Aging and Antiretroviral Neurotoxicity

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Disclosures

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- Gilead Sciences
- ViiV Healthcare

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- ViiV Healthcare

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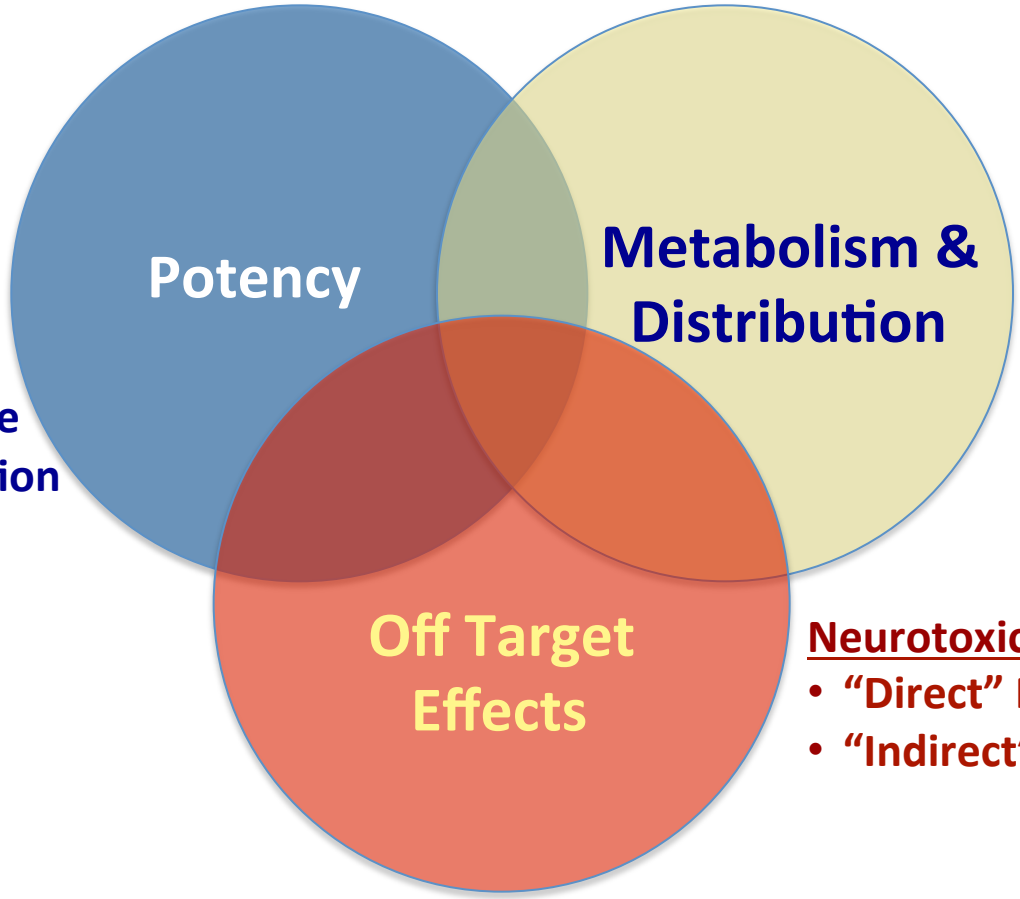
- None

Several ART Drug Characteristics Can Influence CNS Effectiveness

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

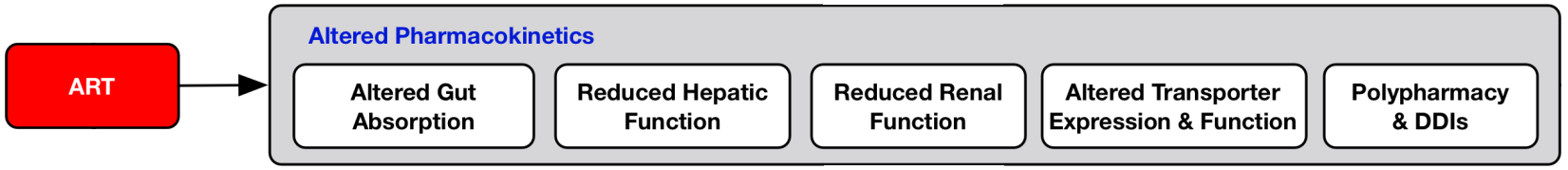


- **Long Half-Life**
- **Protein Binding**
- **Lipophilicity**
- **Molecular Weight**
- **Molecular Transporters**

Neurotoxicity

- **"Direct" Neurotoxicity**
- **"Indirect" Neurotoxicity**

Conceptual Construct for Worsened Neurotoxicity with Aging



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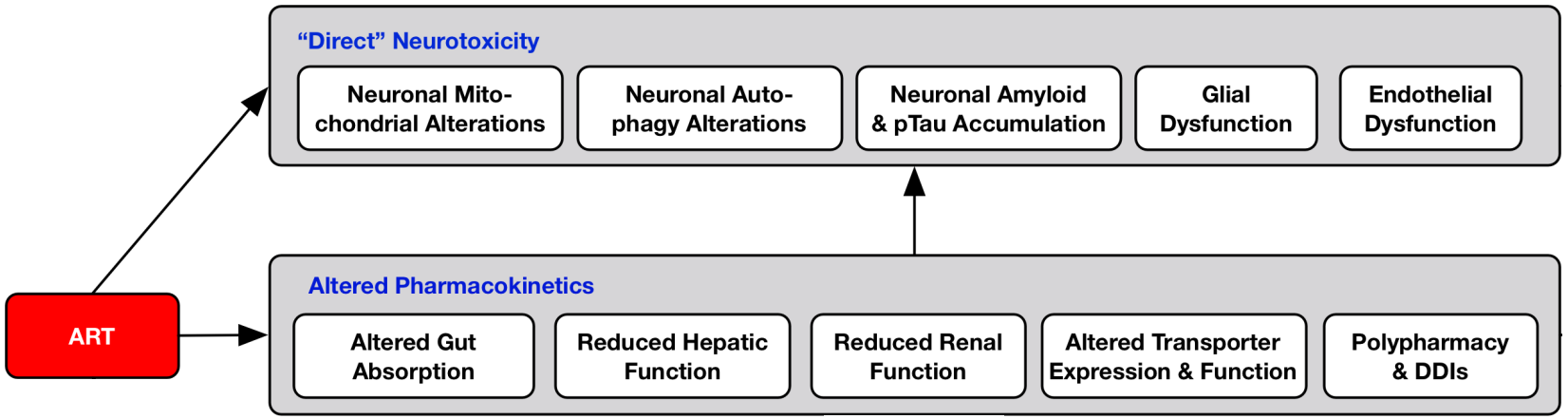

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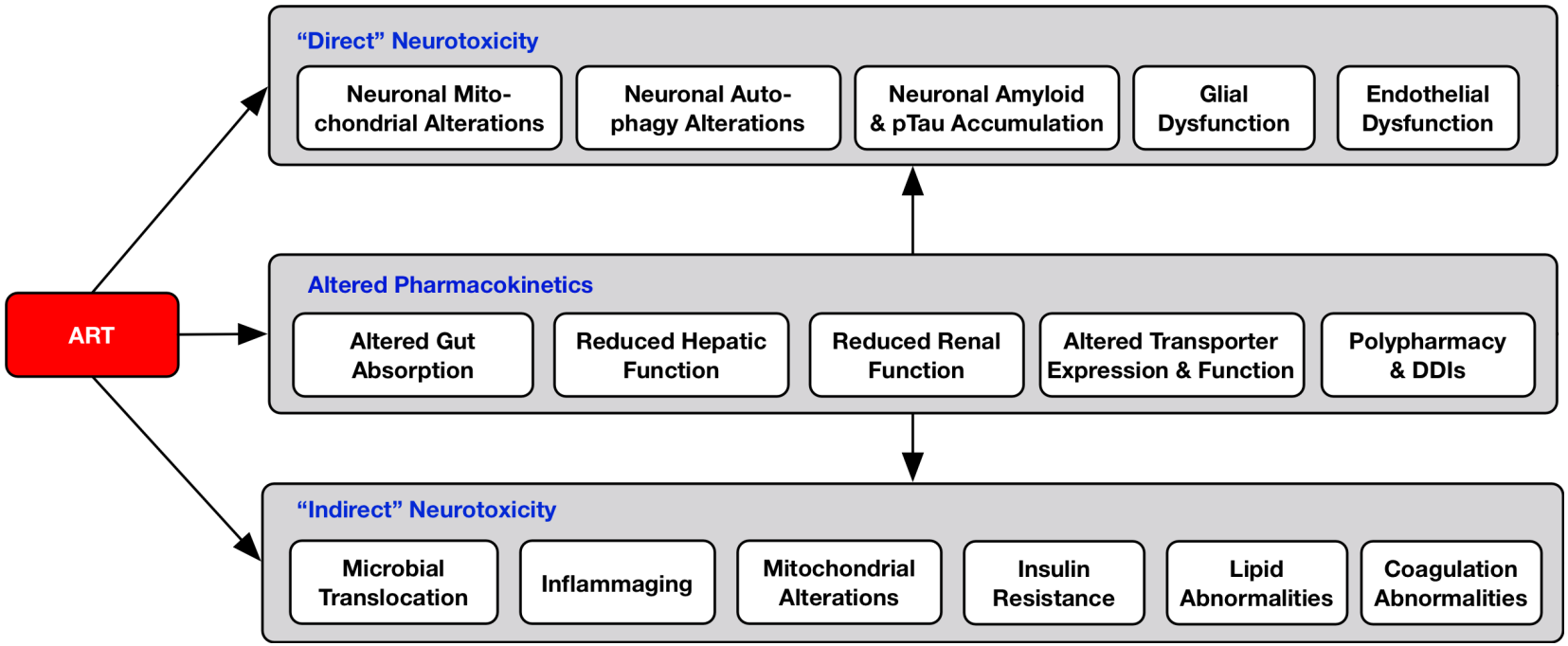

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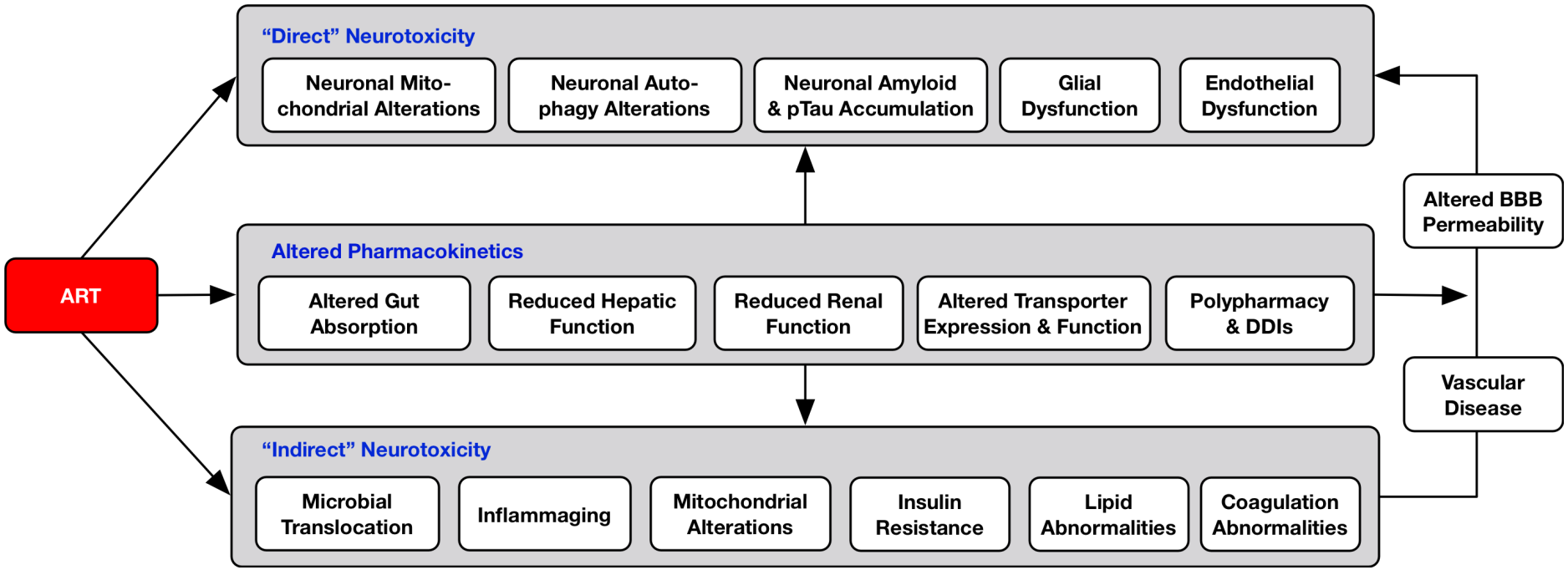
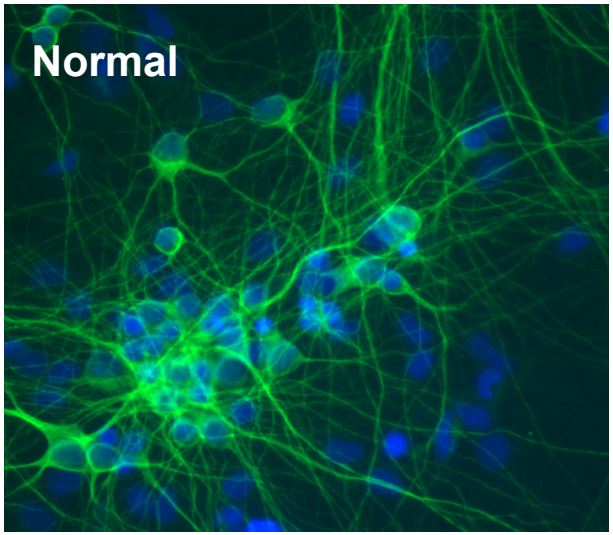
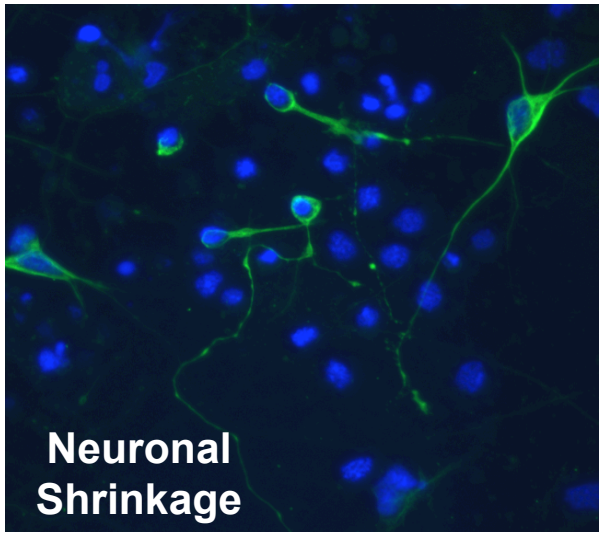
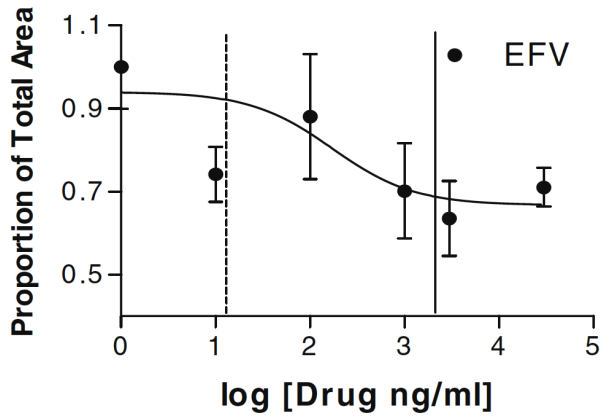


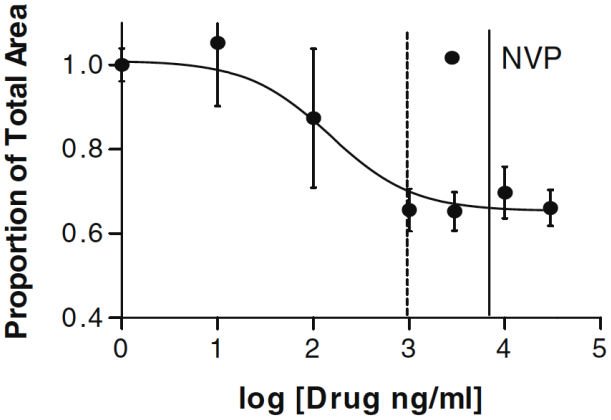
Neurotoxicity in Neuronal Culture

- **Fetal rat cortical neurons** exposed to increasing ART concentrations
- All drugs caused Injury
- Dose-effect curves and toxicity indices were calculated



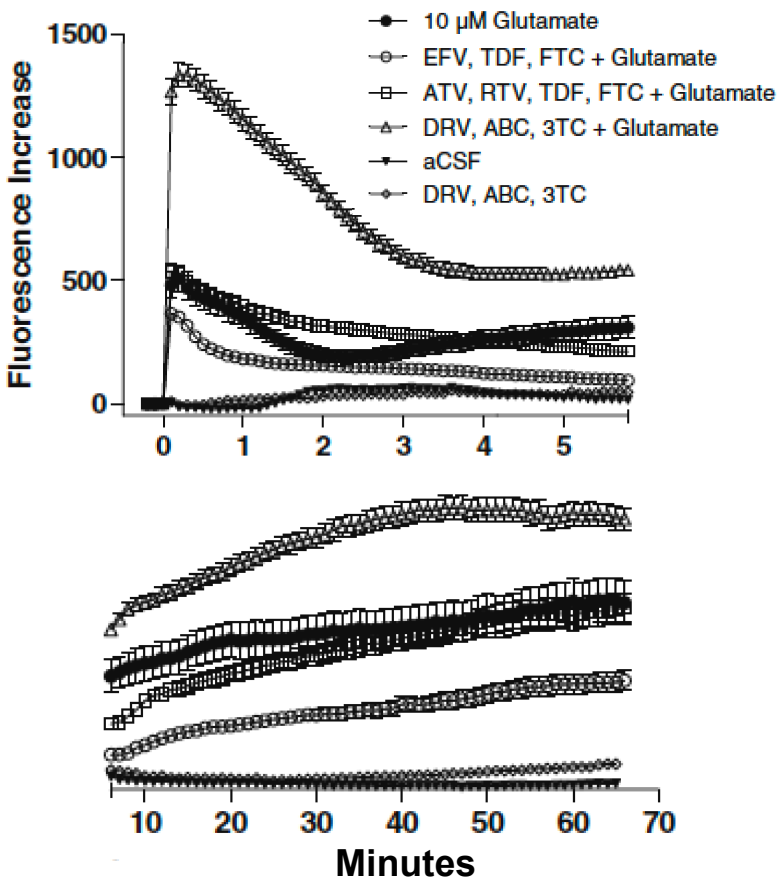




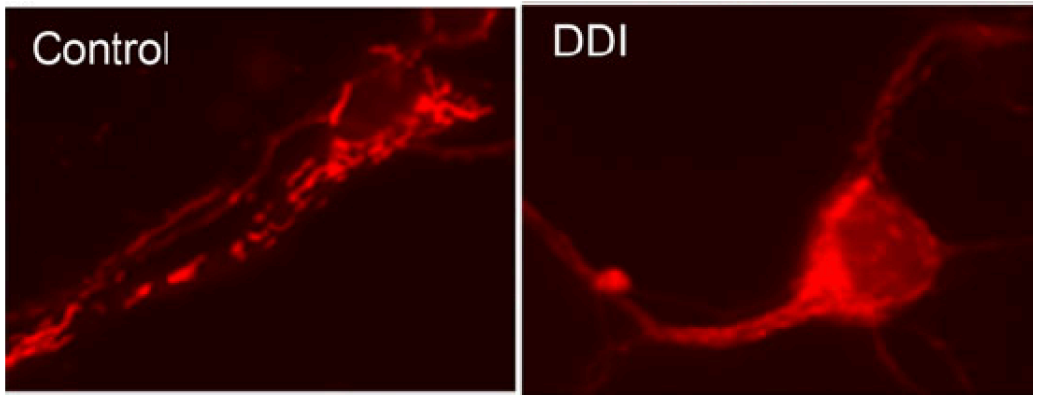


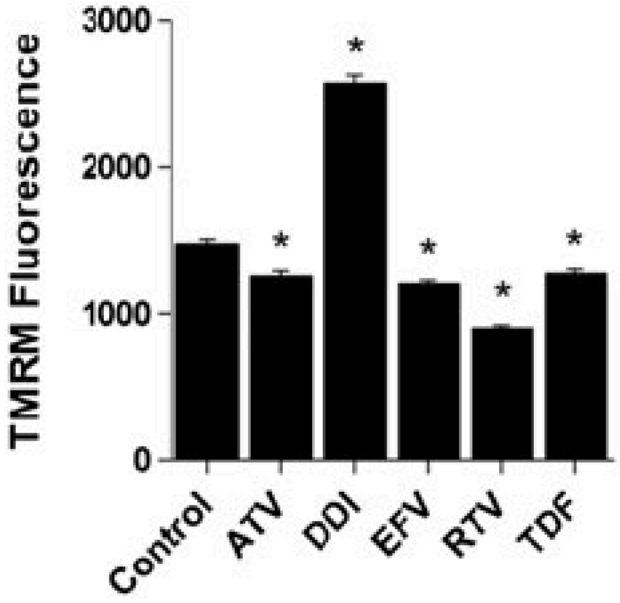
Robertson et al, J Neurovirol 2012, 18: 388-299

ART Drugs, Neuronal Calcium Flux, & Mitochondrial Potential

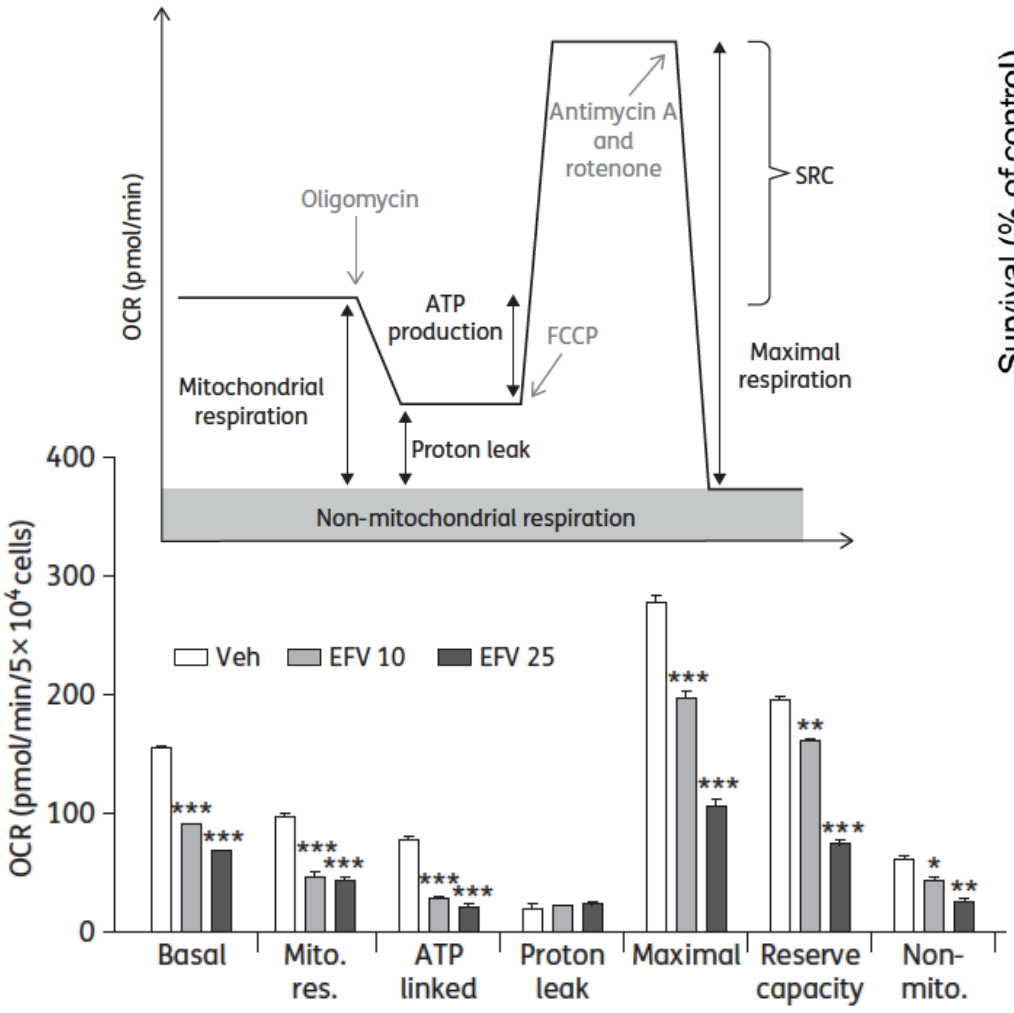


Robertson et al, J Neurovirol 2012, 18: 388-299

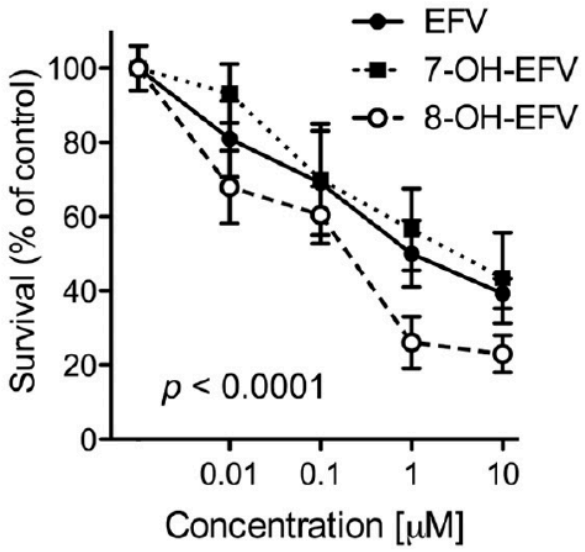


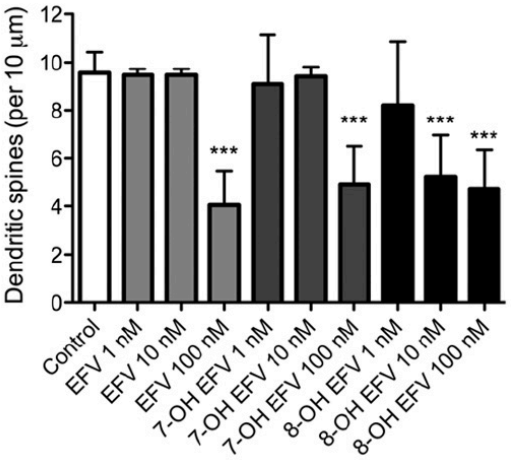


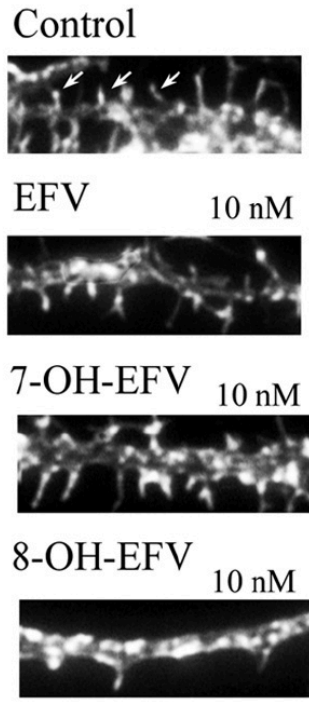
Efavirenz, Mitochondrial Respiration, and Neurotoxic Metabolites



Funes et al, JAC 2015; 70: 2249–2254

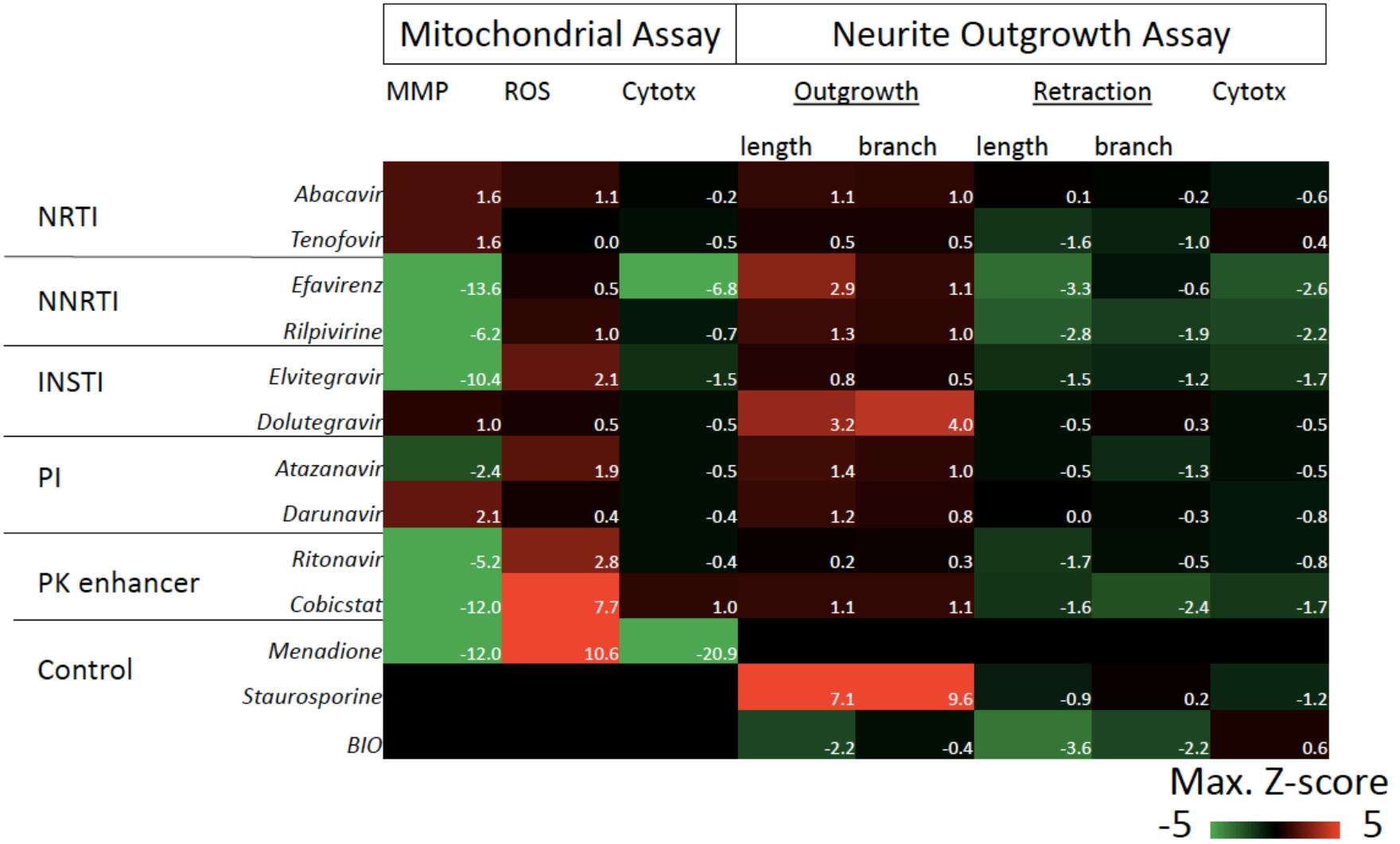






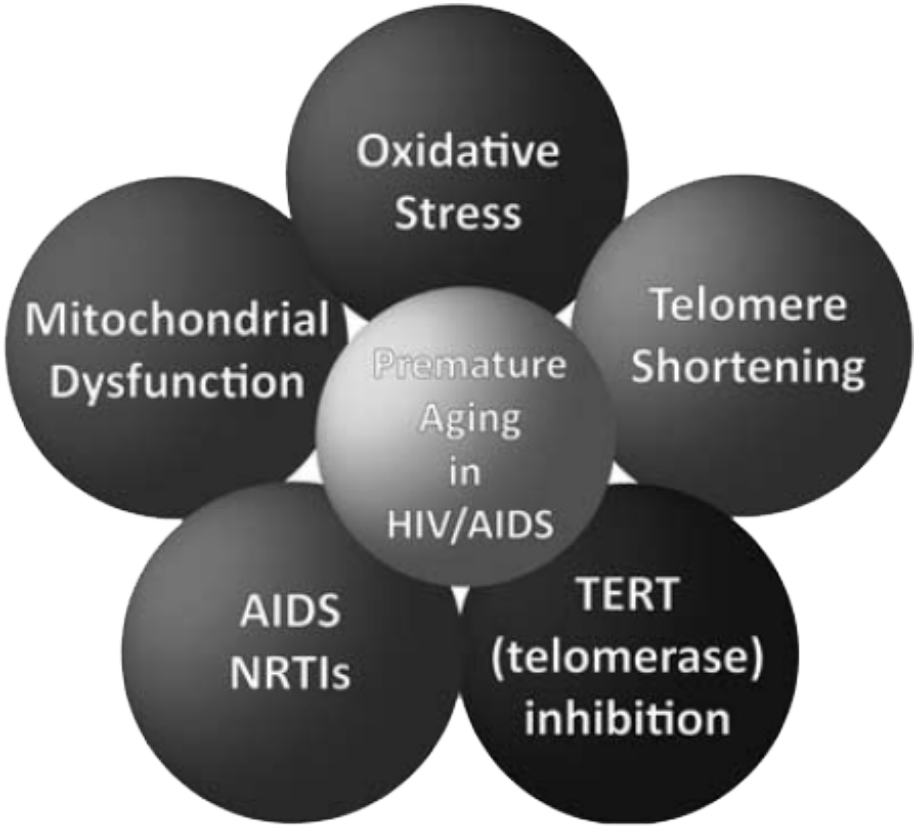
Tovar-y-Romo et al, JPET 2012, 343(2): 696-703

Neurotoxicity Screening of ART Drugs With Human iPSC-Derived Neurons

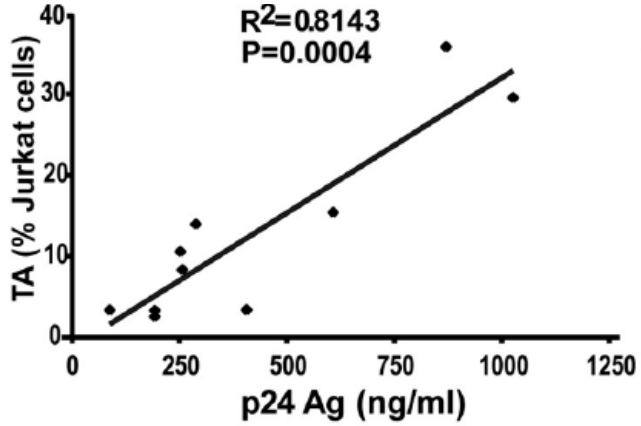


Hinckley et al, CROI 2016, Abstract 395

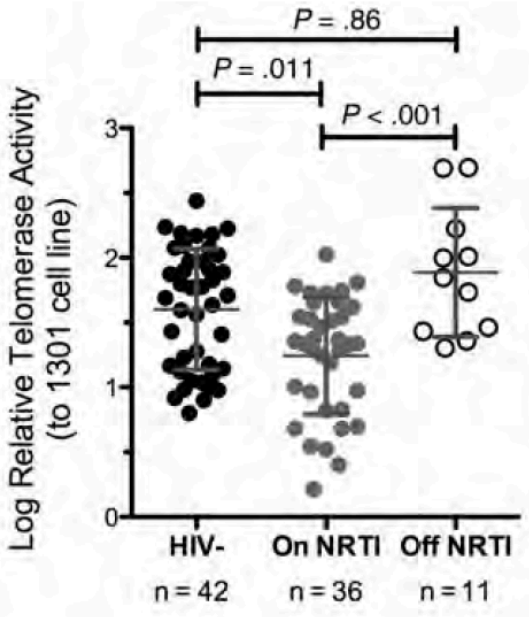
Higher NRTI Levels in CNS May Increase Mitochondrial and Telomere Toxicity



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



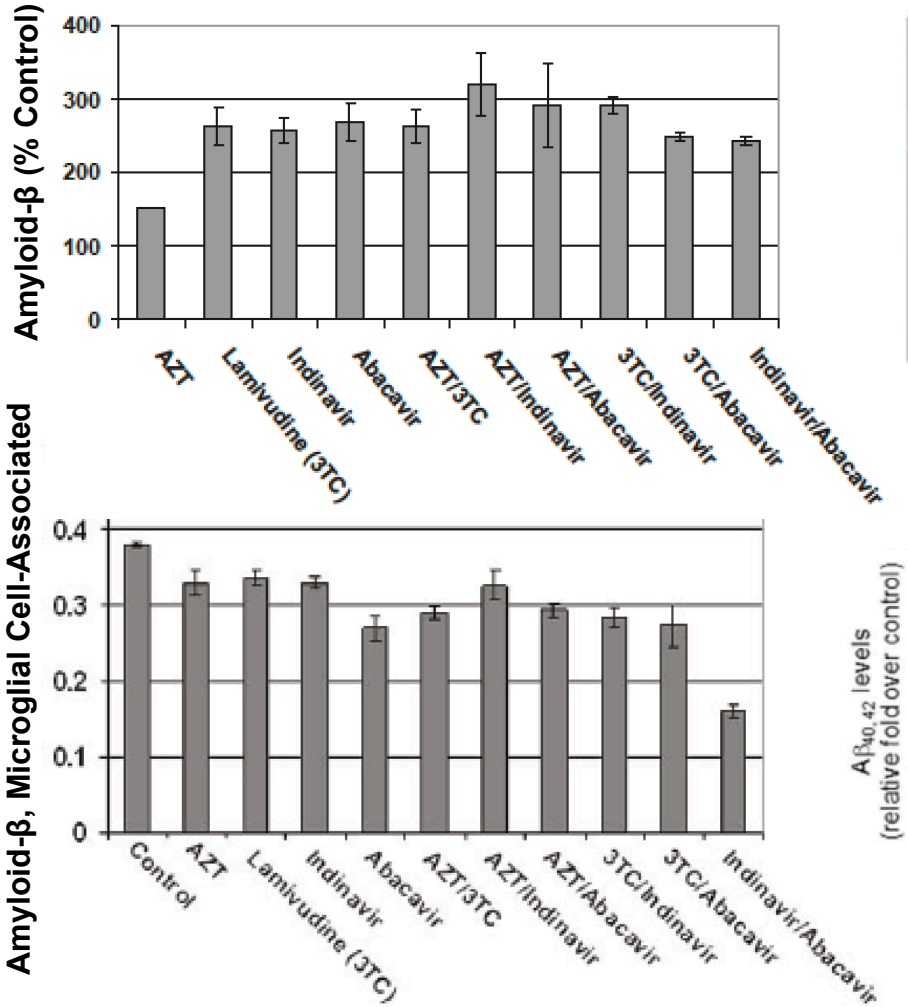
Reynoso et al, J Virol 2012; 86(19):10327



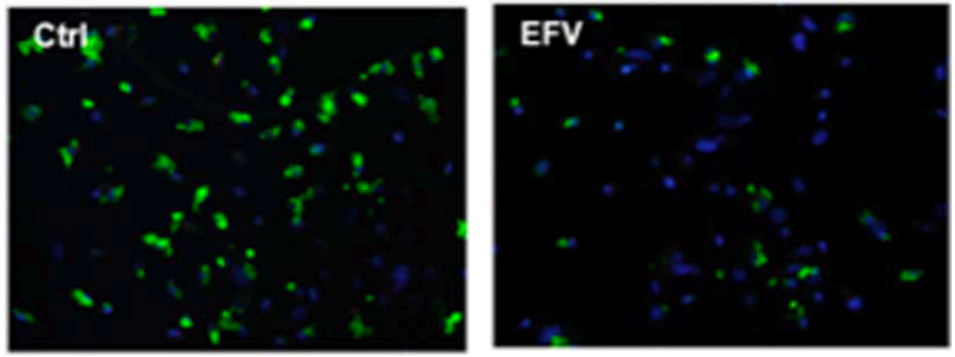
Leeansyah et al, JID 2013; 207:1157

Tenofovir was the most potent inhibitor of telomerase activity

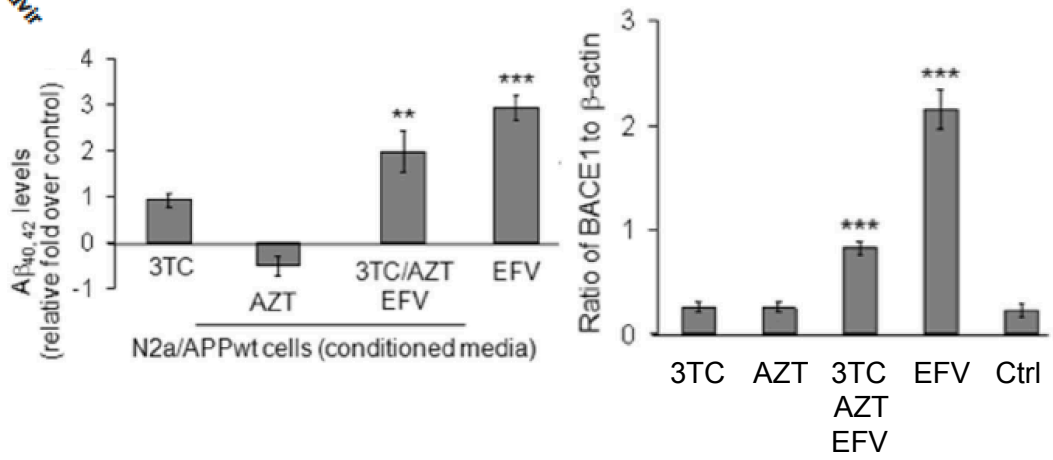
ART Drugs Can Increase Amyloid-β & Reduce Microglial Phagocytosis



Giunta et al, Molecular Brain 2011, 4:23

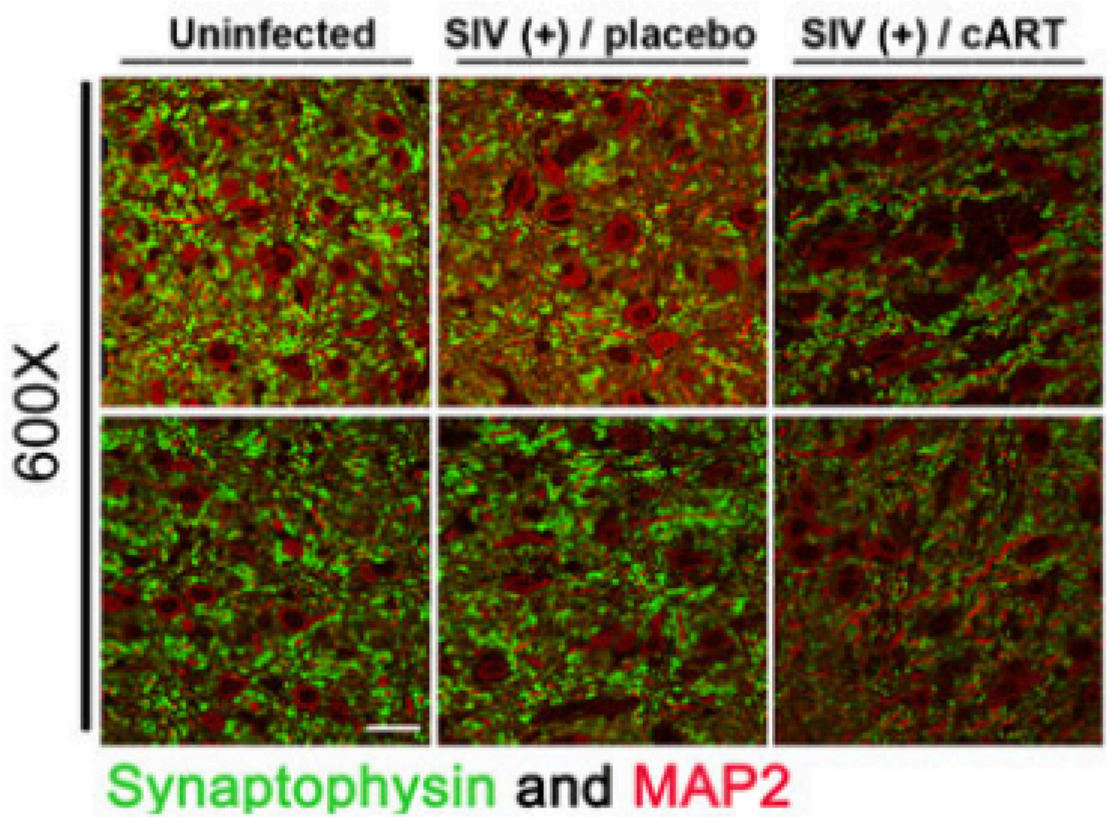


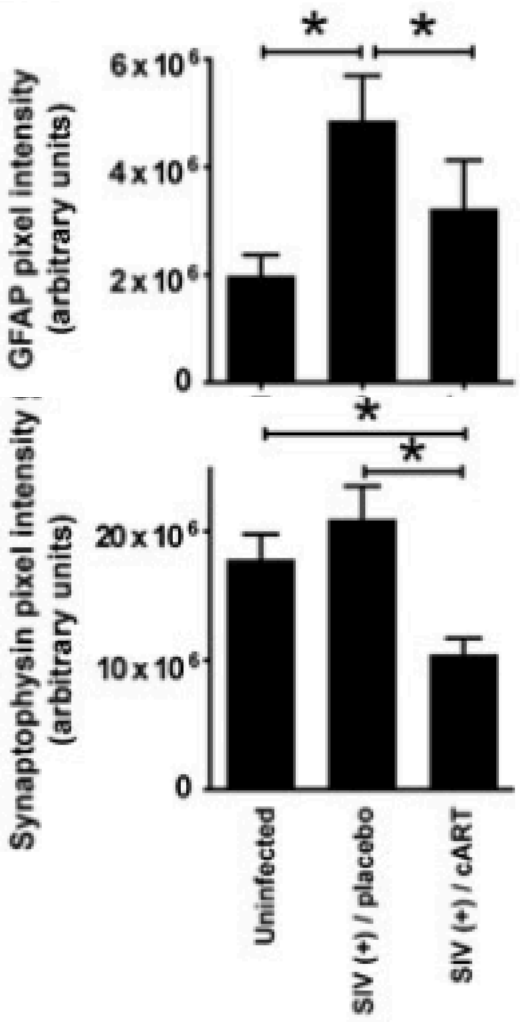
EFV Reduces Microglial Phagocytosis of $A\beta_{1-42}$



Brown et al, PLoS ONE 2014, 9(4): e95500

Evidence of Neurotoxicity in Macaques and Rodents





Akay-Espinoza et al, J. Neurovirol. (2014) 20:39–53

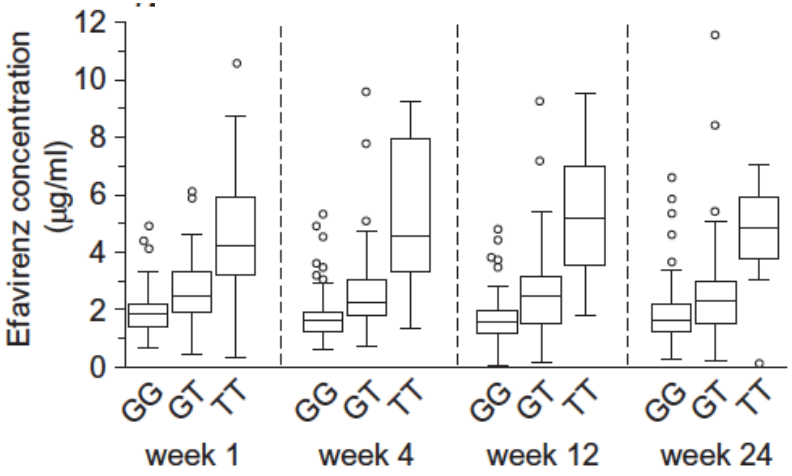
cART = AZT + SQV/r

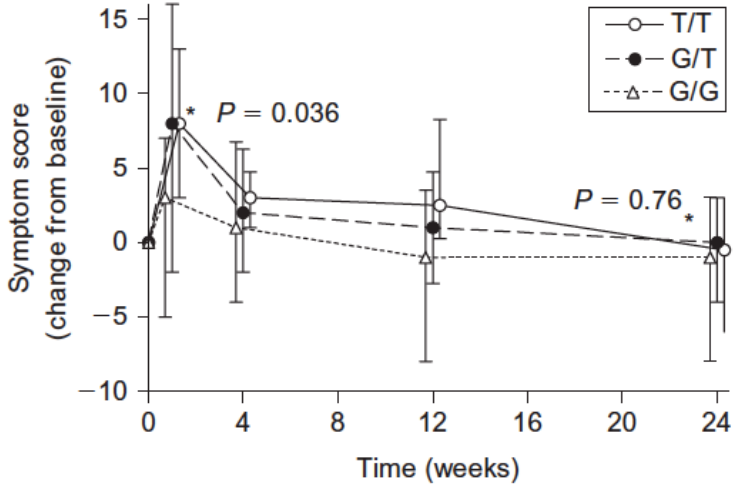
More *in vitro* and Animal Evidence than Human Evidence

Antiretroviral	In-vitro evidence	Animal evidence	Imaging evidence	Clinical evidence
NRTIs				
Tenofovir [19,25]	+/–	+		
Abacavir [19,26,40,41]	++		+/–	
Emtricitabine [19]	+/–			
Lamivudine [14,19,26,40]	+/–	+	–	
Zidovudine [14,19,25,26,40,41]	+/–	+	+/–	
Stavudine [14,40]	+/–	+	+	
Didanosine [14,19,40]	+	+	+	
Zalcitabine [19]	+/–			
NNRTIs				
Efavirenz [19,22–24,27,41,42,47–50]	++	+	+/–	++
Nevirapine [19,24]	+	+		
Etravirine [19]	+			
PIs				
Darunavir [19]	–			
Atazanavir [19,25,41,42]	+	+	+/–	
Amprenavir [19]	+			
Ritonavir [19,25]	+/–	+		
Saquinavir [25]	+	+		
Indinavir [26]	+			
Others				
Maraviroc [19]	–			
Raltegravir [51]				+/–

Underwood et al, AIDS 2015, 29:253–261

Greater Efavirenz Exposure is Associated with Worse Outcomes

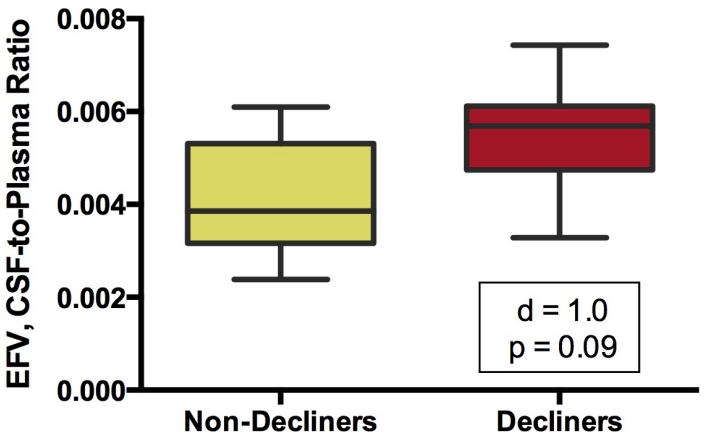




Haas et al, AIDS 2004, 18:2391–2400

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**

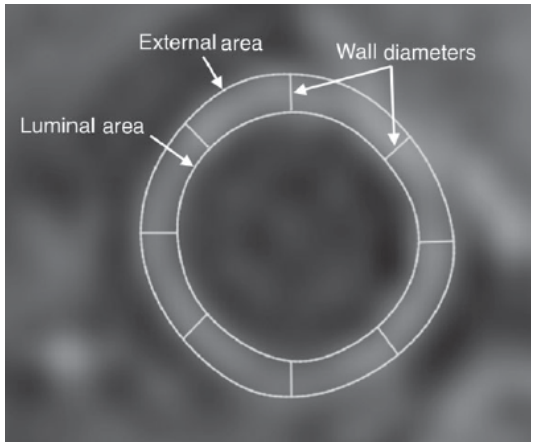
Ciccarelli et al, Neurology 2011, 76: 1403



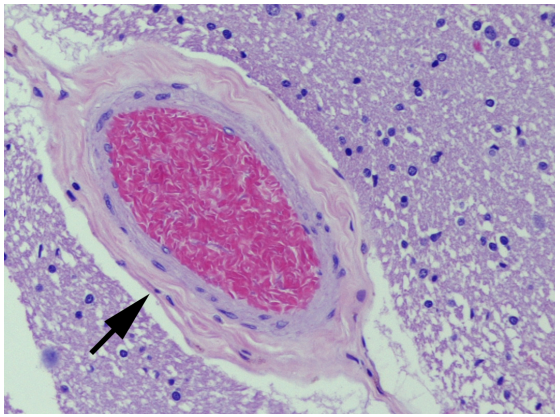
Ma et al, CROI 2015, Abstract 444

Protease Inhibitors & NRTIs

Protease Inhibitors

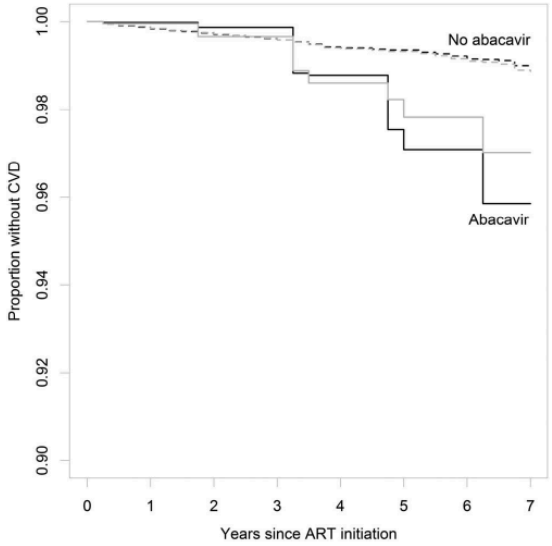


LaBounty et al, HIV Medicine 2016, 17(7):516-23

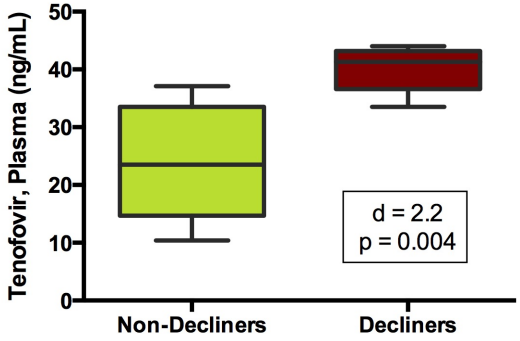


Soontornniyomkij et al, AIDS 2014, 28:1297–1306

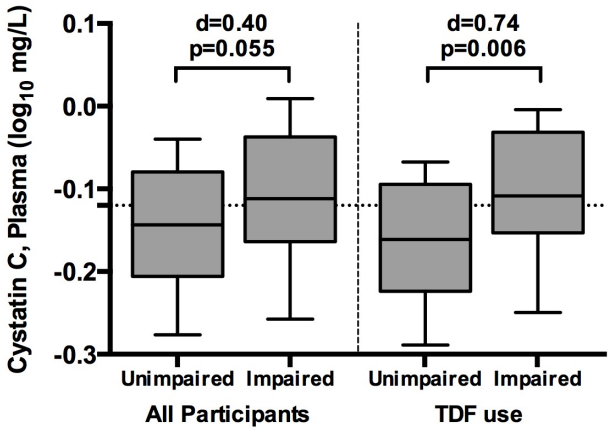
NRTIs



Marcus et al, JAIDS 2016; 71:413–419



Ma et al, CROI 2015, Abstract 444



Sakoda et al, JAIDS 2017; 74(3):243-249

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

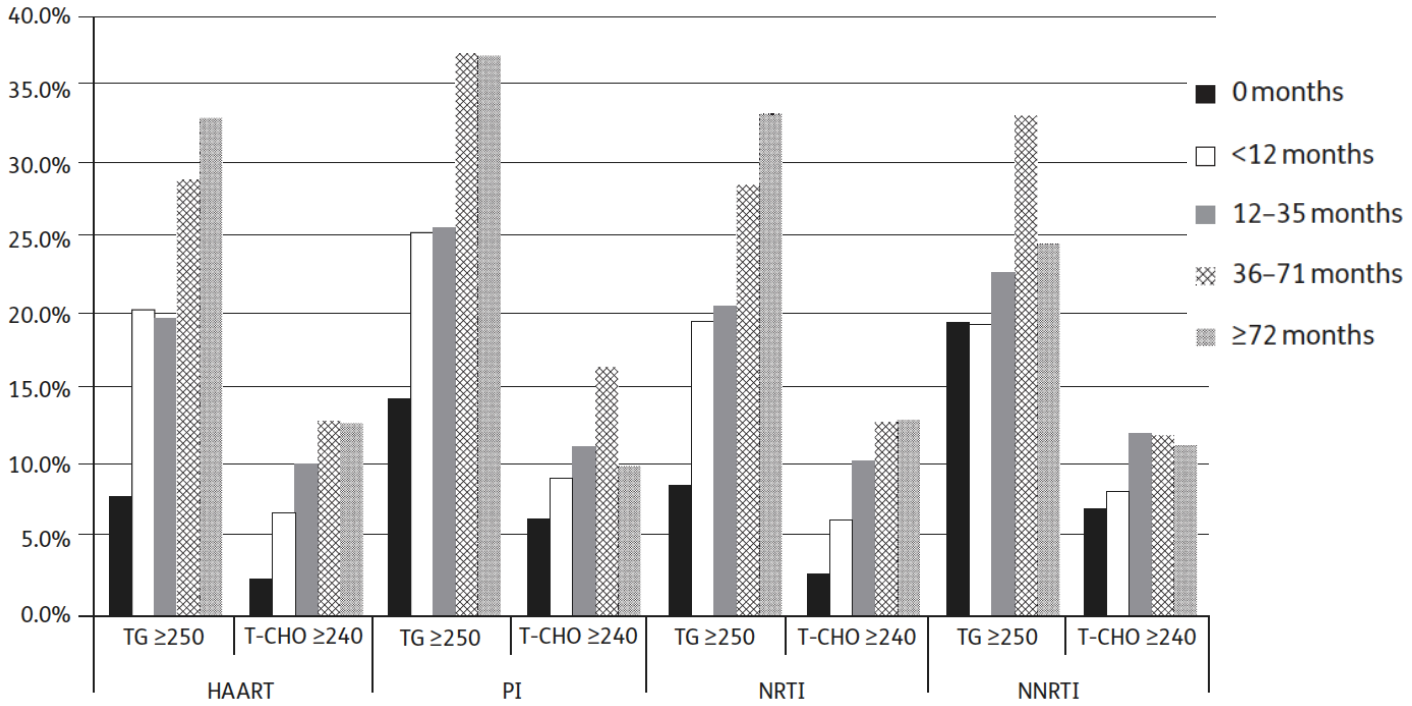
	Risk	OR	p
Prior CVD	Yes	6.2	0.01
Total cholesterol	Higher	1.1	0.06
AIDS	No	0.41	0.08
Race	Black	2.2	0.08

- 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

Metabolic Syndrome Linked to Longer Durations of ART

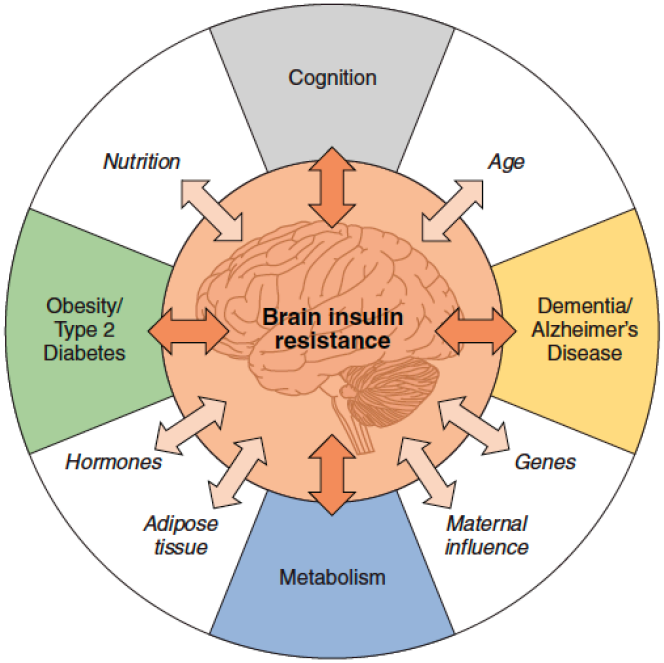


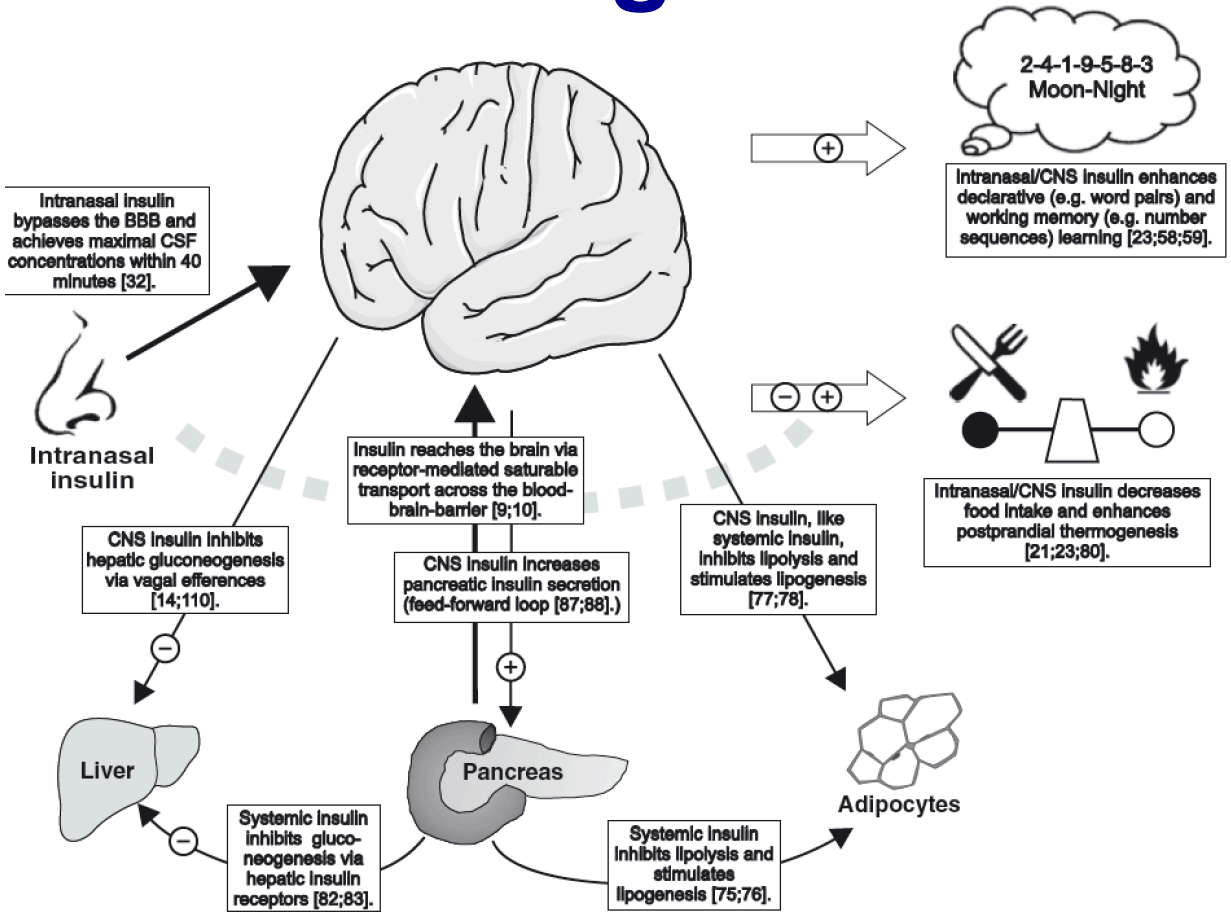
	0 months, reference	<12 months OR (95% CI)	12–35 months OR (95% CI)	36–71 months OR (95% CI)	≥72 months OR (95% CI)	*P* for trend
HAART duration	1	0.79 (0.42, 1.51)	1.20 (0.67, 2.15)	1.59 (0.91, 2.79)	1.96 (1.13, 3.42)	0.0006
PI duration	1	1.25 (0.78, 2.00)	1.47 (0.89, 2.31)	1.78 (1.03, 3.07)	1.98 (0.96, 4.06)	0.02
NRTI duration	1	0.76 (0.40, 1.43)	1.18 (0.67, 2.09)	1.43 (0.82, 2.49)	1.91 (1.11, 3.30)	0.0008
NNRTI duration	1	0.77 (0.43, 1.39)	1.37 (0.80, 2.34)	1.17 (0.70, 1.98)	1.52 (0.92, 2.50)	0.06

*Associations were present after adjustment for age, gender, smoking, family history, baseline plasma viral load, and CD4

Wu et al, J Antimicrob Chemother 2012; 67: 1001–1009

Brain Insulin Resistance Worsens with Age



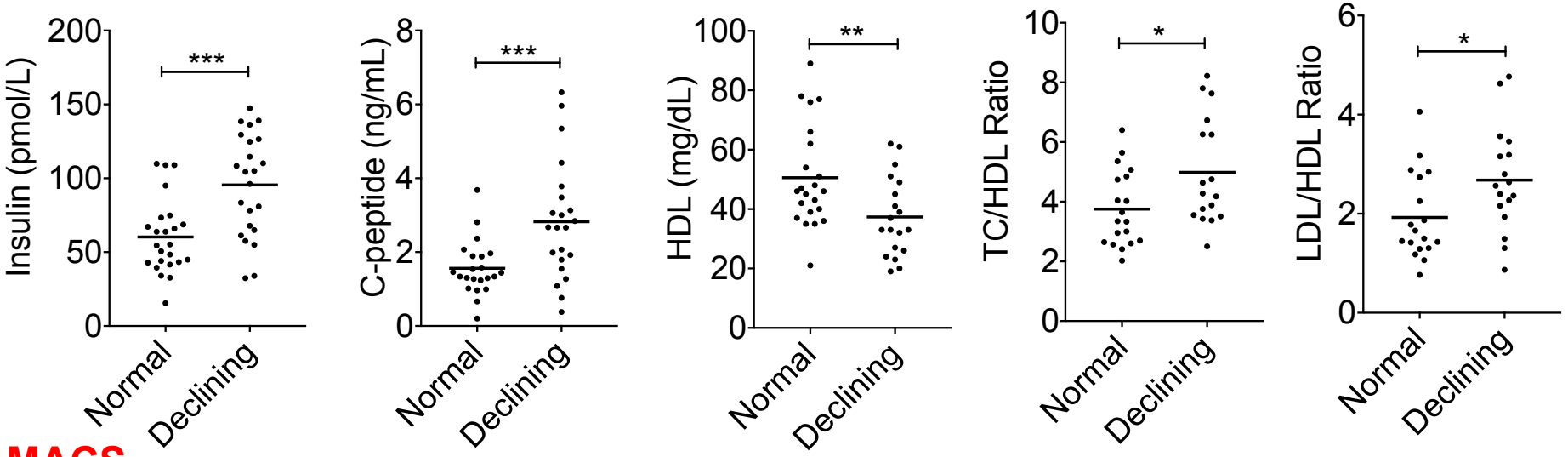


Kullmann et al, Physiol Rev 2016, 96: 1169–1209

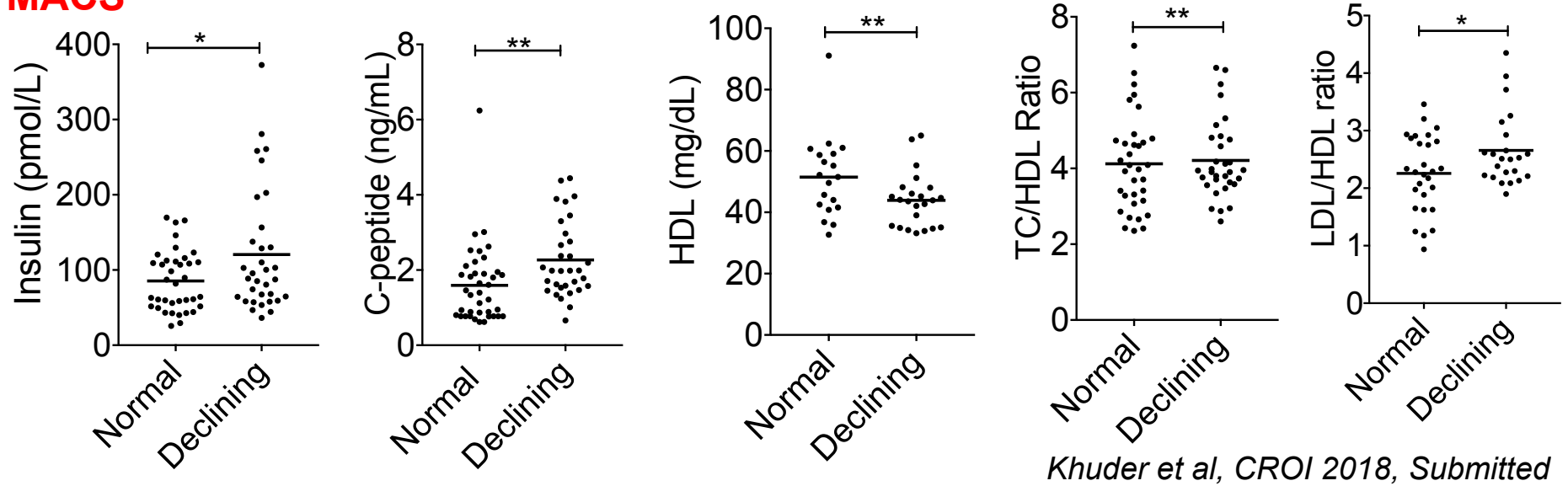
Ott et al, Diabetes, Obesity and Metabolism 2012, 14: 214–221

Neurocognitive Decline Associated with Reduced Insulin Sensitivity

CHARTER

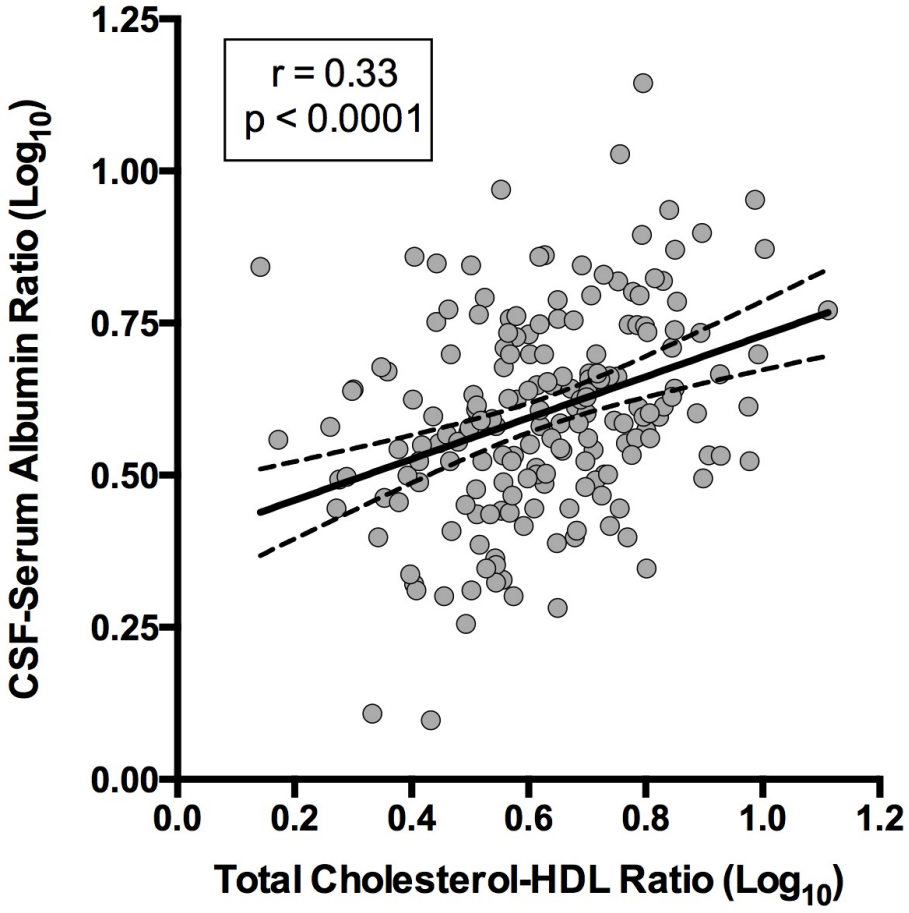


MACS



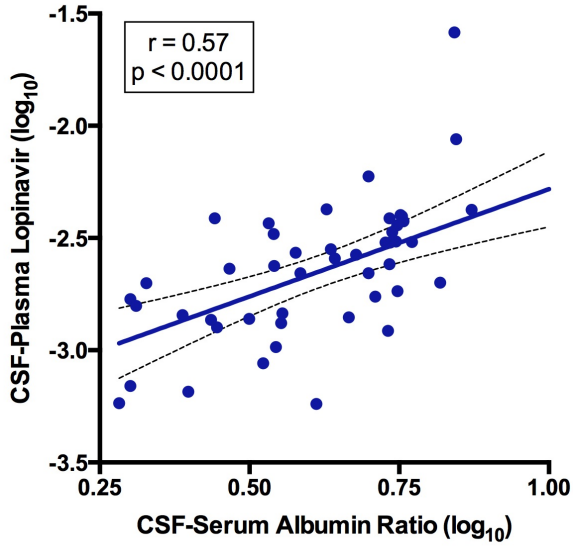
Khuder et al, CROI 2018, Submitted

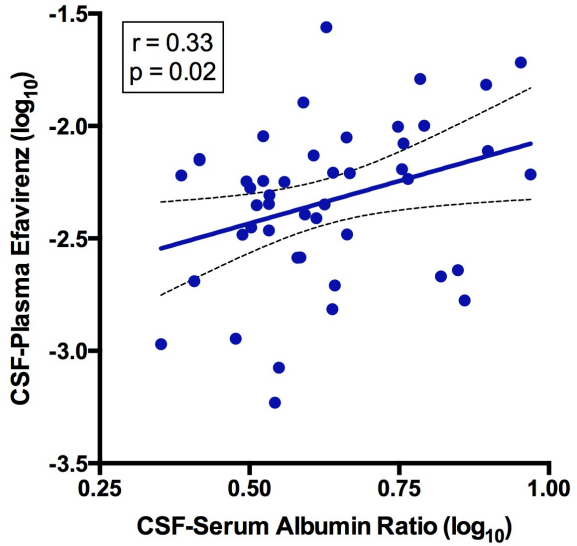
Lipids May Influence BBB Permeability, Which May Alter CNS Drug Distribution



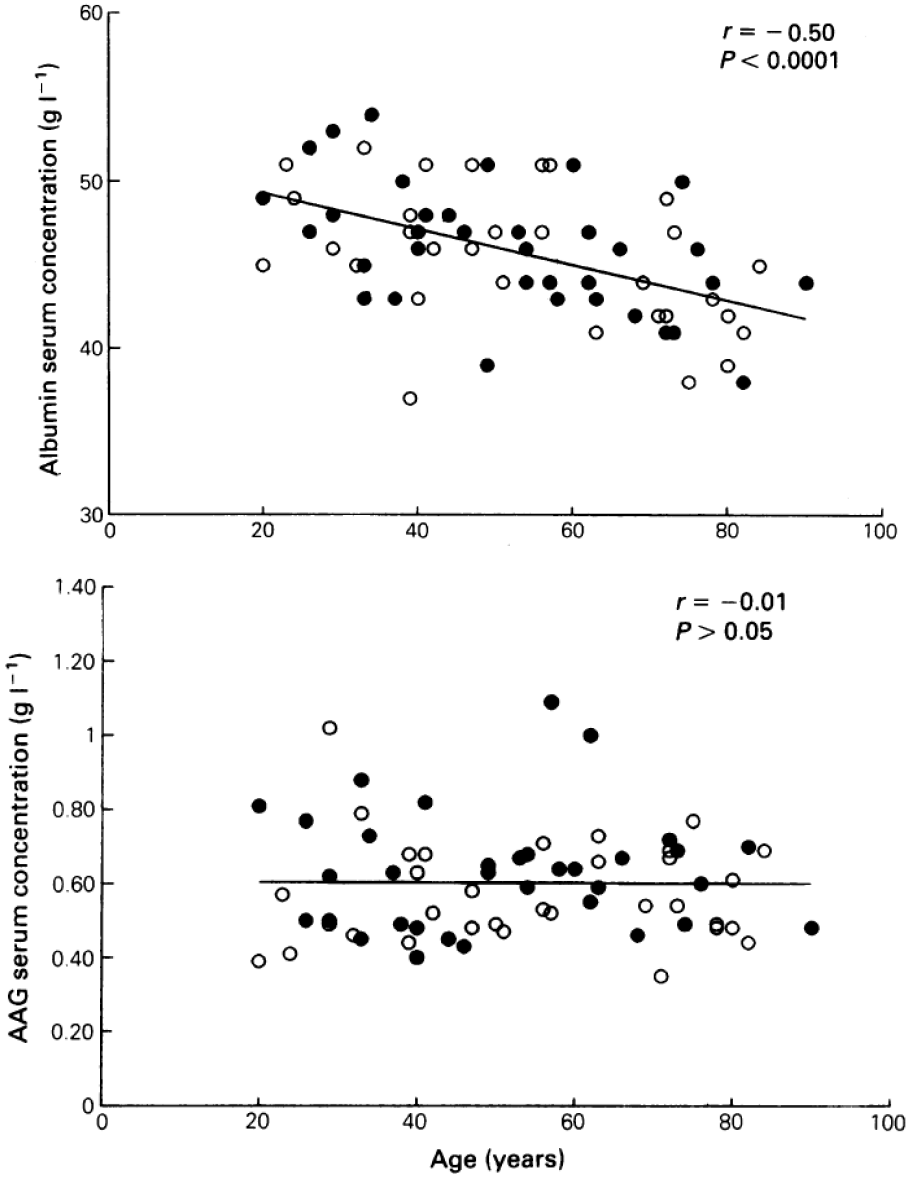
Letendre et al, 18th CROI, 2011, Abstract 408

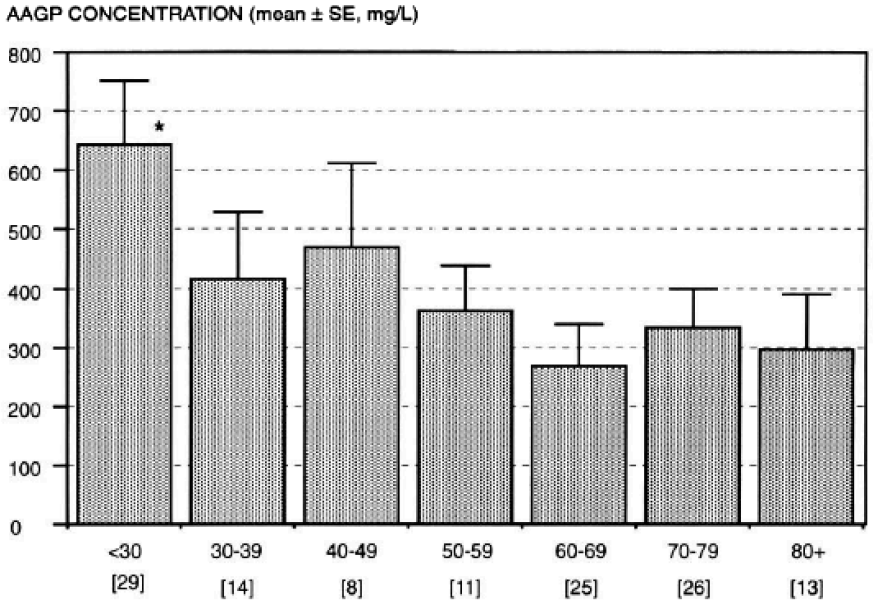
Unpublished CHARTER Data





Aging and Drug Binding Proteins





Veering et al, Br. J. Clin. Pharma, 1990, 29, 201-206
Woo et al, Clinical Biochemistry, 1994, 27(4): 289-292

ART Drug Concentrations in Brain Tissue: Regional Variation, CSF Comparability

	n	Overall Mean	WM mean (ng/mL)	GP mean (ng/mL)	CGM mean (ng/mL)	CSF (ng/mL)
Concentrations Similar to Historical CSF Concentration						
Atazanavir (ATV)	2	< 25	< 25	< 25	< 25	10.3[1]
Efavirenz (EFV)	2	38.6	45.2	34.8	35.9	15.6[2]
Emtricitabine (FTC)	4	181.3	230.4	173.2	140.3	109.0[3]
Lamivudine (3TC)	3	196.9	205.5	209.8	175.4	107.8[4]
Concentrations in White Matter Higher than Historical CSF Concentration						
Lopinavir (LPV)	4	153.3	410.6	< 25	< 25	16.8[5]
Concentrations Higher than Historical CSF Concentration						
Tenofovir (TDF)	6	206.0	220.0	212.1	185.8	5.5[6]

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

Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test)

Bumpus et al, CROI 2015, Abstract 436

[1]Best et al, AIDS 2009; 23:83; [2]Best et al, JAC. 2011; 66:354; [3]Calcagno et al, AIDS. 2011; 25:1437; [4]Haas et al, ARHR. 2000; 16:1491; [5]Capparelli et al, AIDS. 2005; 19: 949; [6]Best et al, JAIDS. 2012; 59: 376

Greater Than Expected 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 (1.6%)	2 (3.1%)	4 (1.2%)

- **Overall 62 of 387 (16%) discontinued dolutegravir**
- **56 of 62 these (90.3%) discontinued due to adverse events**
- **These 56 had 78 adverse events:**

54 (69.2%) were nervous system-related

van den Berk et al, CROI 2016, Abstract 948

CNS Safety Data from Dolutegravir Clinical Trials

	SPRING-1[1]		SPRING-2[2]		FLAMINGO[3]		SINGLE[4]	
	DTG n=51	EFV n=50	DTG n=411	RTG n=411	DTG n=242	DRV/r n=242	DTG n=357	EFV n=362
Headache	10%	4%	14%	13%	17%	11%	6%	7%
Dizziness	6%	18%	6%	6%	6%	5%	7%	33%
Insomnia	6%	10%	6%	5%	8%	7%	10%	6%
Depression	*	*	6%	5%	6%	4%	**	**
Anxiety	*	*	4%	5%	5%	4%	**	**
Abnormal Dreams	*	*	**	**	**	**	7%	16%

* < 3%
** < 5%

All data are from 96 weeks

[1]*Stellbrink et al, AIDS 2013, 27:1771–1778*
[2]*Raffi et al, Lancet 2013, 13: 927–35*
[3]*Molina et al, Lancet HIV 2015; 2: e127–36*
[4]*Walmsley et al, JAIDS 2015, 70:515–519*

CNS Safety Data from Elvitegravir Clinical Trials

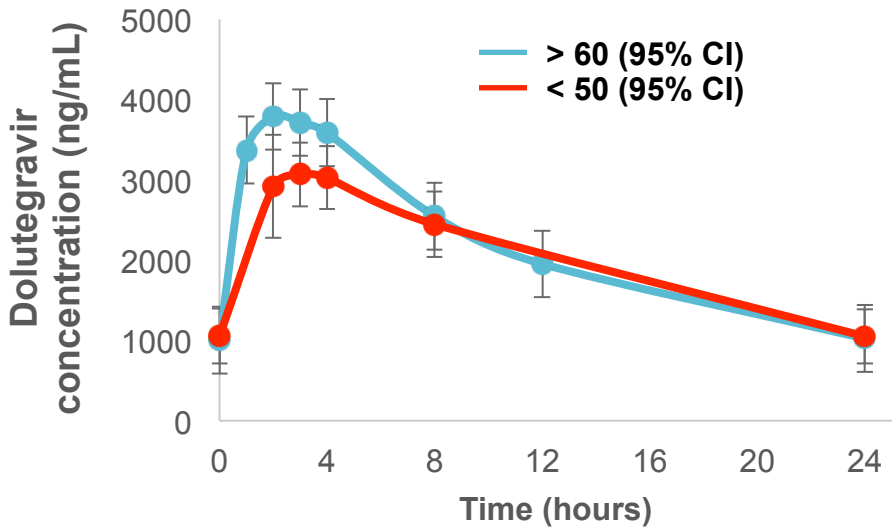
	Study 102[1]		Study 103[2]		STRATEGY-NNRTI[3]		STRATEGY-PI[4]	
	EVG/c n=348	EFV n=352	EVG/c n=353	ATV/r n=355	EVG/c n=291	NNRTI n=143	EVG/c n=293	PI/r n=140
Headache	16%	11%	17%	15%	10%	3%	6%	6%
Dizziness	7%	26%	*	*	**	**	**	**
Insomnia	11%	16%	*	*	6%	5%	3%	5%
Depression	12%	14%	10%	12%	**	**	4%	6%
Anxiety	*	*	*	*	**	**	6%	4%
Abnormal Dreams	15%	28%	*	*	**	**	**	**
Back Pain	*	*	12%	5%	**	**	**	**

* < 10%
** < 5%

[1]*Zolopa et al, JAIDS 2013, 63: 96–100*
[2]*Rockstroh et al, JAIDS 2013, 62: 483–486*
[3]*Pozniak et al, Lancet Inf Dis 2014; 14: 590–99*
[4]*Arribas et al, Lancet Inf Dis 2014, 14: 581–89*

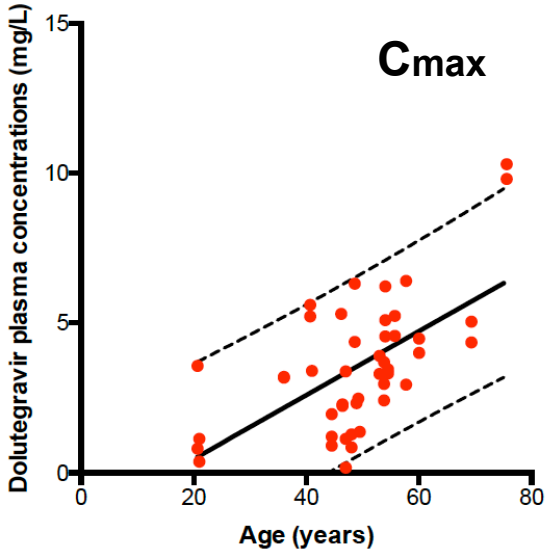
Dolutegravir, Age, Sleep, & Mood

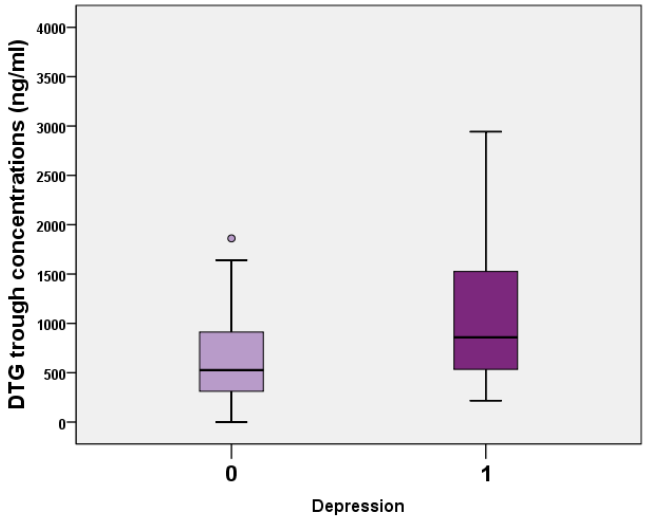
Courtesy Andrea Calcagno and Marta Boffito



	C_{max}	AUC_{0-24}
Pittsburgh Sleep Quality Index		
Duration of sleep (n=36)	**0.330 (0.05)**	**0.353 (0.03)**
Sleep disturbance (n=38)	-0.100 (0.55)	-0.121 (0.47)
Sleep latency (n=37)	-0.247 (0.14)	-0.053 (0.75)
Day dysfunction (n=37)	-0.181 (0.28)	-0.206 (0.22)
Sleep efficiency (n=35)	0.120 (0.49)	0.032 (0.86)
Sleep quality (n=38)	-0.212 (0.20)	0.207 (0.21)
Medication (n=37)	0.016 (0.92)	0.021 (0.90)
PSQI total (n=32)	0.074 (0.69)	-0.042 (0.82)

Elliot et al, 18th International Workshop on Clinical Pharmacology of Antiviral Therapy, 2017





Borghetti et al, Italian Conference on AIDS and Antiviral Research, 2017

Women Have Different Exposure of Some Antiretrovirals Than Men

- **Reviews of ART pharmacokinetics indicate that women may have higher exposure of some drugs**
- **Difference exists for:**
  - **Zidovudine**
  - **Lamivudine**
  - **Ritonavir-Boosted PIs**
- **Mixed data for non-nucleoside RTIs**

- Body weight and composition, blood and organ volumes (e.g. bone mass)
- Absorption, intestinal motility and secretions
- Transport and distribution
- Protein binding and tissue affinity
- Metabolism: phase I (hydrolysis, reduction, oxidation, cyclization, decyclization)
- Metabolism: phase II (conjugation)
- Excretion (glomerular filtration rate, renal clearance)
- Intracellular metabolism
- Activity of drug transporters
- Differential (hormone-mediated) gene expression

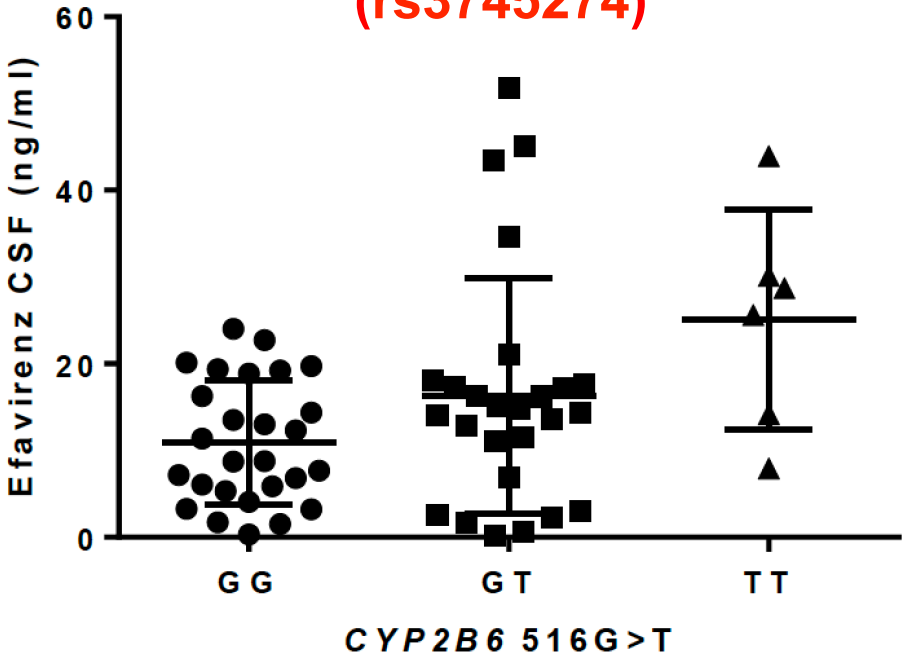
Effect modifiers:

- Adherence
- Diet and nutritional factors
- Nutritional status
- Concomitant treatments
- Hormonal environment
- Reproductive status
- Smoking

Floridia et al, Pharmacological Research 2008, 58:173–182
Ofotokun et al, Gender Medicine, 2007, 4(2):106-19

Pharmacogenomics May Also Influence Drug Distribution into the CNS

CYP2B6 516 (rs3745274)



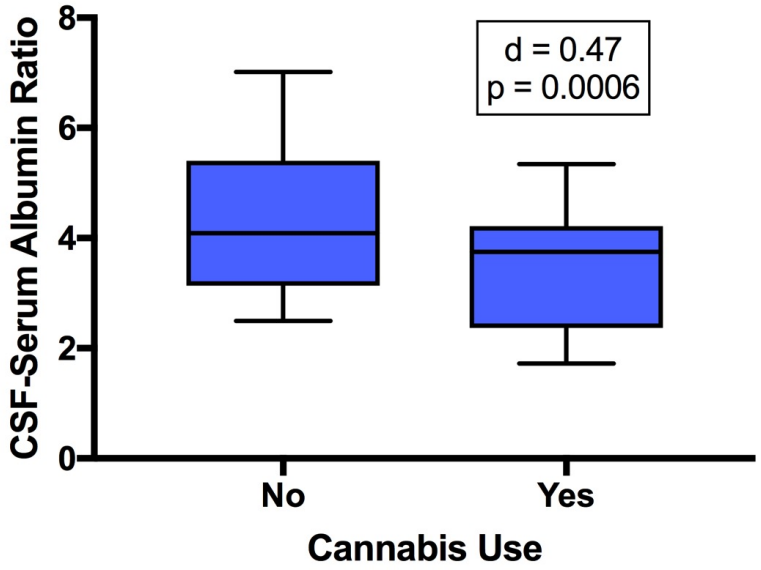
ABCB1 3435 (rs1045642)

	Plasma	CSF
CC	2798 (2029-5383)	15.4 (3.27-21.5)
CT	2440 (1814-3810)	11.5 (5.90-17.7)
TT	1710 (1183-2430)	12.3 (12.6-24.0)
p	0.090	0.335
ABCB1 3435C>T, Kruskal-Wallis Test		

Ma et al, CROI 2016, Abstract 446

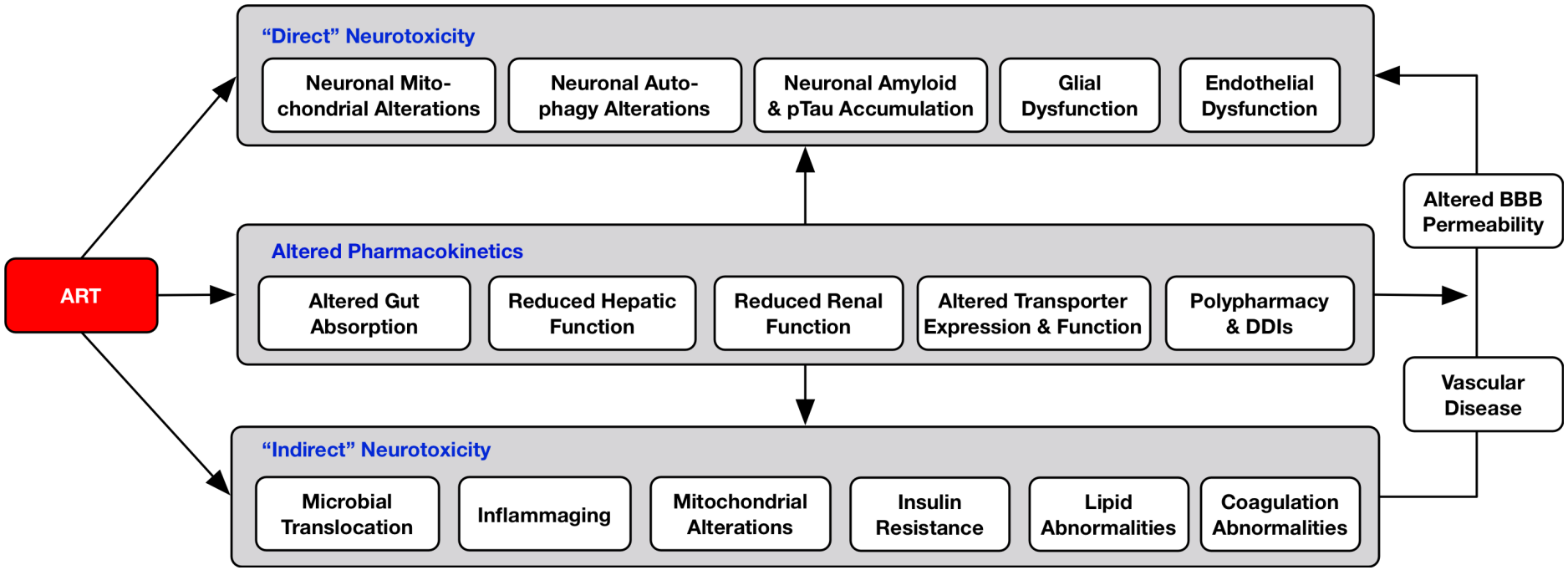
Nicotine and Cannabis Use May Also Affect the Blood-Brain Barrier

		CSAR (rho)	Age (rho)	Cotinine Levels (ES)
Endothelial Adhesion Molecules		(higher=more permeable)	(older)	(higher= user)
Plasma	VCAM1	**0.23***	**0.37****	-0.27
Plasma	PECAM1	0.11	0.19	0.06
Plasma	sE-Selectin	-0.22	0.09	**0.72****
CSF	VCAM1	**0.41****	**0.38****	-0.22
CSF	PECAM-1	0.11	0.14	-0.49
Basement Membrane Proteins				
Plasma	MMP-2	0.11	**0.29****	0.29
Plasma	MMP-7	**0.20**	**0.40****	0.09
Plasma	TIMP-1	**0.29**	**0.37****	**0.70***
Plasma	TIMP-2	-0.07	0.15	0.15
CSF	MMP-2	**0.35****	**0.19**	0.43
CSF	MMP-7	**0.36****	**0.33****	-0.27
CSF	TIMP-1	**0.58****	0.16	**0.99****
CSF	TIMP-2	**0.52****	0.15	0.47
Tight Junction Proteins				
Plasma	Occludin	**-0.32***	-0.01	0.26
Plasma	ZO-1	0.05	**0.31****	0.15
CSF	Claudin-1	**0.31****	0.13	0.08
CSF	Claudin-5	**0.23***	0.03	-0.29
CSF	ZO-1	0.10	-0.04	0.10



Letendre et al, Preliminary Data, 2017

Conceptual Construct for Worsened Neurotoxicity with Aging



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