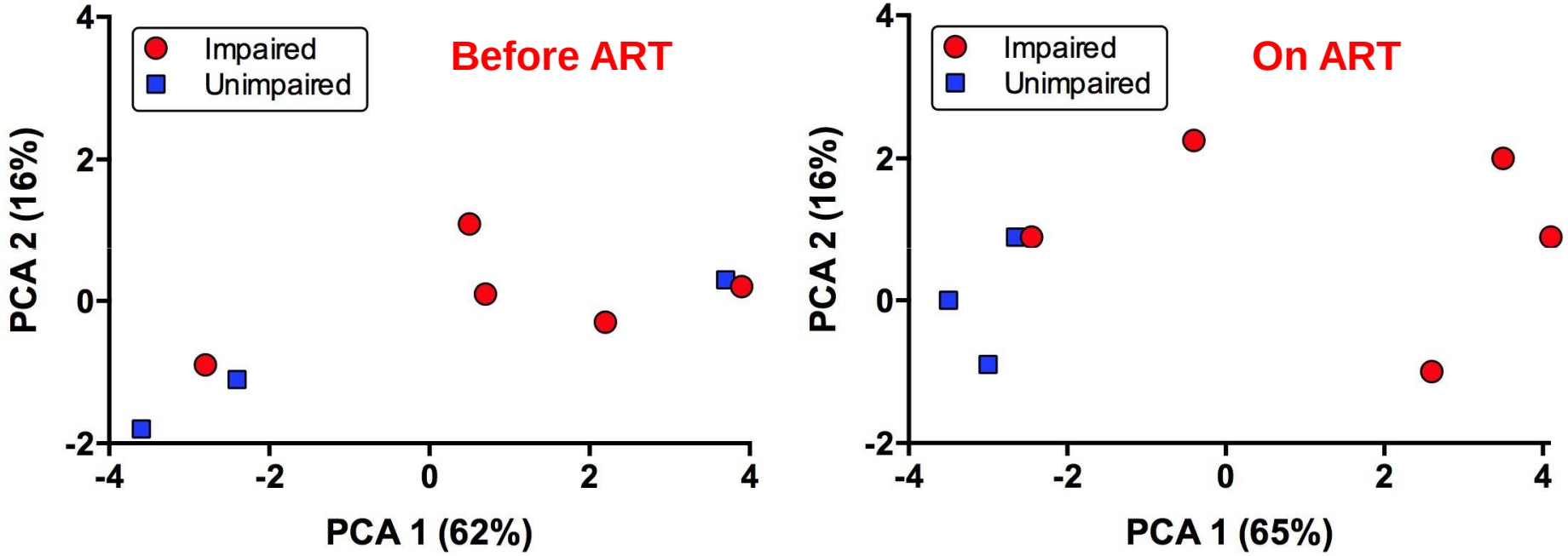


Insulin
Resistance



Steatohepatitis
Liver Fibrosis

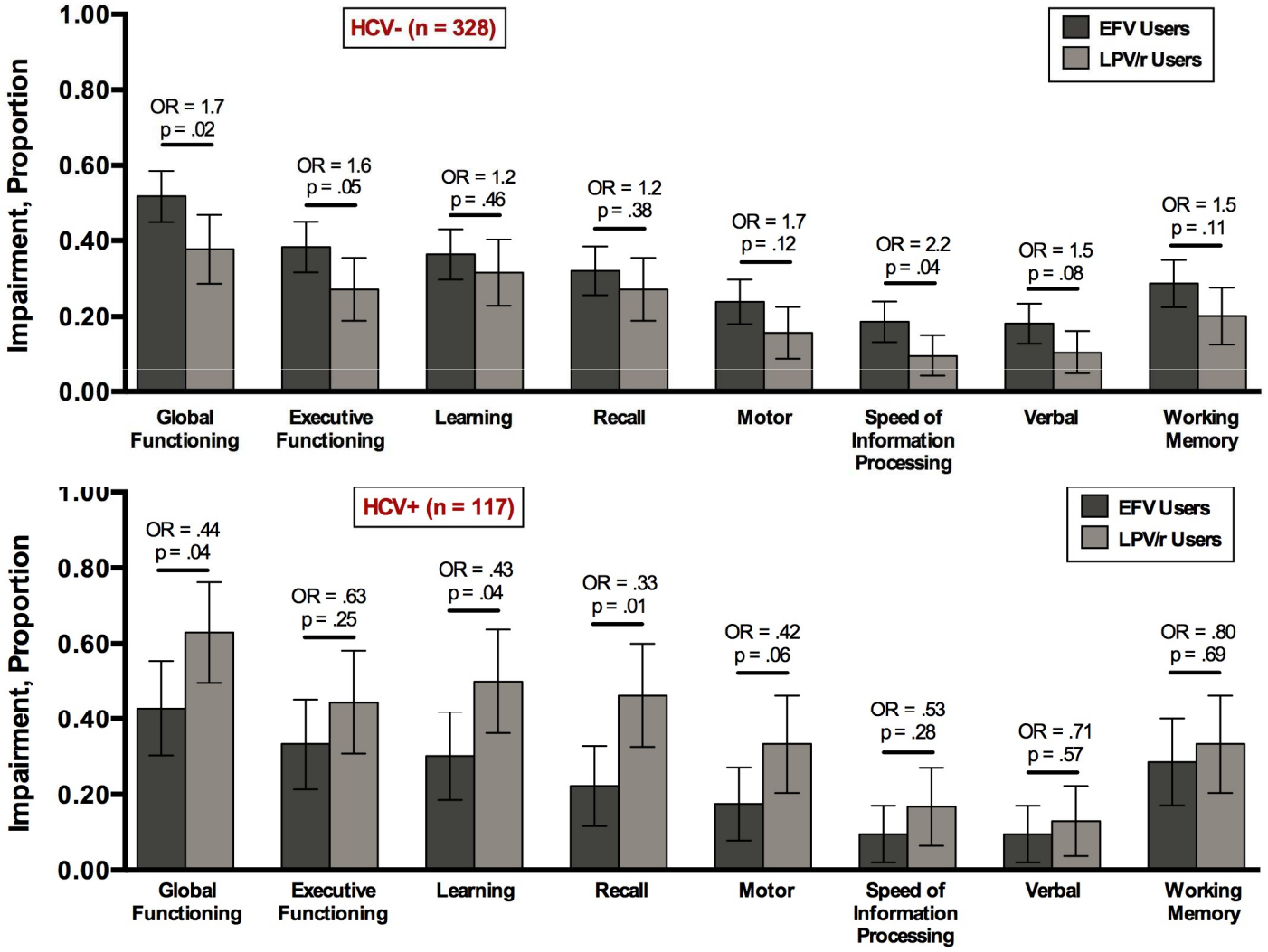
Gut Microbiome Appears to Differ between Impaired and Unimpaired



Pérez Santiago et al, International Symposium on Neurovirology 2015

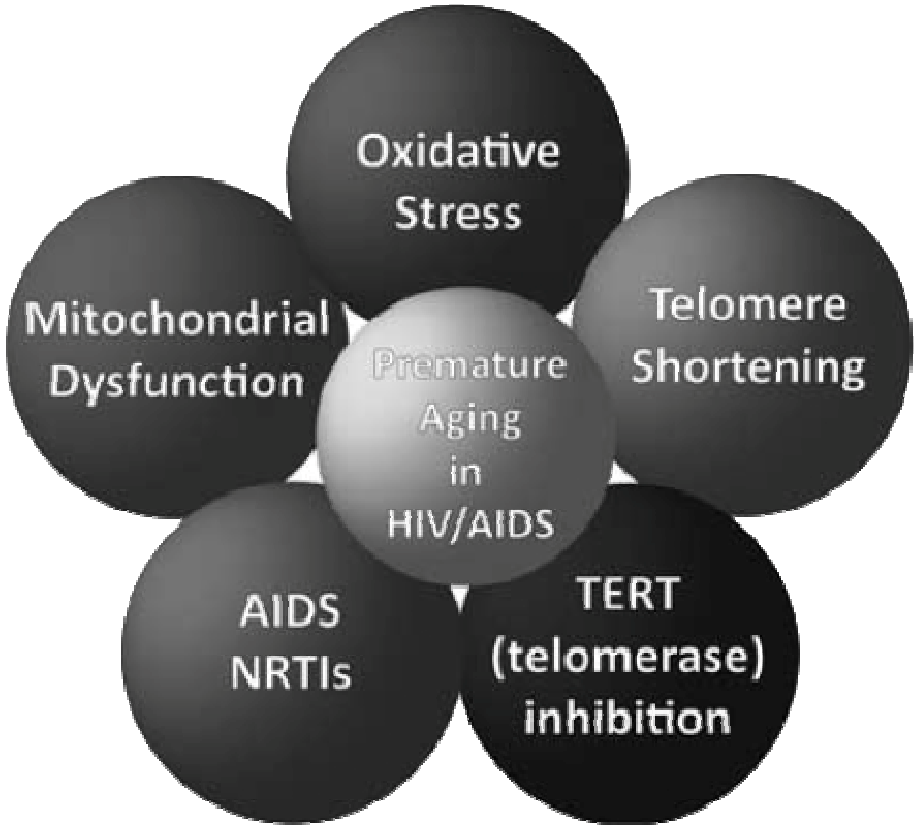
UC San Diego

Protease Inhibitors May be More Neurotoxic with HCV Co-infection

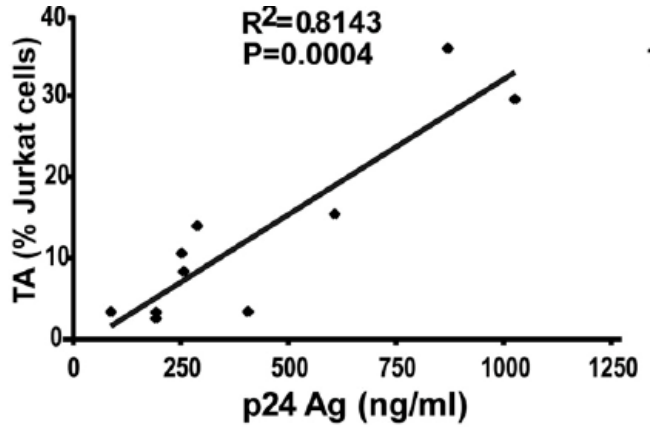


Ma et al, J. Neurovirol. (2016) 22:170–178

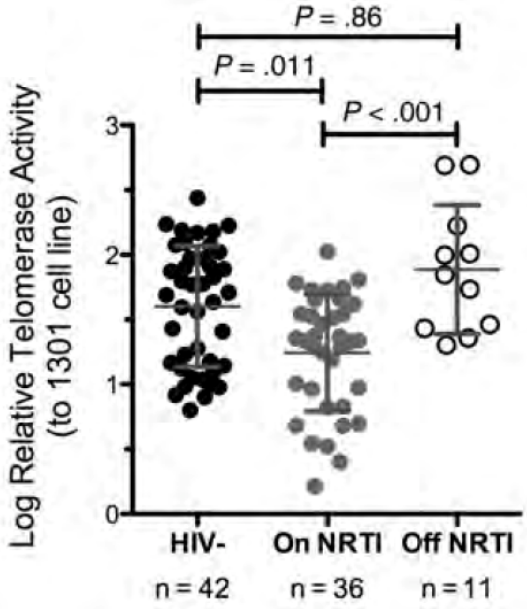
Higher NRTI Levels in CNS May Increase Mitochondrial and Telomere Toxicity



Torres & Lewis, Laboratory Investigation (2014) 94, 120–128

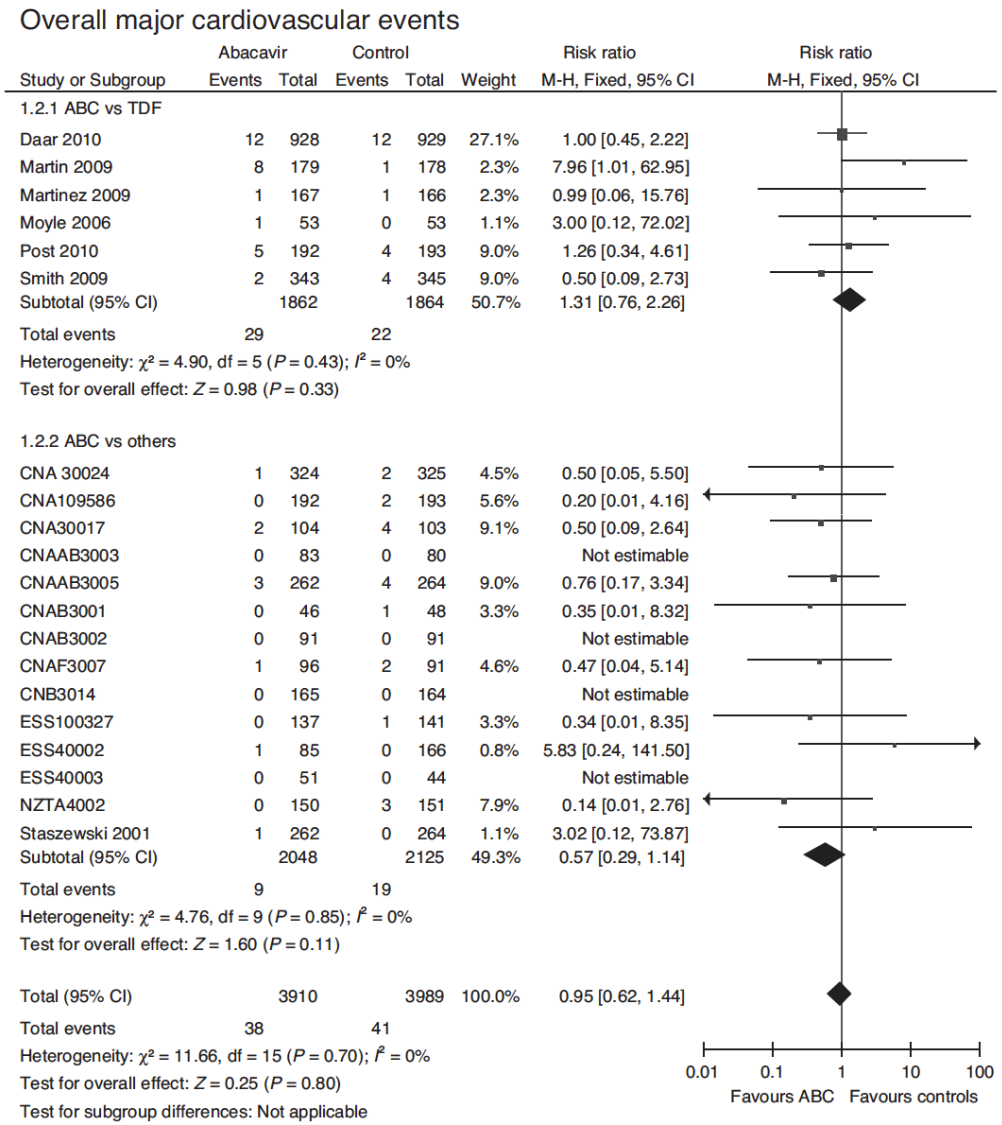


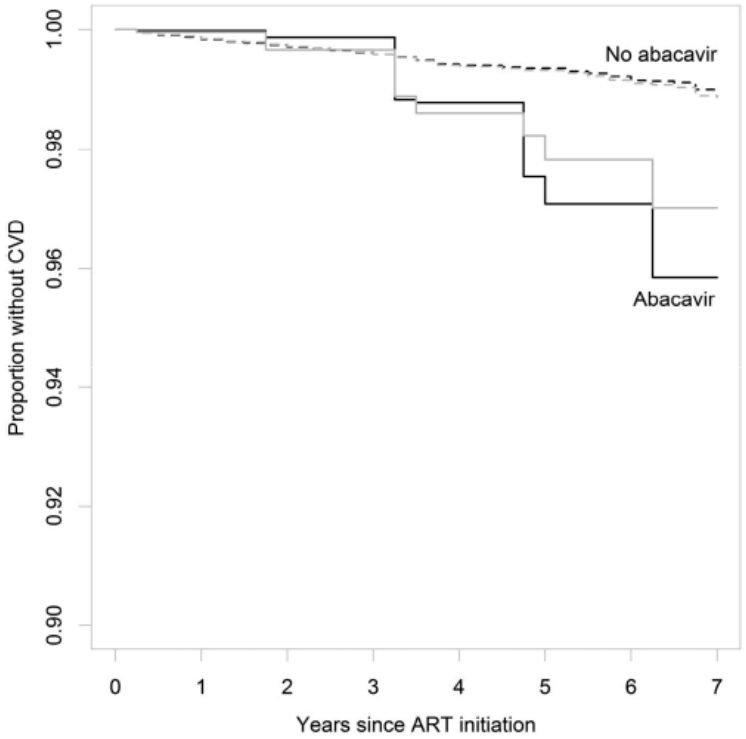
Reynoso et al, J Virol 2012; 86(19):10327



Leeansyah et al, JID 2013; 207:1157

Abacavir and Cardiovascular Risk

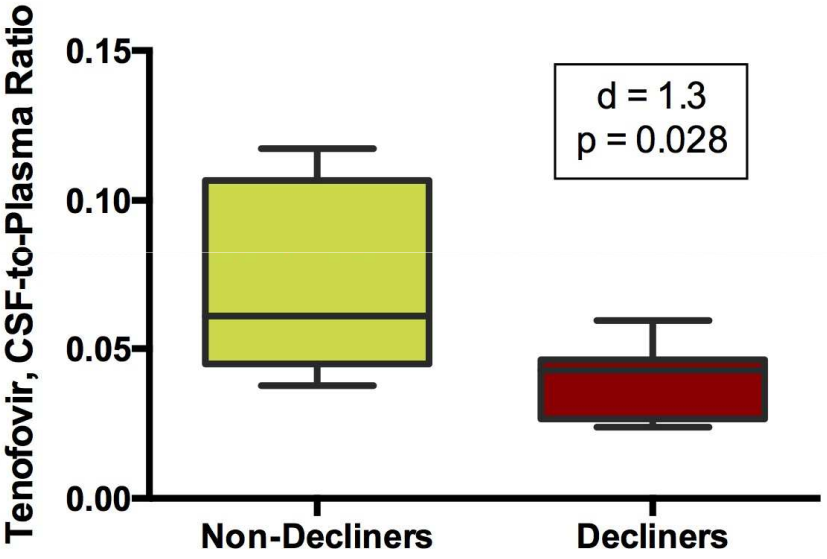




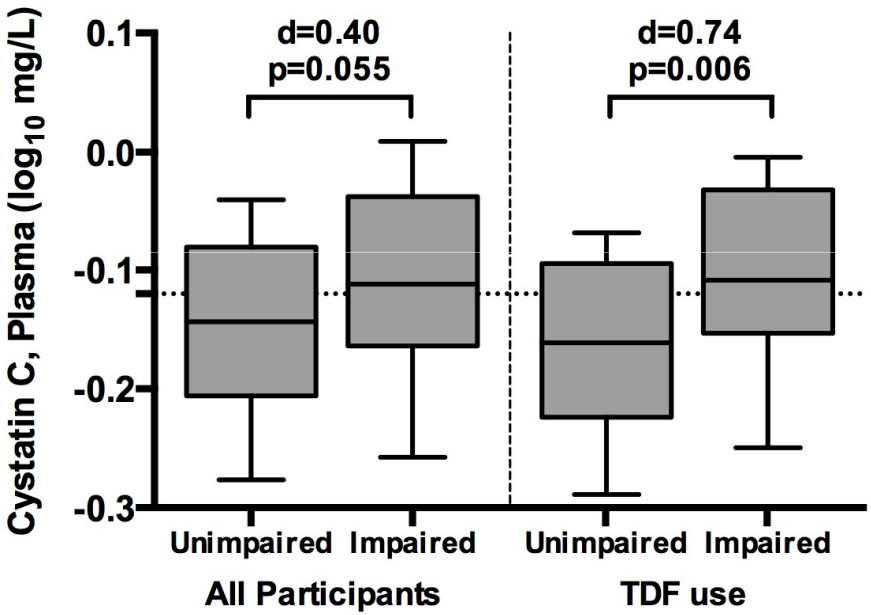
Cruciani et al, AIDS 2011, 25:1993–2004

Marcus et al, JAIDS 2016; 71:413–419

Tenofovir May Also Influence Neurocognition

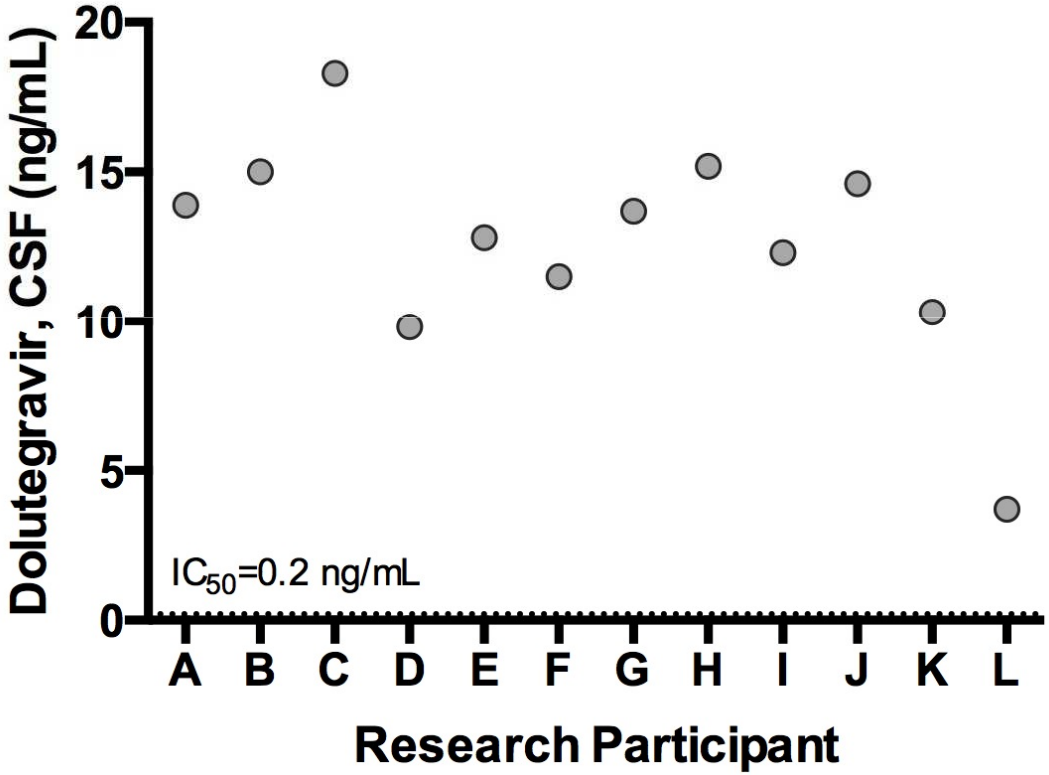


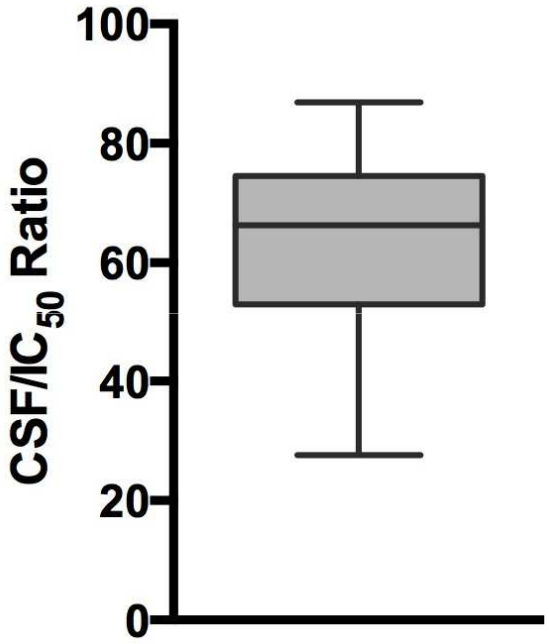
Ma et al, CROI 2015, Abstract 444



Sakoda et al, CROI 2015, Abstract 484

Dolutegravir Reaches Therapeutic Concentrations in CSF





Letendre et al, Clinical Infectious Diseases 2014;59(7):1032–7

Dolutegravir May be Associated with CNS Adverse Events

	DTG (n=242)		DRV/r (n=242)		RR	p value
Headache	40	16.5%	26	10.7%	1.54	0.06*
Depression	15	6.2%	9	3.7%	1.67	0.21*
Anxiety	13	5.4%	9	3.7%	1.44	0.38*
Insomnia	19	7.9%	16	6.6%	1.19	0.60*
Dizziness	14	5.8%	13	5.4%	1.08	0.84*
Suicide Attempt	3	1.2%	0	0%	-	0.25**

**2-sided t-test, **2-sided Fisher's Exact Test*
p values calculated by me

Molina et al, Lancet HIV 2015; 2: e127–36

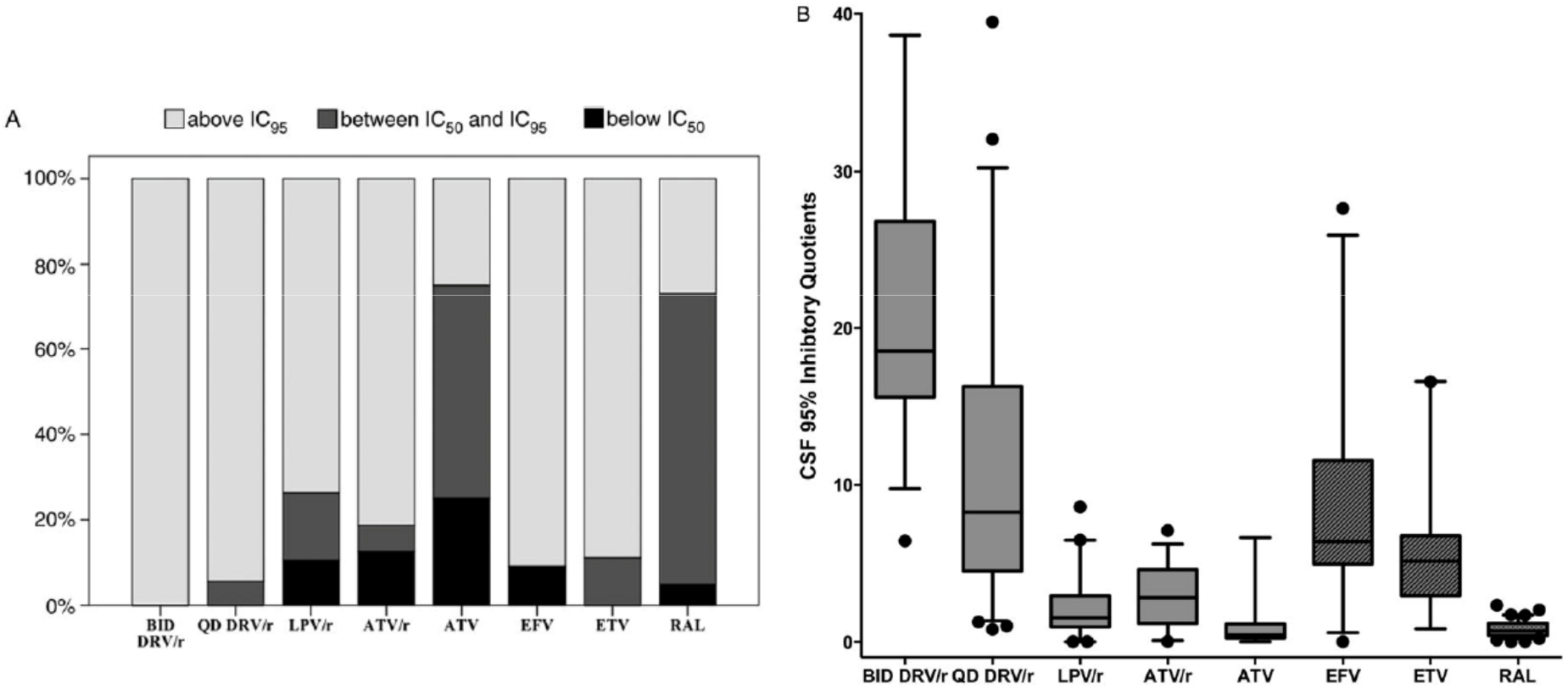
Dolutegravir Intolerance in Holland

	Total (N=387)	ART Naive (n=65)	ART Experienced (n=322)
Sleep Disturbance	19 (4.9%)	5 (7.7%)	14 (4.3%)
Gastrointestinal	18 (4.6%)	4 (6.2%)	19 (5.9%)
Neuropsychiatric	12 (3.1%)	3 (4.6%)	9 (2.8%)
Fatigue	9 (2.3%)	1 (1.5%)	8 (2.5%)
Headache	8 (2.1%)	0 (0%)	8 (2.5%)
Paresthesias	6 (1.6%)	0 (0%)	6 (1.9%)
Other	6 (%)	2 (%)	4 (%)

- **Overall 62 of 387 (16%) cohort participants discontinued dolutegravir**
- **56 of 62 (90.3%) discontinued due to adverse events**

van den Berk et al, CROI 2016, Abstract 948

IC_{95} May Be a Better Comparator than IC_{50}

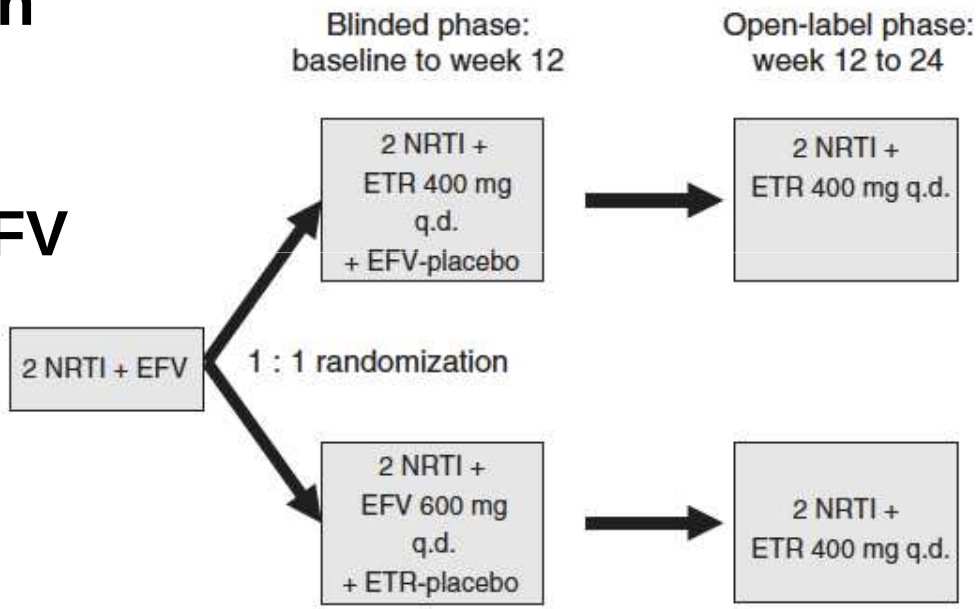


Calcagno et al, Clin Inf Dis 2015;60(2):311–7

Switch, Simplify, or Intensify?

Switching Efavirenz to Etravirine Reduces CNS Adverse Events

- **Randomized, double-blind trial in 38 HIV+ adults with viral suppression but ongoing CNS AEs after more than 12 weeks of EFV**
- **Immediate vs. delayed switch to ETR**
- **Decline in grade 2-4 CNS adverse events**
  - **Overall: 89% to 60% (p=0.009)**
  - **Insomnia, abnormal dreams and nervousness**

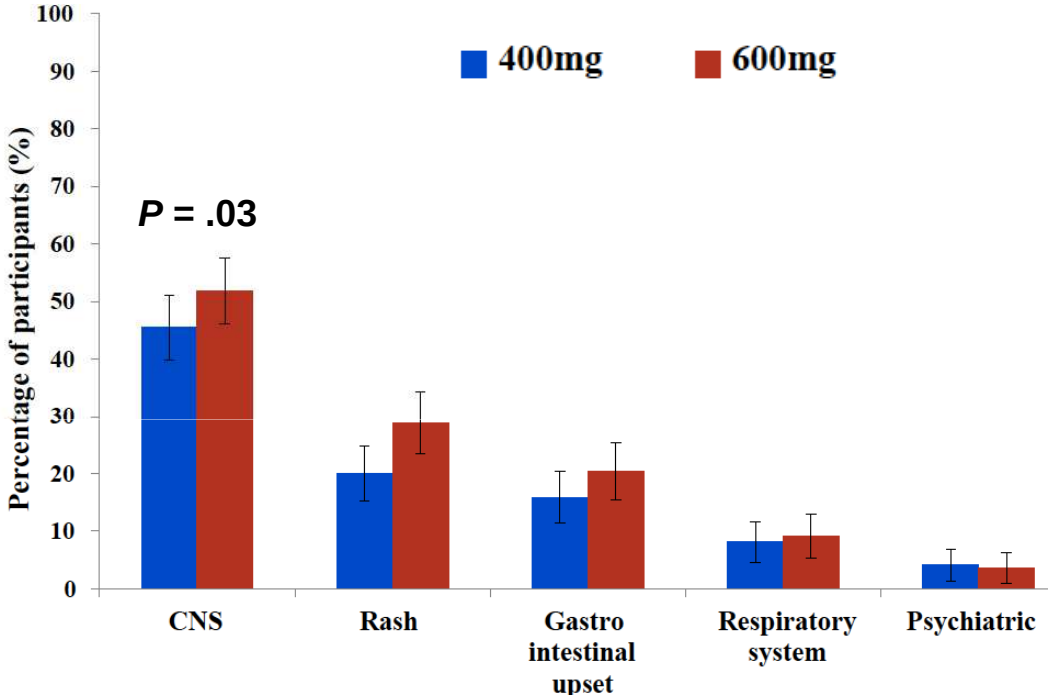


Waters, et al. AIDS 2011, 25:65–71

BB1

ENCORE1: Lower Efavirenz Dose Results in Fewer CNS Adverse Events

- 630 HIV+ adults
- Double-blind, placebo-controlled, non-inferiority, 96-week trial
- 400 mg EFV was non-inferior to 600 mg in efficacy
- 400 mg arm had fewer AEs and fewer discontinuations due to EFV



- **AEs due to EFV: 39% vs. 48%, RR 0.86**
- **Discontinuations due to EFV: 13% vs. 23%, RR 0.45**

ENCORE1 Study Group. Lancet Infect Dis 2015; 15: 793–802

Diapositiva 29

BB1 la dosis de EFV de 400 no esta en FT
Belen Box; 25/05/2016

Fewer CNS Adverse Events with Doravirine or Rilpivirine

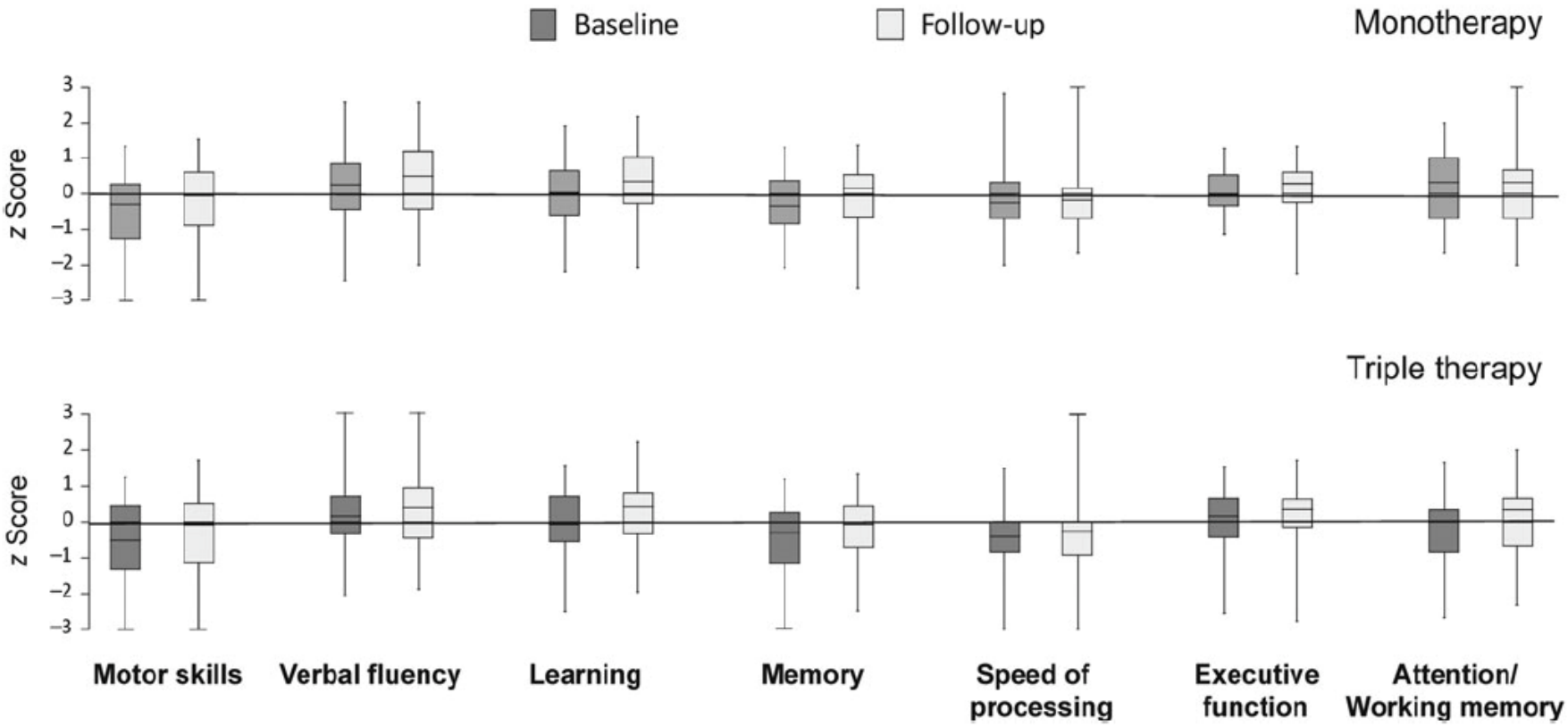
	DOR n=108	EFV n=108	p value
Dizziness	6.5%	25.9%	< 0.001
Abnormal dreams	5.6%	14.8%	0.04
Headache	2.8%	5.6%	0.50
Nightmares	5.6%	8.3%	0.59
Sleep disorder	4.6%	6.5%	0.77
Insomnia	6.5%	2.8%	0.33

Gatell et al, CROI 2016, Abstract 470

	RPV n=288	EFV n=255	p value
Dizziness	10.4%	27.8%	<0.001
Abnormal dreams	7.6%	13.7%	0.02
Somnolence	2.8%	6.3%	0.06
Sleep disorder	1.4%	3.9%	0.10
Anxiety	1.0%	3.1%	0.13
Attention Disturbance	0.7%	2.4%	0.16
Depressive Disorder	4.5%	2.7%	0.36

Behrens et al, AIDS Pat Care & STDs 2014, 28(4): 168

Regimen Simplification May be Safe for the CNS in Certain Patients



Pérez Valero, et al. Clinical Infectious Diseases 2014;59(11):1627–34

Safe is Not the Same as Therapeutic (for HAND)

Week 48 efficacy and central nervous system analysis of darunavir/ritonavir monotherapy versus darunavir/ritonavir with two nucleoside analogues

Andrea Antinori[a], Amanda Clarke[b], Veronika Svedhem-Johansson[c], José R. Arribas[d], Alejandro Arenas-Pinto[e], Jan Fehr[f], Jan Gerstoft[g], Andrzej Horban[h], Bonaventura Clotet[i], Diego Ripamonti[j], Pierre-Marie Girard[k], Andrew M. Hill[l] and Christiane Moecklinghoff[m]

Central Nervous System HIV Infection in "Less-Drug Regimen" Antiretroviral Therapy Simplification Strategies

Francesca Ferretti, MD[1] Nicola Gianotti, MD[1] Adriano Lazzarin, MD[1] Paola Cinque, MD, PhD[1]

Protease inhibitor monotherapy and the CNS: peace of mind?

Ignacio Perez-Valero[1], Carmen Bayon[2], Irene Cambron[2], Alicia Gonzalez[1] and Jose R. Arribas[1]*

Is There a Higher Risk of CNS Adverse Events for PI Monotherapy Versus Triple Therapy? A Review of Results From Randomized Clinical Trials

William Powderly,[1] Andrew Hill,[2] and Christiane Moecklinghoff[3]

BB3

Maraviroc Intensification May Improve N-Acetyl Aspartate on MRS

- **12 HIV+ NA adults on suppressive ART**
- **Intensified with MVC**
- **14 days later, NAA/Cr in right basal ganglia improved and correlated with:**
  - Higher plasma MVC concentrations
  - Lower IP-10 in CSF

	Right basal ganglia		PK parameters	
Chemokines	NAA/Cr	mI/Cr	Maraviroc plasma (ng/mL)	Maraviroc CSF (ng/mL)
IP-10 correlation*	–0.618 (*.028*)	0.100 (*NS*)	–0.629 (*.028*)	–0.308 (*NS*)
MCP-4 correlation**	–0.253 (*NS*)	0.604 (*.049*)	–0.264 (*NS*)	–0.333 (*NS*)
MIP-1β correlation**	–0.206 (*NS*)	0.645 (*.032*)	–0.300 (*NS*)	0.164 (*NS*)
MCP-1 correlation**	0.101 (*NS*)	0.121 (*NS*)	–0.173 (*NS*)	–0.109 (*NS*)

Garvey et al, J Antimicrob Chemother 2012; 67: 206–212
Vera, et al. HIV Clin Trials 2012;13(4):222–227

Diapositiva 33

BB3 la intesnsificacion no esta en FT

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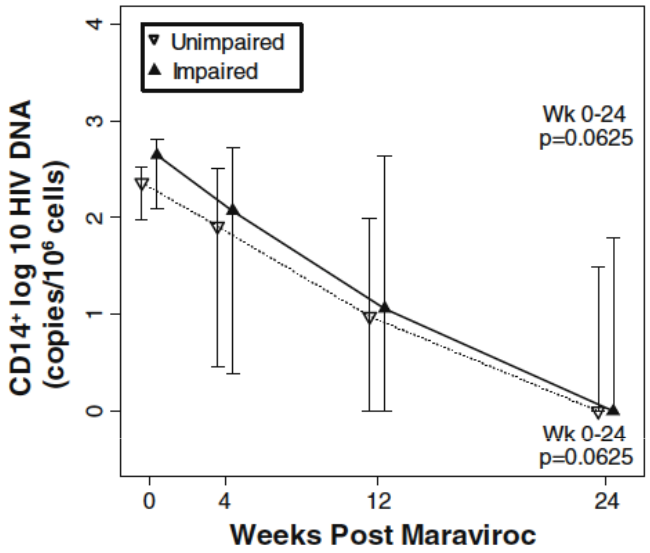
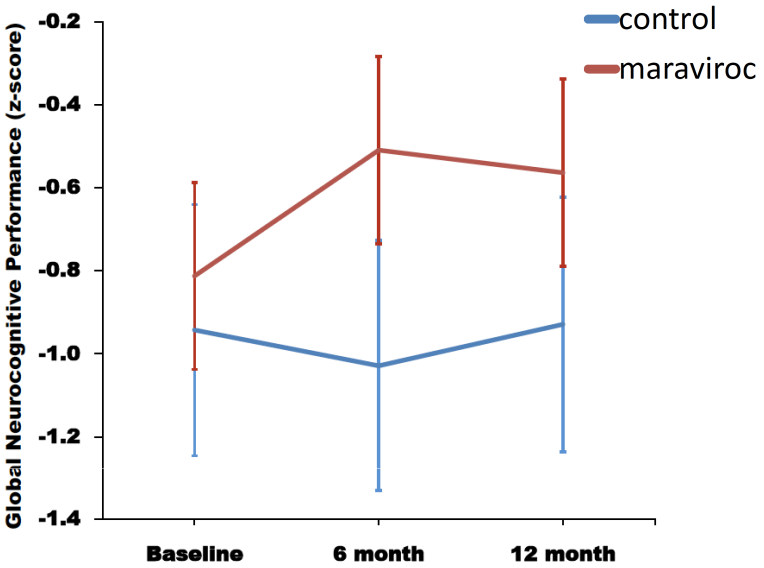
BB4

Maraviroc Intensification May Improve HAND



- Open-label, single-arm intensification trial with MVC In 12 adults on suppressive ART
- MVC reduced circulating CD14+CD16+ monocytes and monocyte HIV DNA content
- **Neurocognitive improvement in the 6 subjects who were impaired at entry**

Ndhlovu et al, J Neurovirol. 2014;20(6):571-82



- 12-month prospective open-label, randomized, placebo-controlled trial
- 14 adults on suppressive ART with recent progression to HAND
- **Large difference at 6-months and medium difference at 12-months**
  - Arm x Time interaction: $p < 0.05$

Gates et al, CROI 2015. Abstract 441

Diapositiva 34

BB4 mismo comentario
Belen Box; 25/05/2016

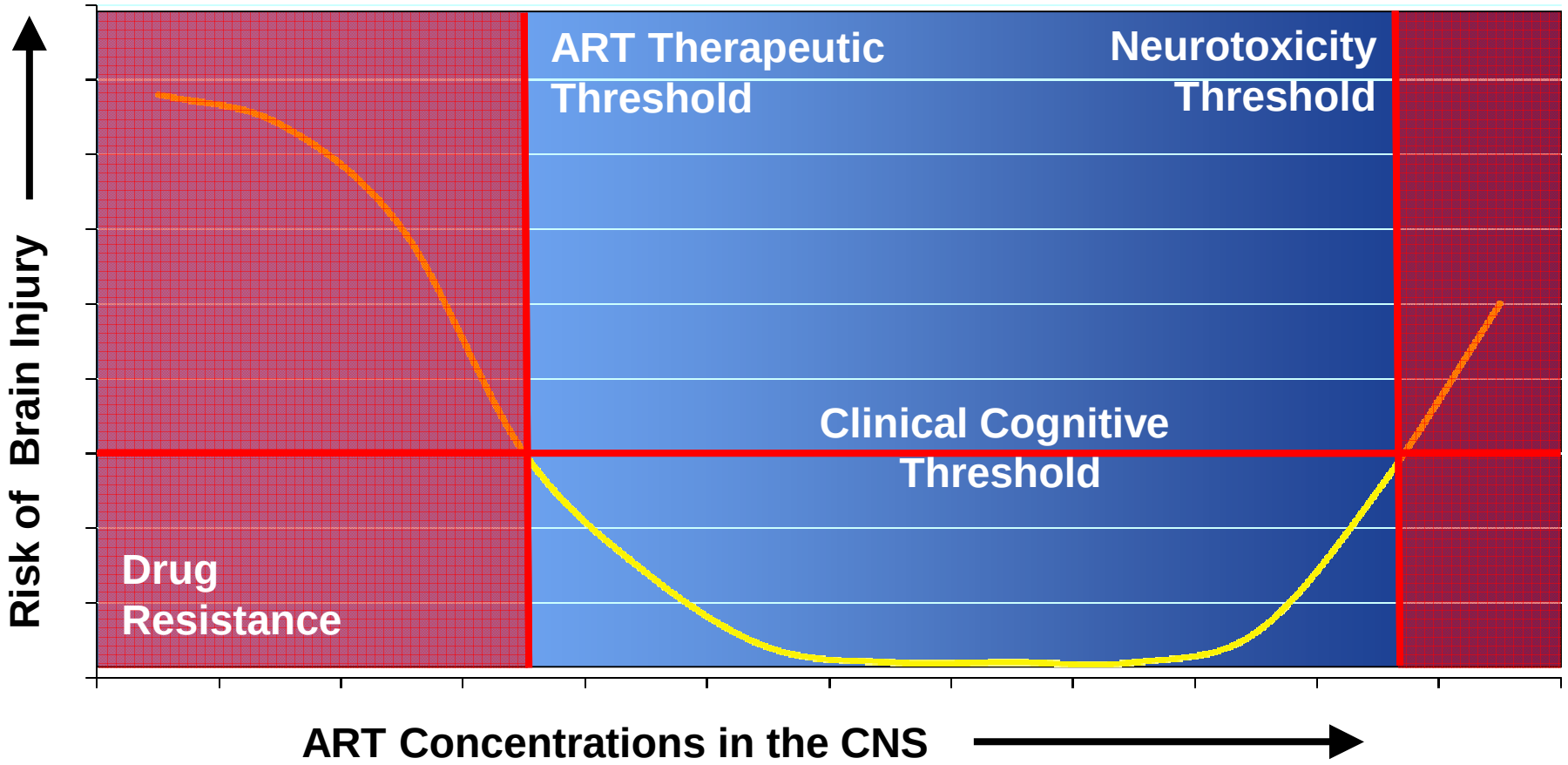
WHO Updated Treatment Guidelines Include Dolutegravir, Reduced Dose Efavirenz, and NRTI-Sparing Regimen

WHAT TO USE IN FIRST-LINE THERAPY IN ADULTS	ARV REGIMEN[1,2]
Preferred Option	TDF+XTC[3]+EFV_{600}
Alternative Options	AZT+3TC+EFV_{600} AZT+3TC+NVP TDF+XTC[3]+NVP TDF+XTC[3]+DTG[4] NEW TDF+XTC3+EFV_{400}[4] NEW

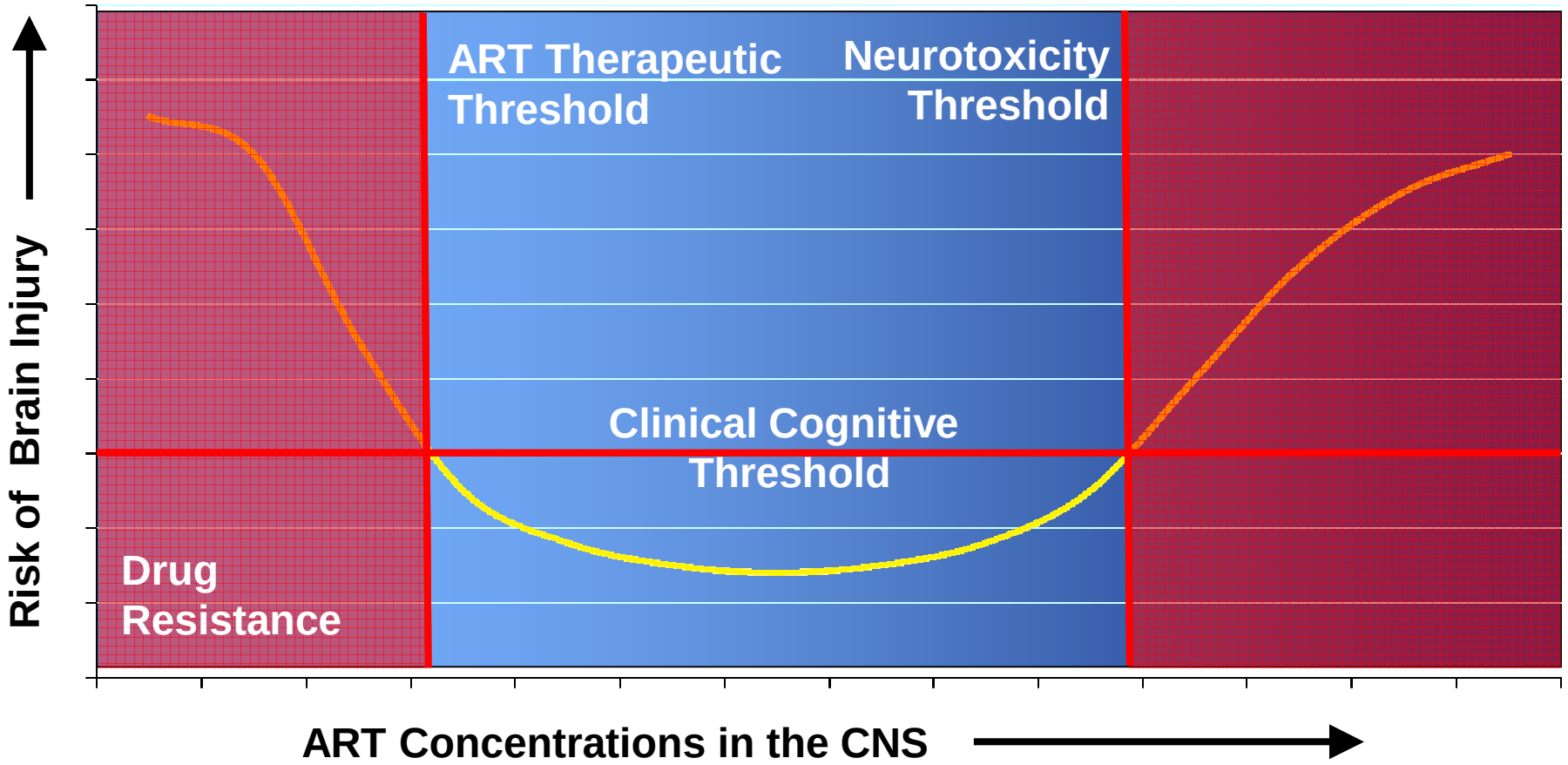
WHAT TO USE IN SECOND-LINE THERAPY IN ADULTS	ARV REGIMEN
Preferred Option	2 NRTI[1]+ATV/r or LPV/r^2
Alternative Options	2 NRTI[1]+$DRV/r^{2,3}$ NEW LPV/r^2+RAL NEW

WHO HIV Treatment and Care Fact Sheet, November 2015

CNS Therapeutic Window



CNS Therapeutic Window



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