Neurotoxicity of antiretrovirals

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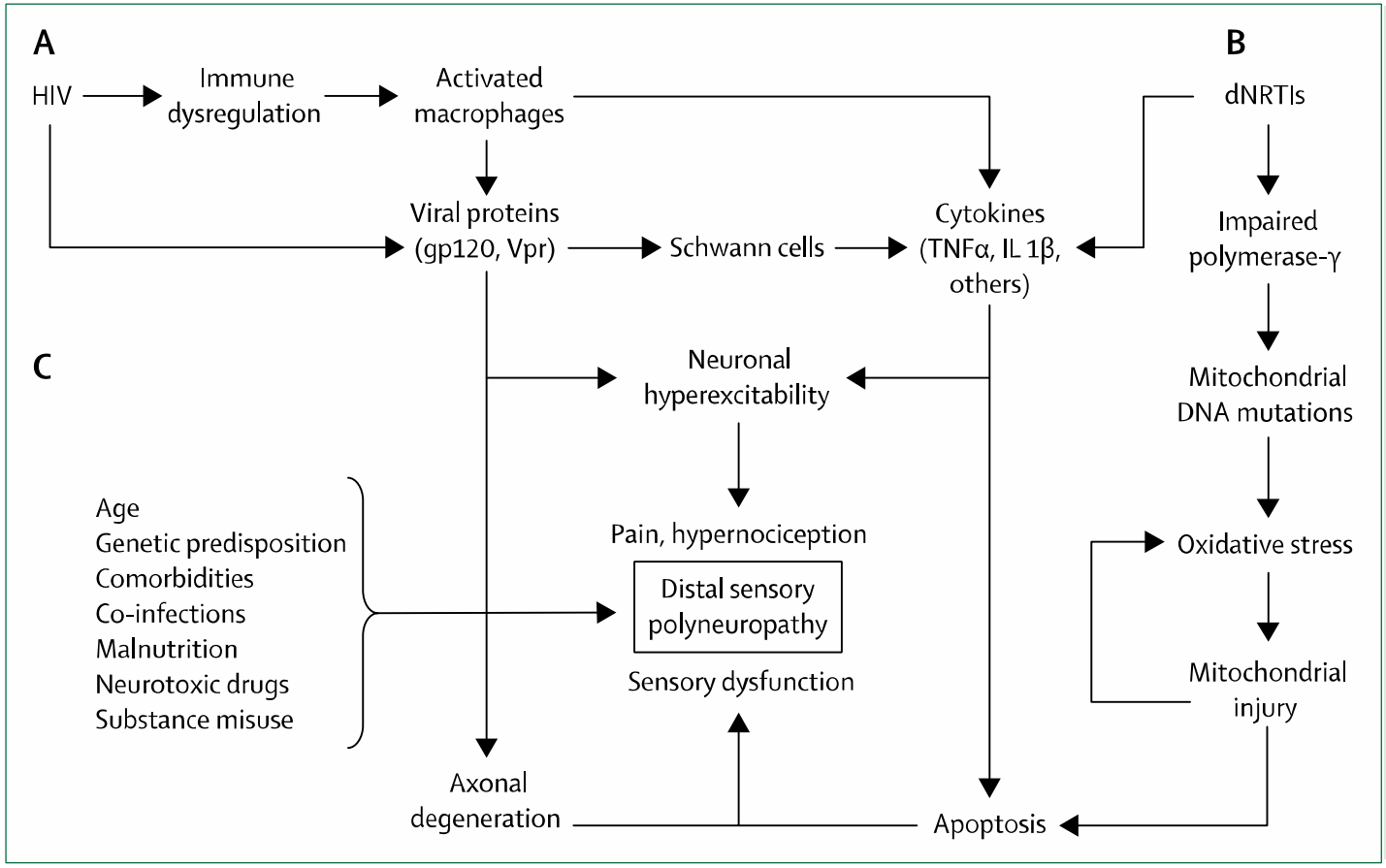
Disclosures

I have read and understood ICMJE policy on declaration of interest and I declare that I have no conflicting interest

In the past five years I received:

- research grants from Gilead, Viiv and BMS;
- speaker's honoraria from Abbvie, BMS, Gilead, Janssen-Cilag, MSD, Viiv.

(Peripheral) Neuropathy



***Panel 1:* Drugs that can cause neuropathy**

- Antiretrovirals
  - Stavudine
  - Didanosine
  - Protease inhibitors
- Antimicrobials
  - Isoniazid
  - Ethambutol
  - Metronidazole
  - Chloramphenicol
  - Dapsone
  - Amphotericin B
- Antineoplastics
  - Cisplatin
  - Vincristine
  - Vinblastine
- Others
  - Phenytoin
  - Corticosteroids
  - Herbal drugs (might contain neurotoxic contaminants)

Centner CM, et al. Lancet Neurology 2013

EDITORIAL REVIEW

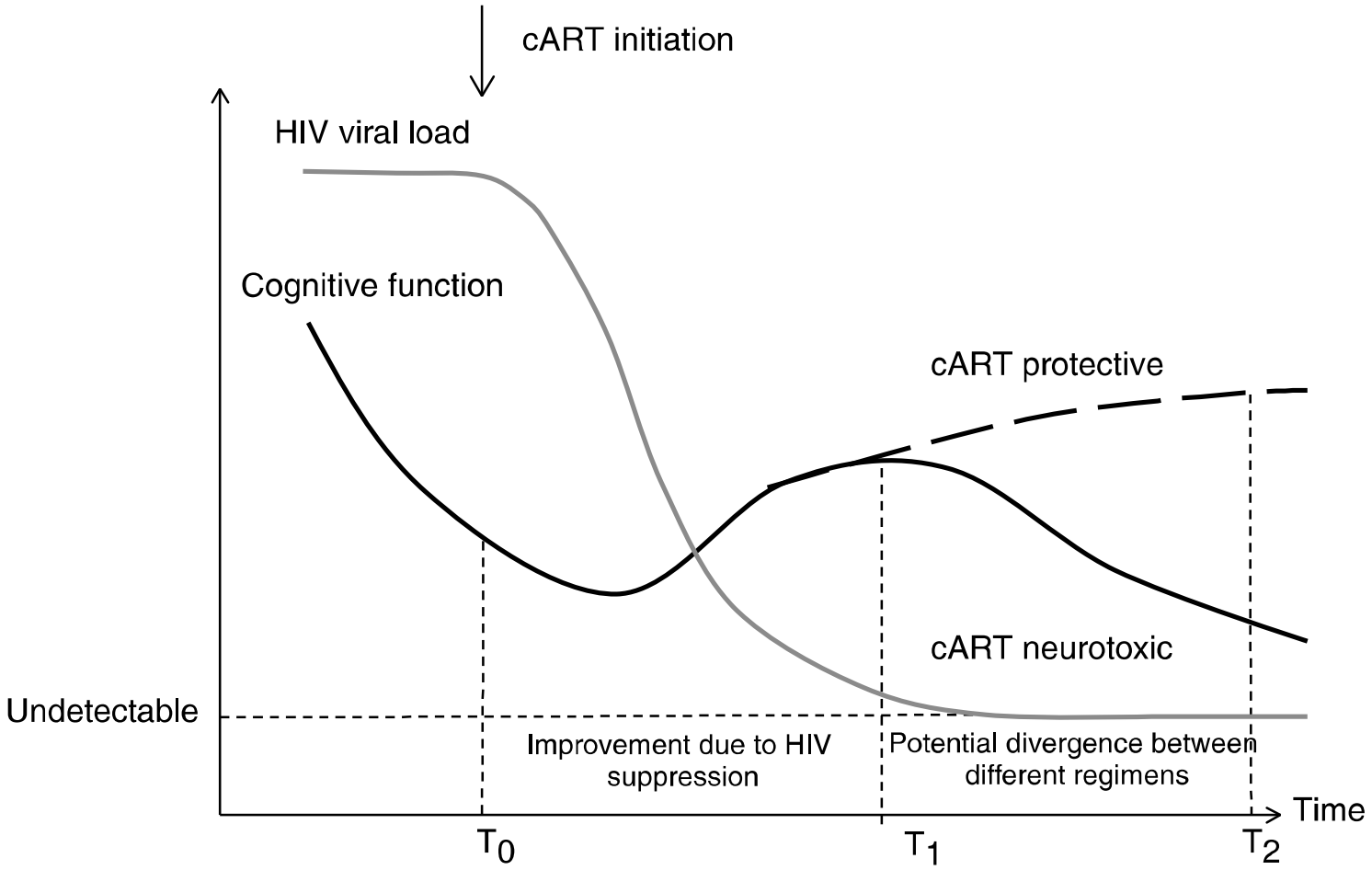
Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease?

Jonathan Underwood[a], Kevin R. Robertson[b] and Alan Winston[a]

Whilst effective antiretroviral therapy is protective against the more severe forms of HIV-associated brain disease, there remains a large burden of clinically symptomatic cognitive impairment in the modern era. Although several potential pathogenic mechanisms have been proposed, the underlying pathology remains elusive. In this review, we summarize the evidence describing neuronal toxicity of antiretroviral agents themselves in both preclinical and clinical situations, as well as the potential pathological mechanisms underlying this toxicity. We also consider the implications for future practice and clinical research in which case determining optimal antiretroviral combinations that effectively suppress HIV replication whilst minimizing neurotoxic effects on the central nervous system may become paramount.

AIDS 2015, **29**:253–261

Neurotoxicity – a potential model



Underwood J, et al. AIDS 2015

Mechanisms of antiretrovirals' CNS toxicity

① Direct Neuronal toxicity

- *In vitro*
- in macaques

② **Beta amyloid** metabolism interference

③ **Astrocytes** and blood brain barrier

④ **Olygodendrocytes** and myelin

⑤ Indirect effect on cerebral **blood vessels**

⑥ Efavirenz (and 8-08-EFV)

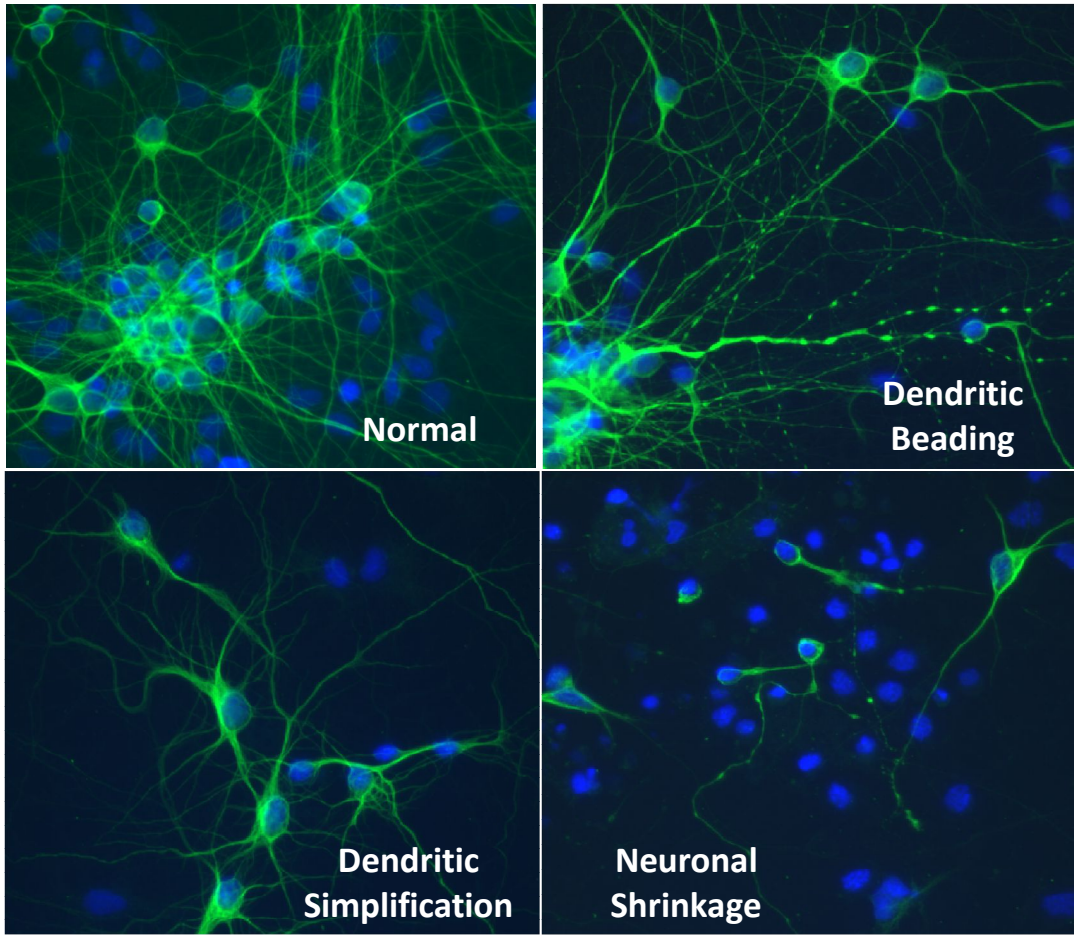
⑦ Interference with neurotransmitters?

Tovar-y-Romo LB, et al. J Pharmacol Exp Ther, 2012; Robertson K, et al. JNV 2012; Akay C, et al. JNV 2014; Giunta B, et al. Mol Brain 2011; Robertson K, et al. Neurology 2010; Achim CL, et al. J Neuroimmune Pharmacol 2009; Ortega M and Ances BM, J Neuroimmune Pharmacol 2014; Ciccarelli N, et al. Neurology 2011; Vivithanaporn P, et al. AIDS 2016

1. DIRECT NEURONAL TOXICITY

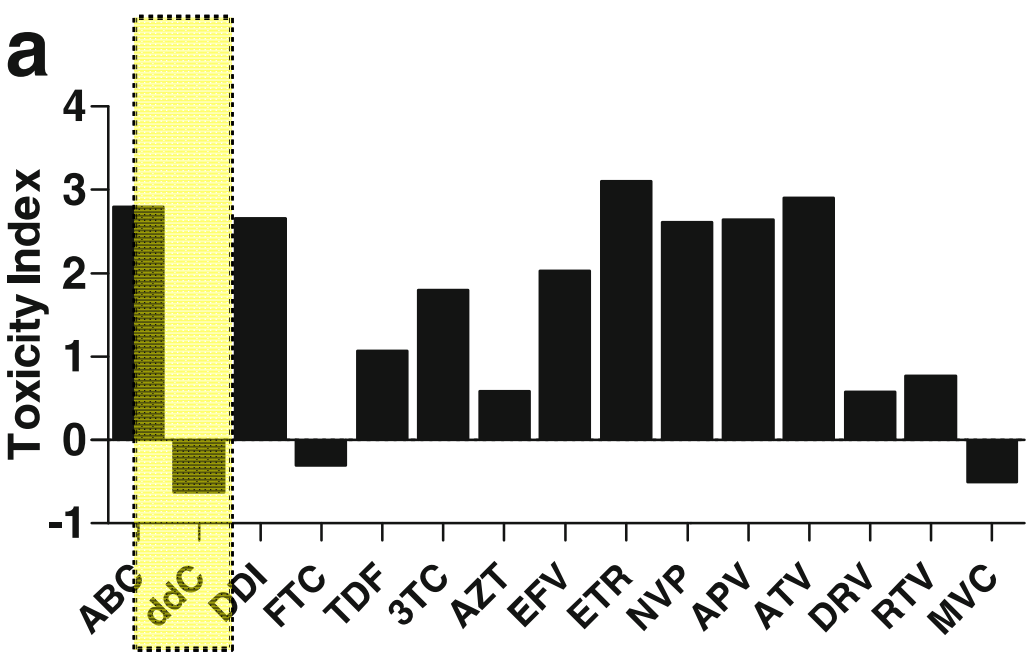
In vitro

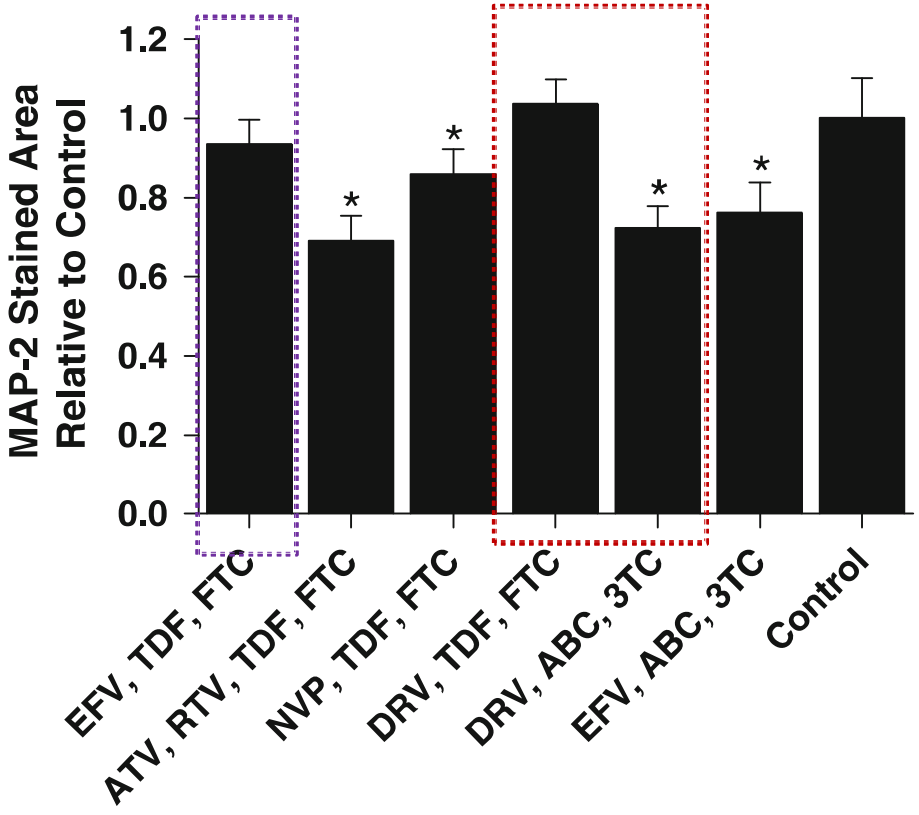
- Fetal rat cortical neuron cultures
- Some mild degree of functional injury seen with all drugs
  - **Mostly dendritic beading and pruning**
- **EFV> others > FTC,TFV, DRV, MVC**
- no additive effect



Robertson K, et al. JNV 2012

In vitro (2)

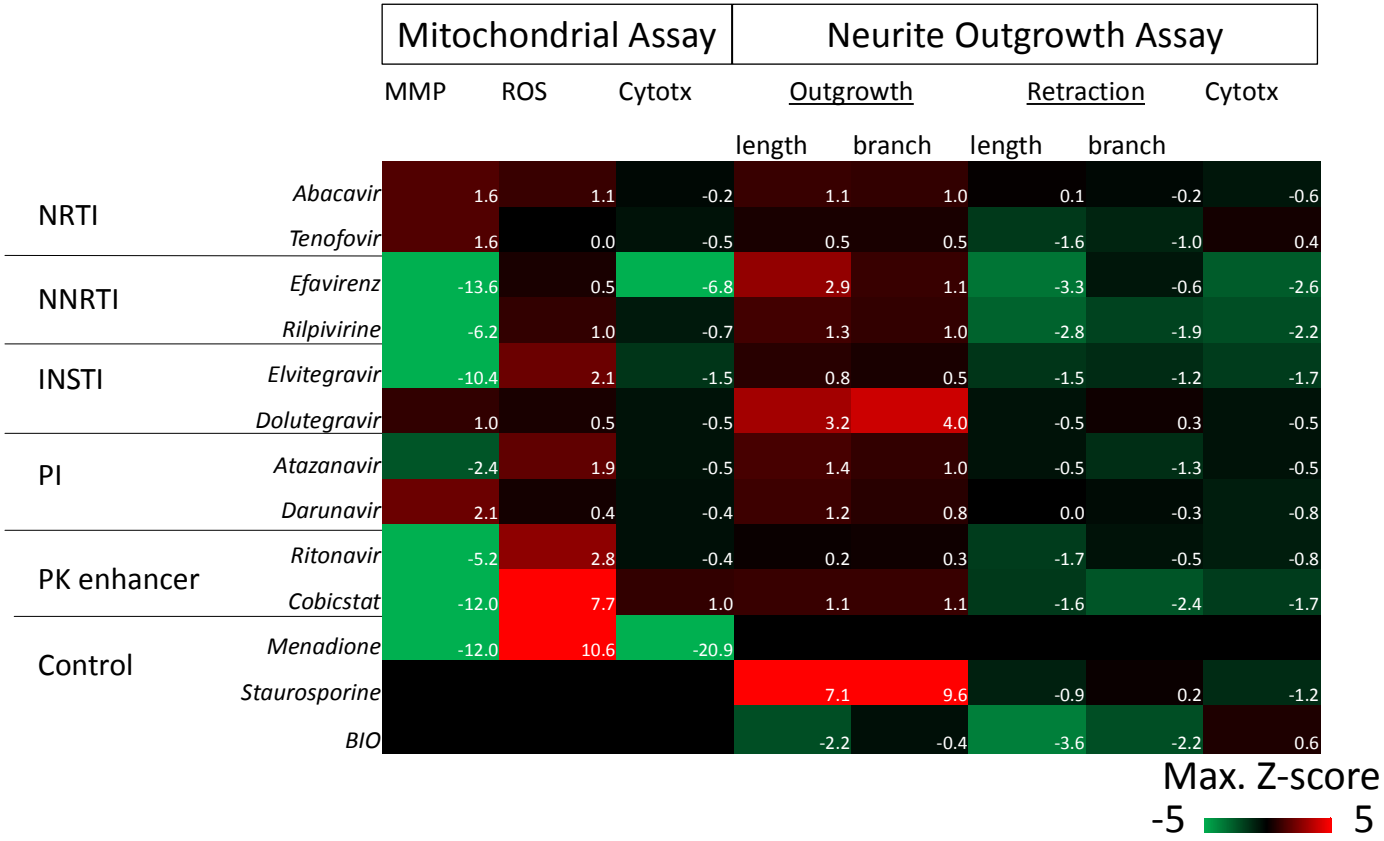




Robertson K, et al. JNV 2012

In vitro (3)

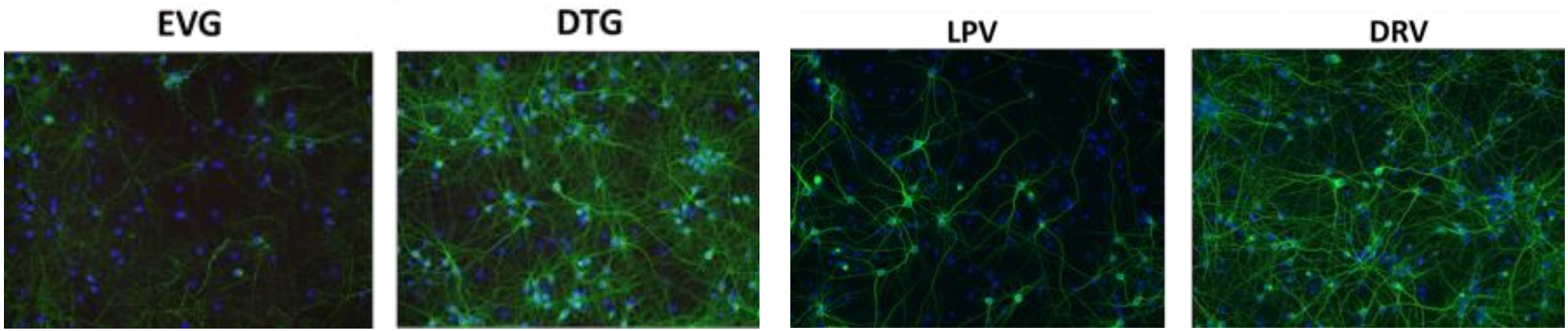
- hIPSC derived iCell cortical neurons (Cellular Dynamics International)
- neurons were loaded with the mitochondrial membrane potentiometric dye TMRE and reactive oxygen species sensor CellROX deep red
- **NNRTI and EVG were mitotoxic** resulting in neurite retraction/cytotoxicity
- In contrast, **PI were mitotoxic** but did not significantly impact neuronal morphology or long-term cell health



Hinckley S, et al. CROI 2016 #395

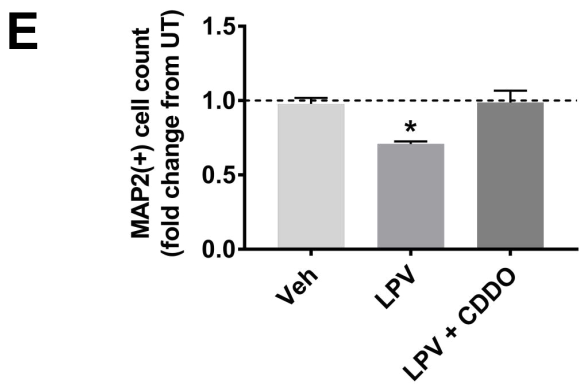
In vitro (4)

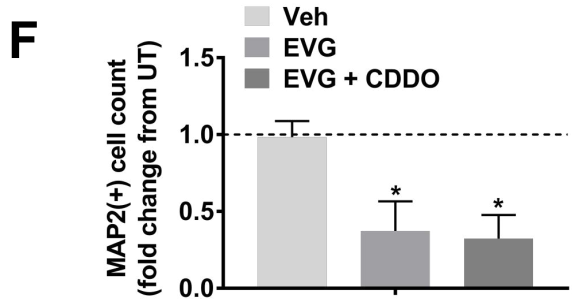
Primary rat cortical neuroglial cultures - 14-16 days *in vitro*



Lopinavir induces mitochondrial dysfunction and oxidative stress.

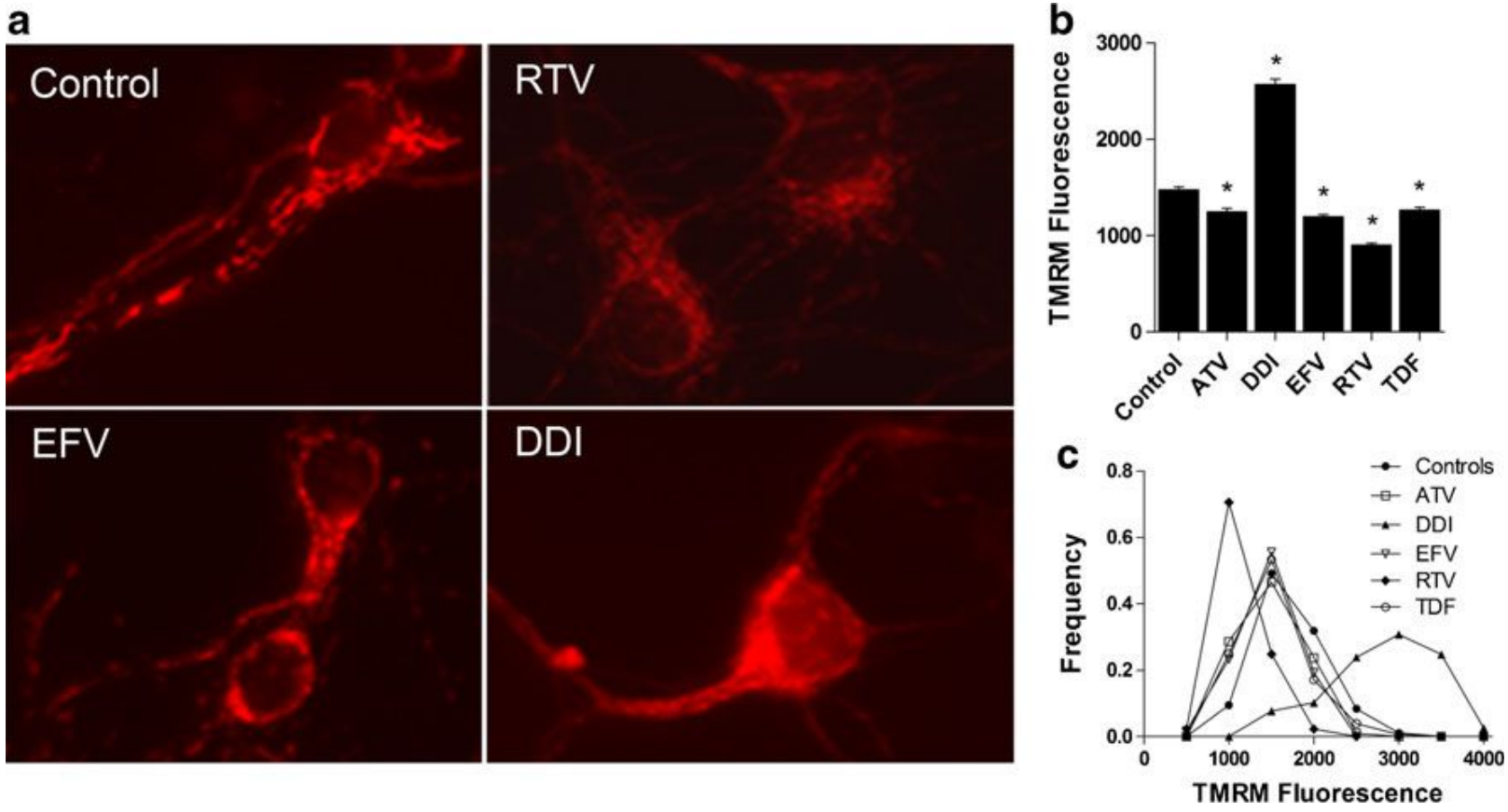
Pharmacological induction of the endogenous antioxidant HO-1 is protective against lopinavir- mediated neuronal death.





Akay-Espinoza C, et al. CROI 2017 #378

Mitochondrial damage



Robertson K, et al. JNV 2012

Available online at www.sciencedirect.com
ScienceDirect
Experimental Neurology 204 (2007) 29–38
Experimental Neurology
www.elsevier.com/locate/yexnr

Oxidative stress and toxicity induced by the nucleoside reverse transcriptase inhibitor (NRTI)—2′,3′-dideoxycytidine (ddC): Relevance to HIV-dementia

Wycliffe O. Opii [a], Rukhsana Sultana [a], Hafiz Mohmmad Abdul [a], Mubeen Ahmad Ansari [a], Avindra Nath [b], D. Allan Butterfield [a,*]

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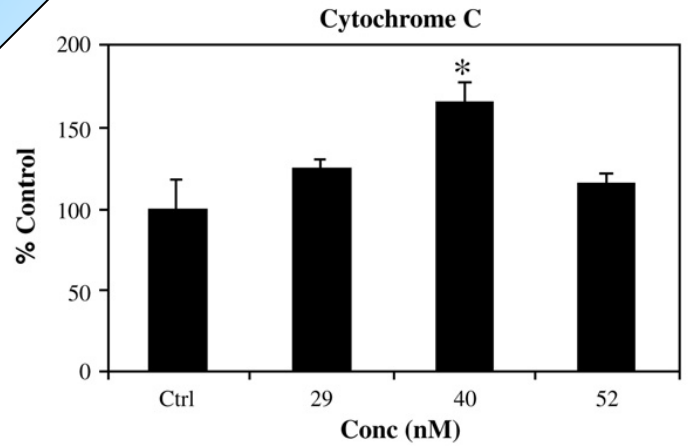
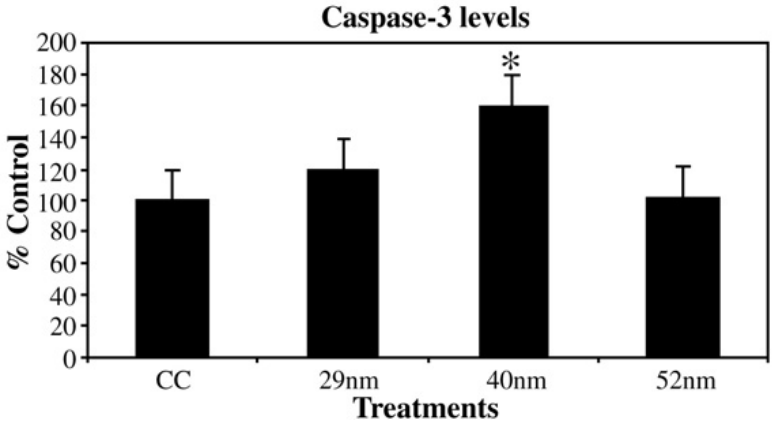
Available online 25 October 2006

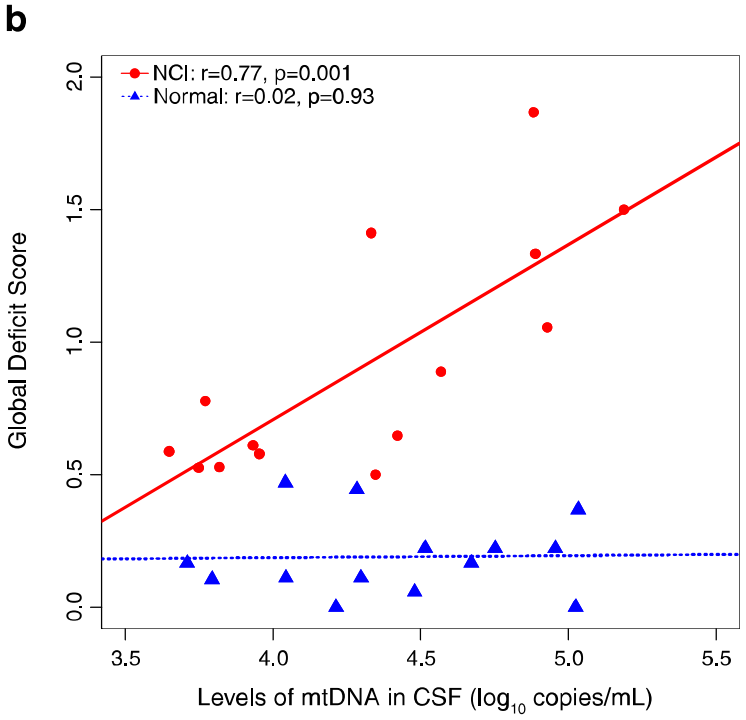
Synaptosomes and isolated mitochondria treated and incubated for 6 h with CSF-achievable concentrations of ddC, -(6–11 ng/ml



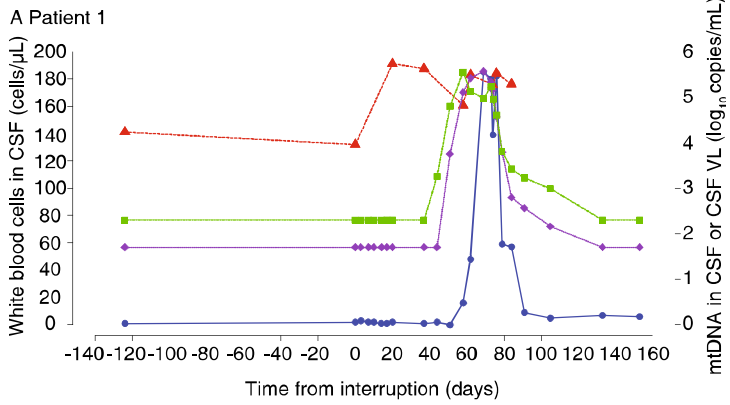


Cell-free Mitochondrial DNA in the CSF

cross-sectional in 28 HIV-infected individuals (14 with NCI)



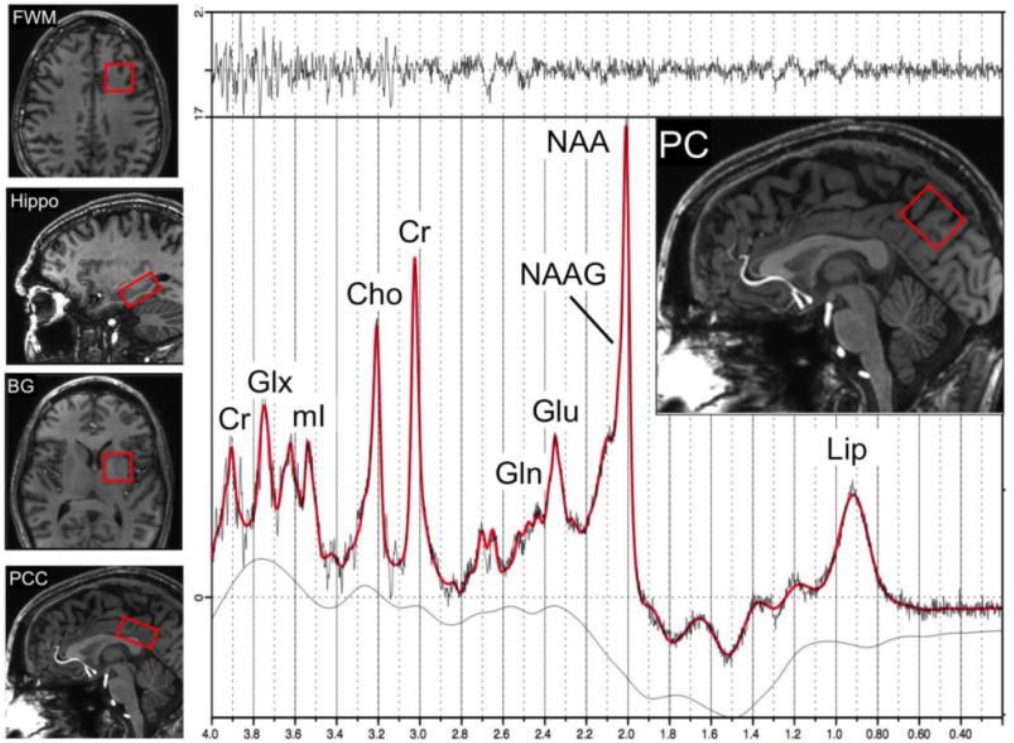
Strong association with soluble and cellular biomarkers of inflammation in CSF and blood of HIV+ pts with NCI (IP-10, MCP-1, CSF lymphocytes) but not with neuronal damage



Perez-Santiago J, et al. JNV 2015

N-acetyl aspartate at MRS

- Localize to neurons (axons)
- Marker of neuronal integrity
- Marker of mitochondrial integrity
  - Reduced following ATP inhibition and impaired oxygen consumption
- Reduced Naa with “old” drugs and in patients with NCI



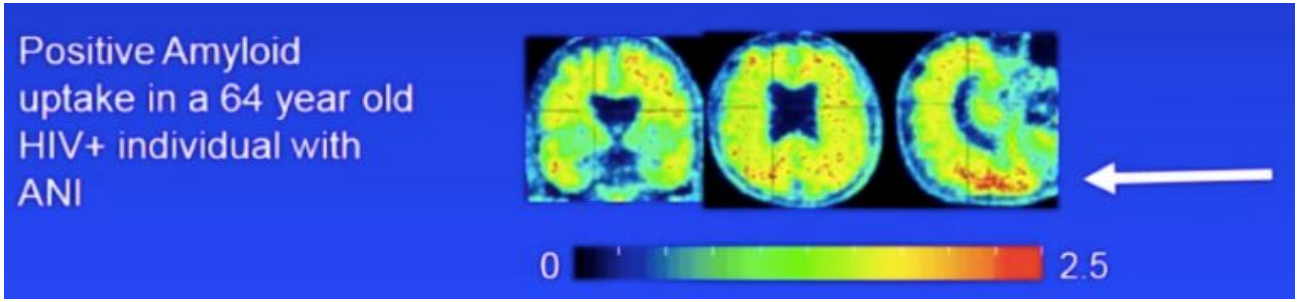
Schweinsburg BC, et al. JNV 2005; Mohamed M, et al. AJNR 2018

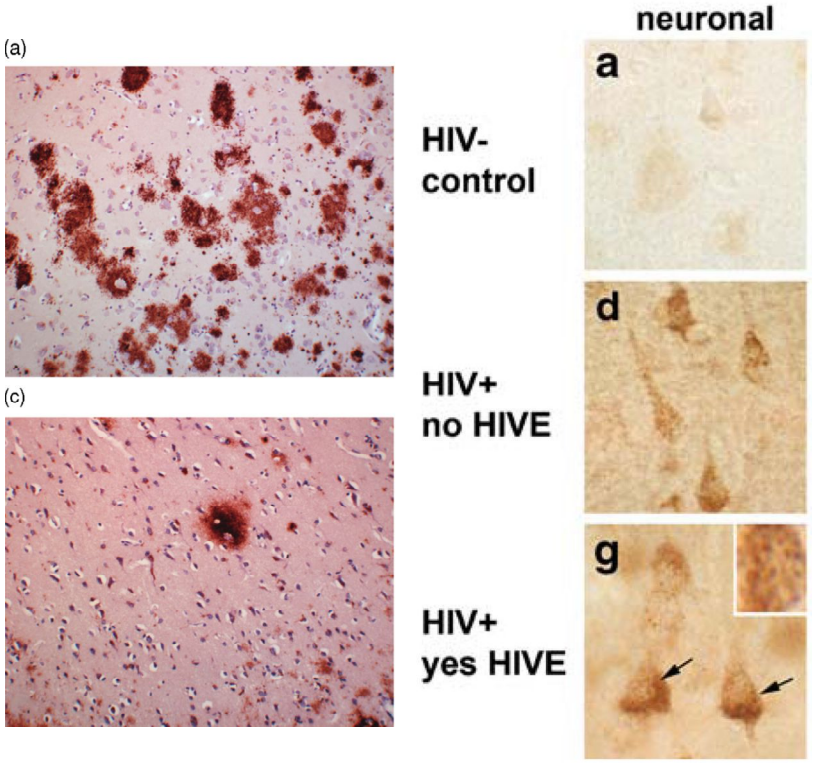
2. INTERFERENCE WITH AMYLOID METABOLISM

Amyloid deposition

Extracellular amyloid plaques (AD) vs. **intra- neuronal** amyloid accumulation or **perivascular diffuse amyloid depositions** have been observed in HIV+ pts .

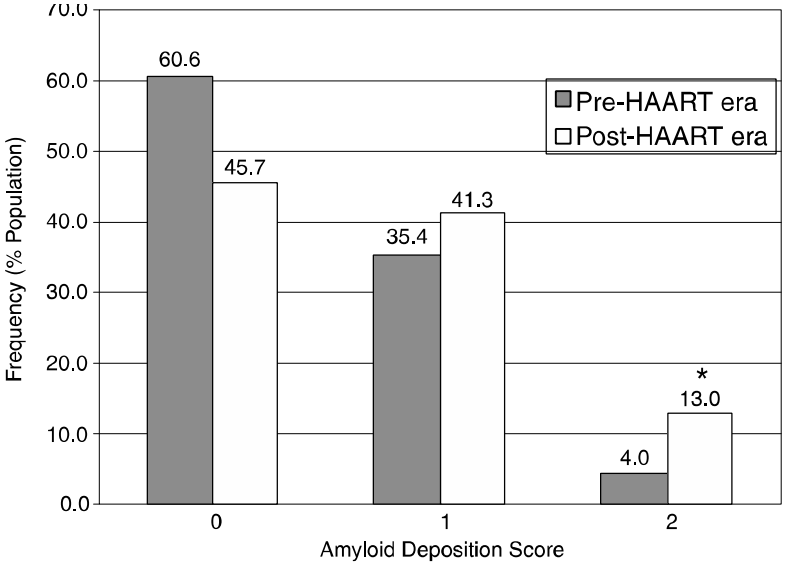
- Intracellular deposition of Aβ correlated with age in the group of patients with HIVE (older subjects with early Aβ deposition)
- Amyloid uptake by PET imaging suggest premature ageing in older individuals





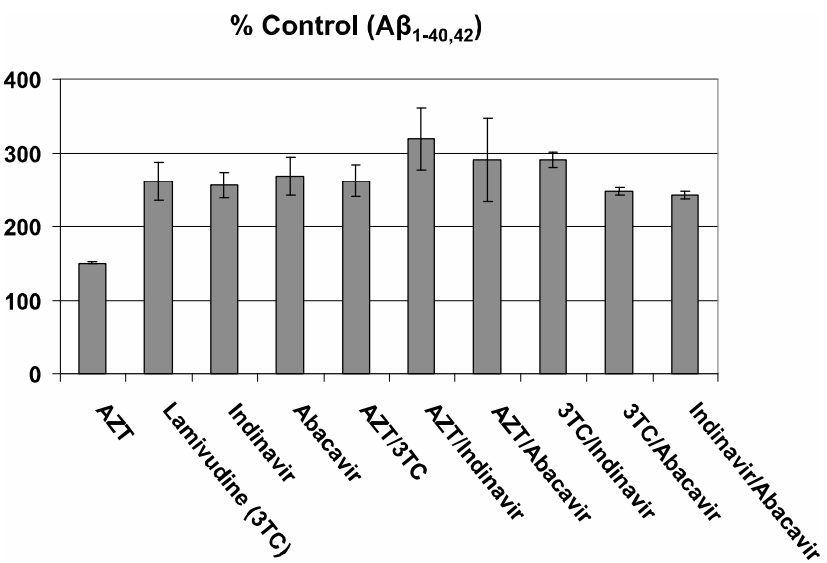
Esiri MM, et al J Neurol Neurosurg Psychiatry 1998; Rempel HC, et al AIDS 2005; Green DA, et al. AIDS 2005; Brew BJ, et al J Neuroimmune Pharmacol 2009; Achim CL, et al J Neuroimmune Pharmacol 2009; Sacktor N, et al. CROI 2018 #438

HAART and amyloid deposition



In patients with access to HAART, there is a clear trend towards decreasing prevalence of Grade 0, and an overall increase in Grades 1 and 2.

Green DA, et al. AIDS 2005



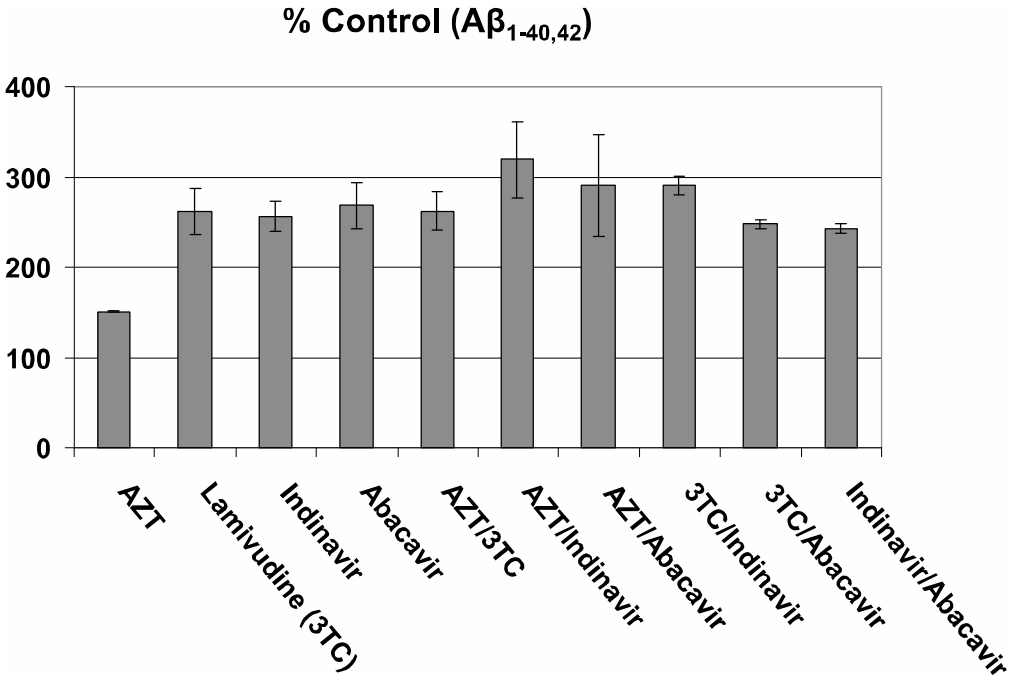
ARVs increase Aβ generation (50-200%) and markedly inhibit microglial phagocytosis of **Aβ1**-42 peptides in murine microglia. The most significant amyloidogenic effects were observed with combined ART.

Giunta B, et al. Molecular Brain 2011

β Amyloid Deposition

Impairment of beta amyloid metabolism:

- *in vitro* additive effect of ARVs;
- EFV (trough reduced microglial phagocytosis)



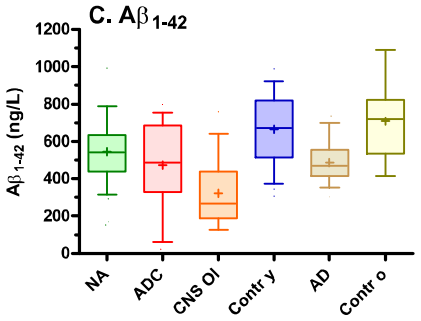
Achim CL, et al. J Neuroimmune Pharmacol 2009; Ortega M and Ances BM, J Neuroimmune Pharmacol 2014; Giunta B, et al. Mol Brain 2011; Brown LAM, et al. PlosOne 2014

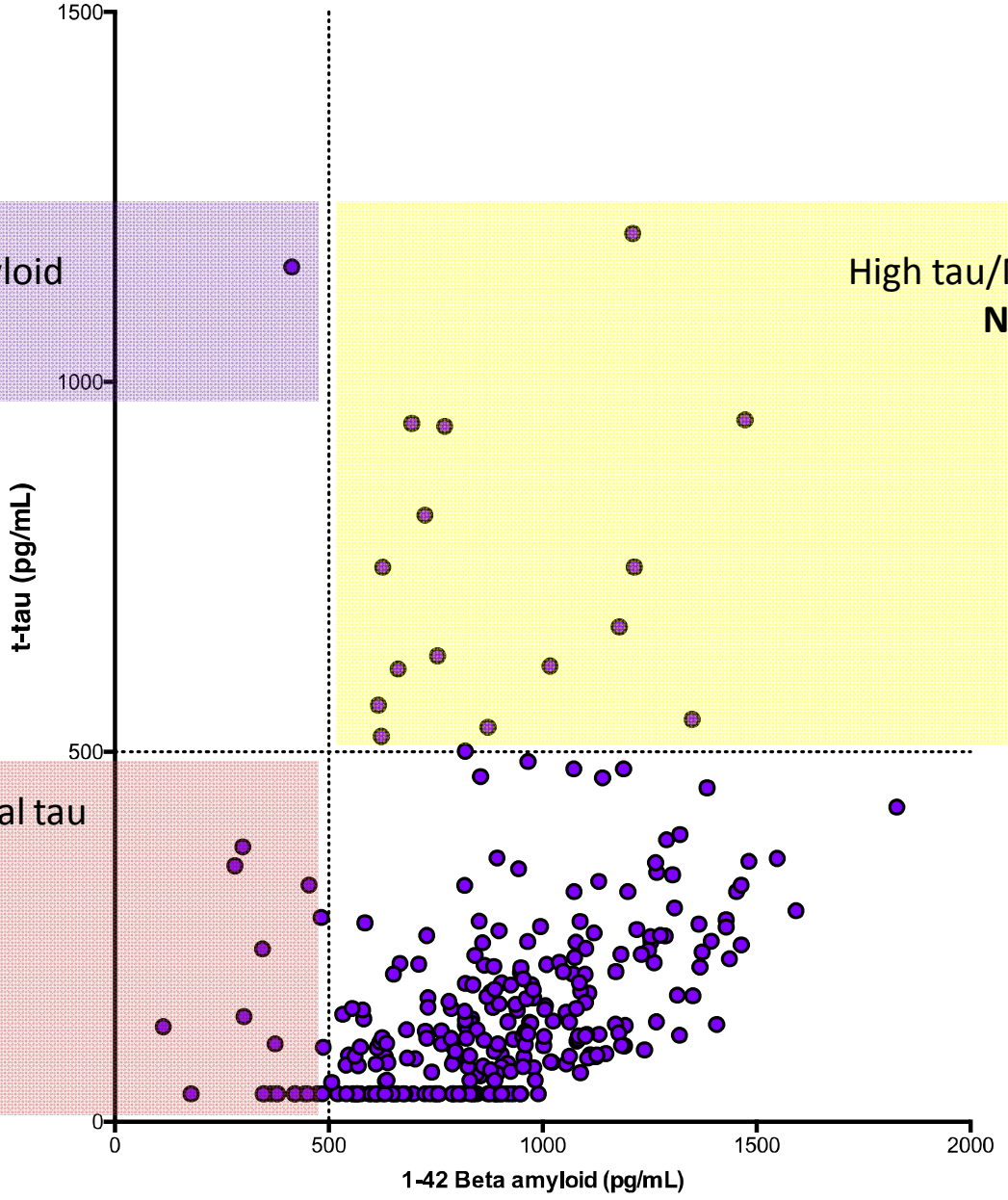
N=288

High tau/Low 1-42 Beta Amyloid
SM

High tau/Normal 1-42 Beta Amyloid
Neuronal damage?

Low 1-42 Beta Amyloid/Normal tau
Inflammation?
Neurotoxicity?

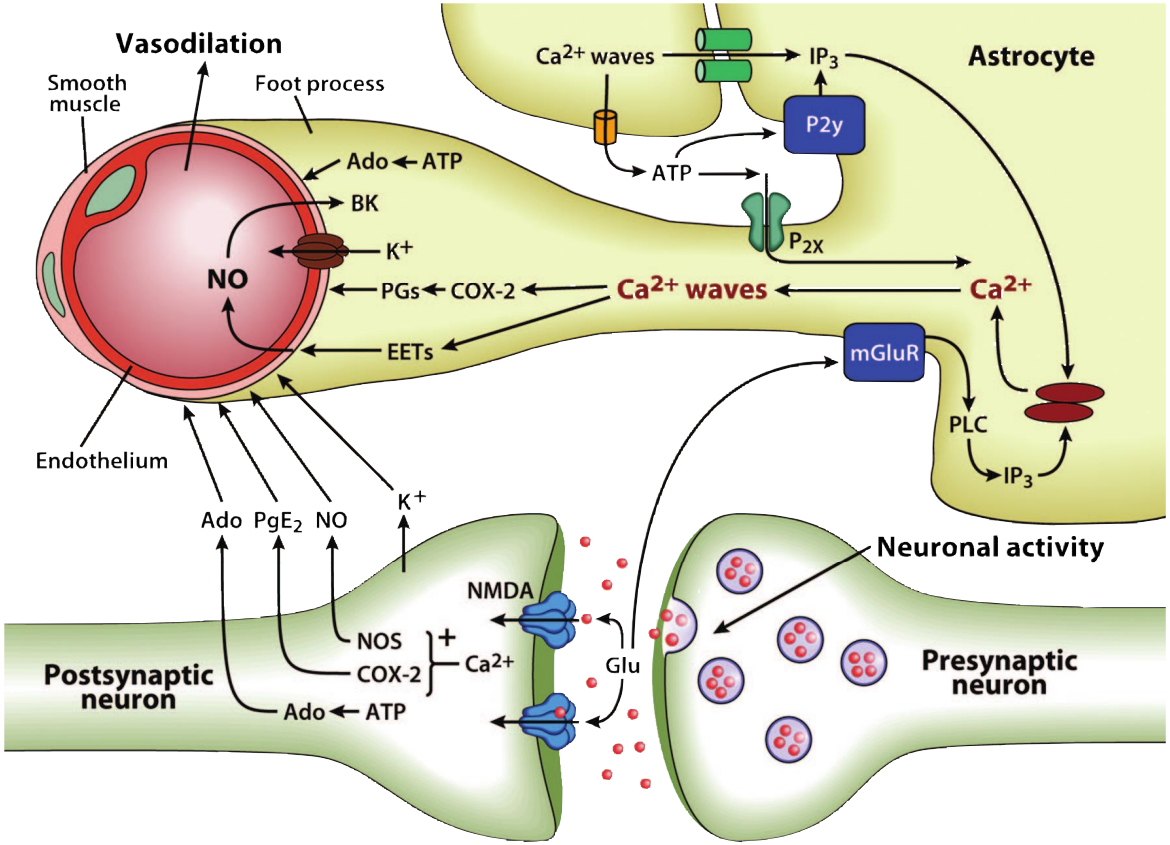




Personal data and Gisslen M, et al. BMC Neurology 2009

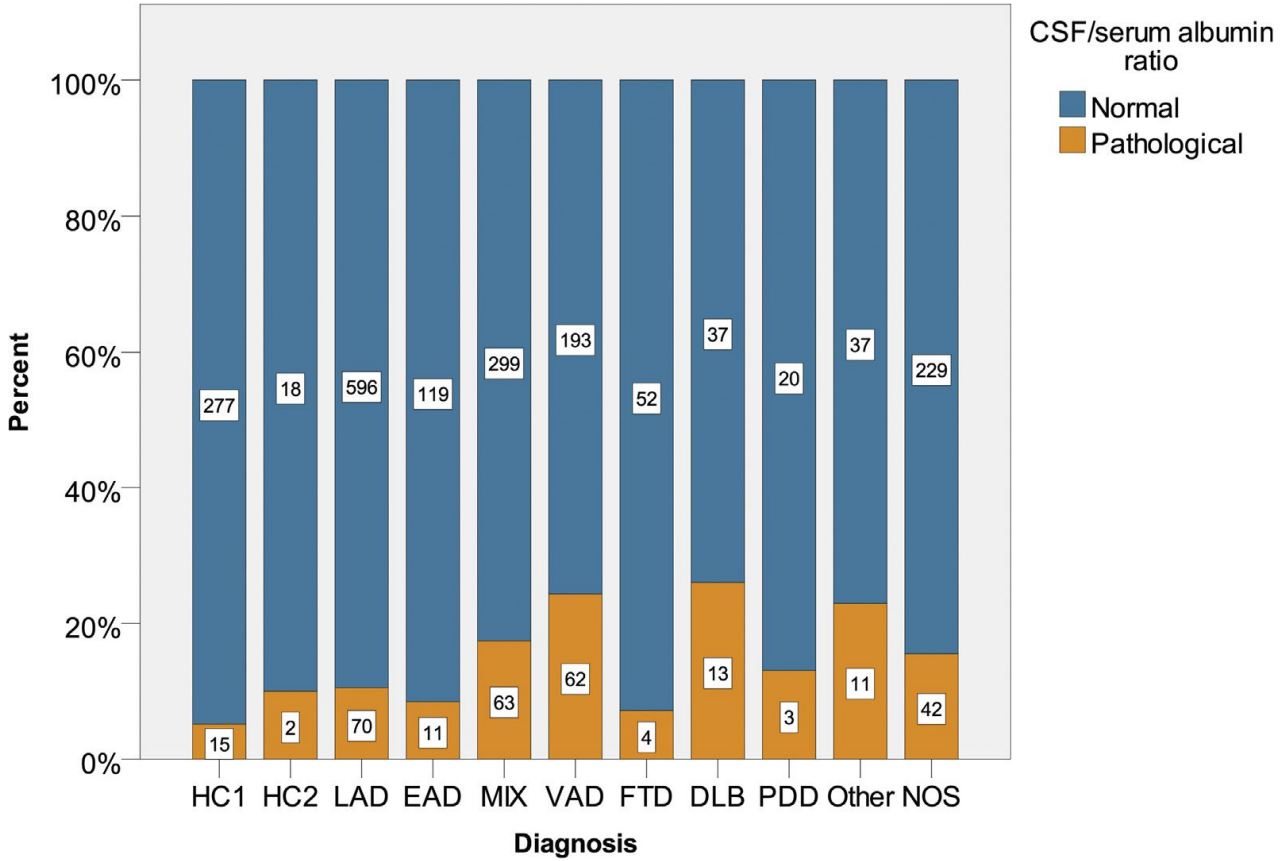
3. ASTROCYTES AND BLOOD BRAIN BARRIER

The Neurovascular Unit



Woods SP, et al. J Clin and Exp Neuropsychology 2007

BBB impairment and dementias in HIV- patients

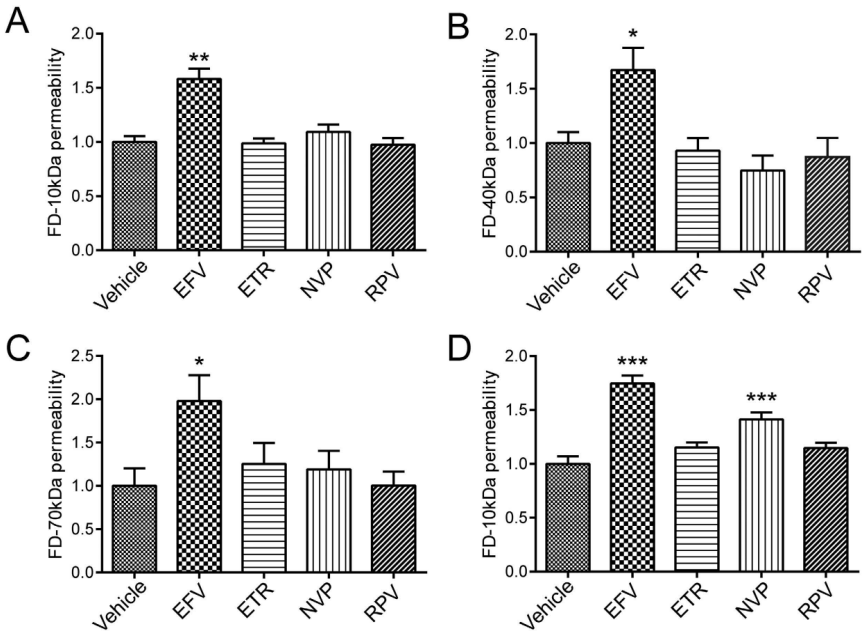


- **Alzheimer's disease** (AD, early onset [EAD, n = 130], late onset AD [LAD, n = 666]),
- **vascular dementia** (VaD, n = 255),
- **mixed AD and VaD** (MIX, n = 362),
- **Lewy body dementia** (DLB, n = 50),
- **frontotemporal dementia** (FTD, n = 56),
- **Parkinson's disease dementia** (PDD, n = 23),
- **other dementias** (other, n = 48),
- dementia not otherwise specified (NOS, n = 271).

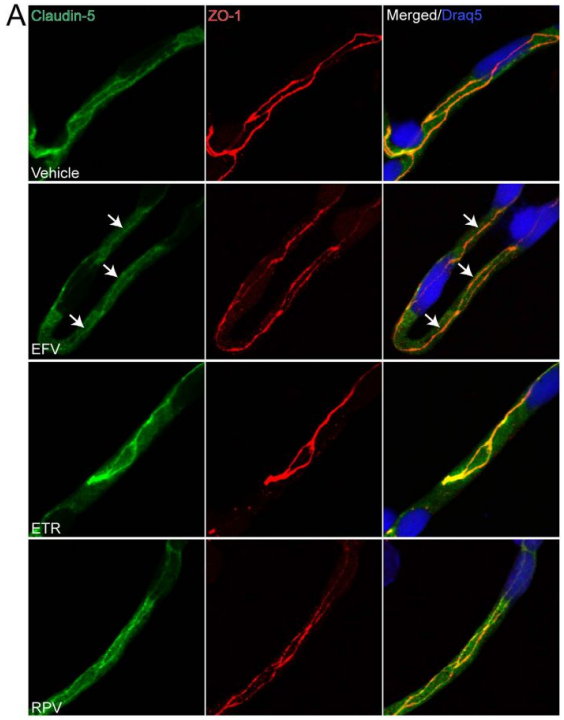
Skillbäck T, et al. Neurobiology of Aging 2017

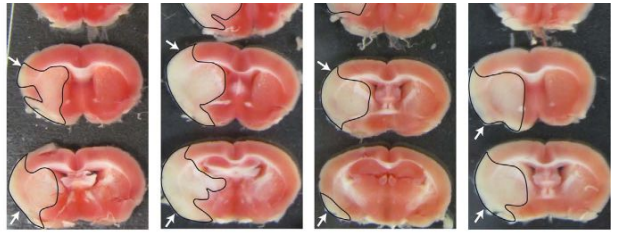
BBB integrity (and severity of stroke)

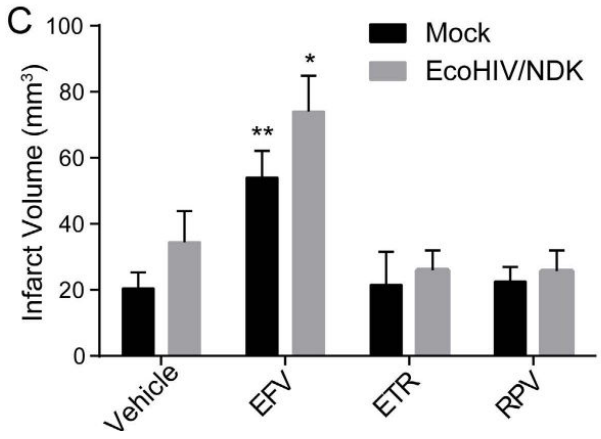
Human cerebral microvascular cells



Mice (infected/uninfected)

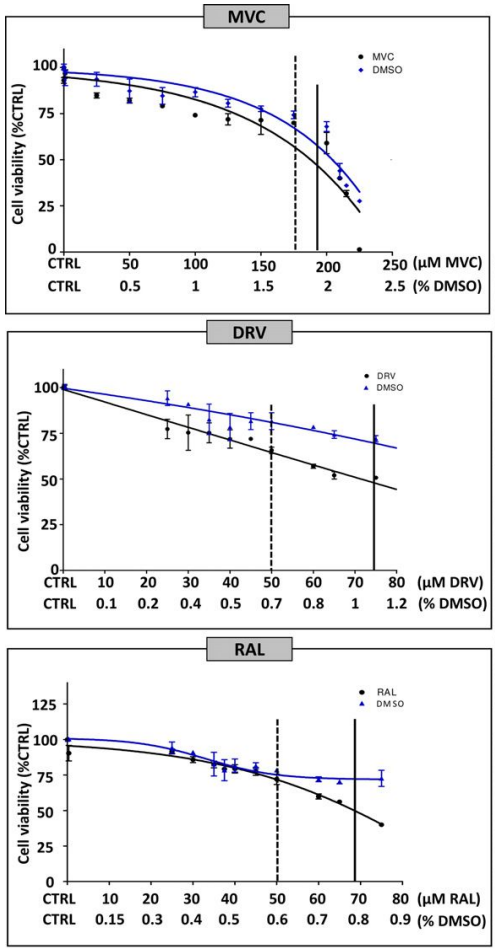


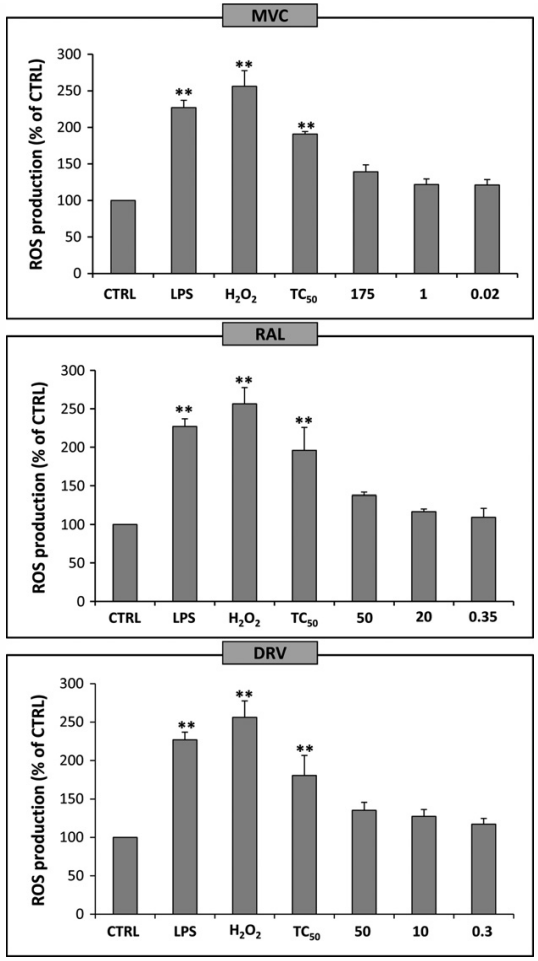


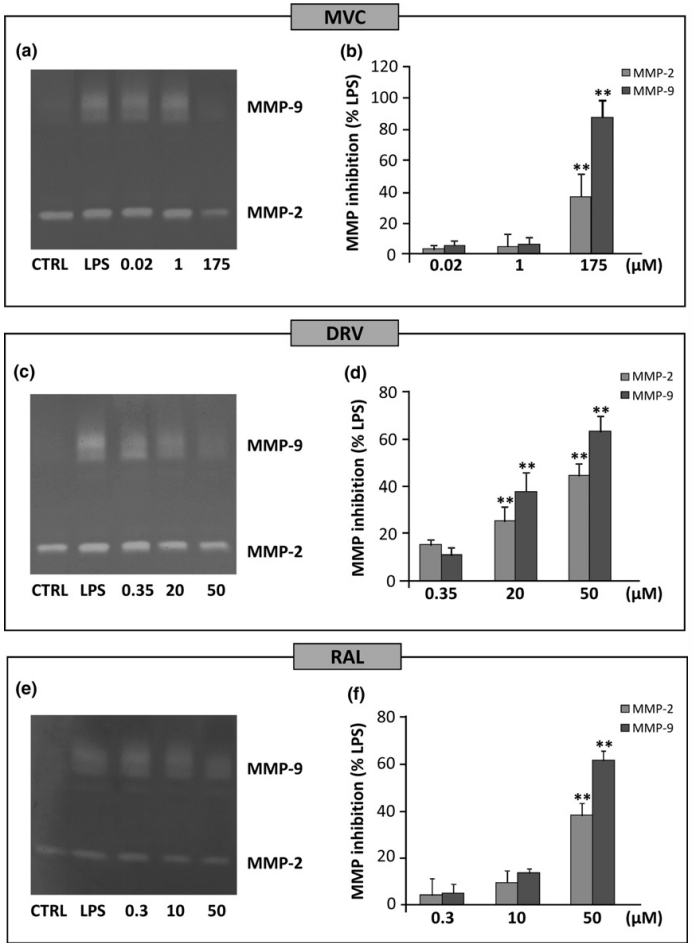


Bertrand L, et al. Sci Rep 2016

Astrocytes *in vitro* – MVC, RAL, DRV were safe





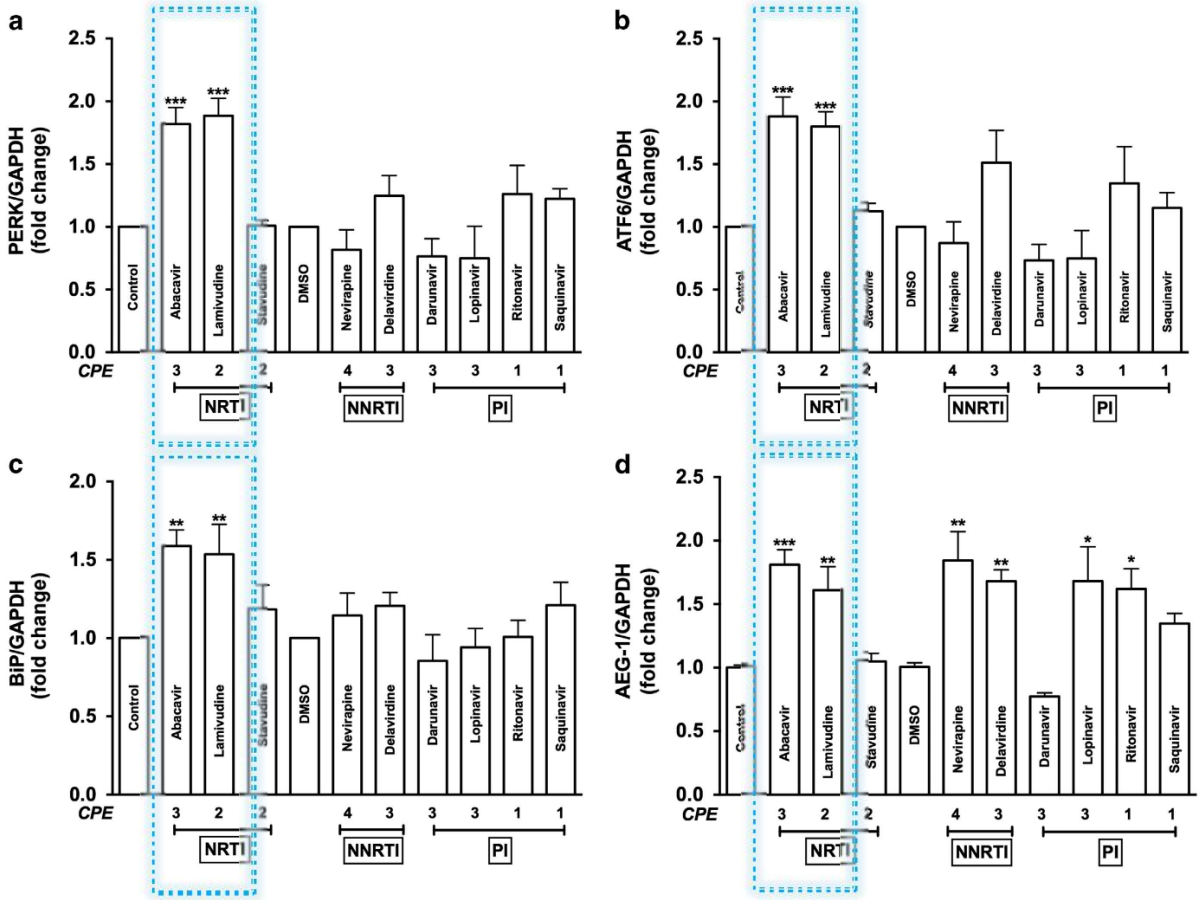


Latronico T, et al. J of Neurochemistry 2018

Astrocytes' endoplasmic reticulum stress response

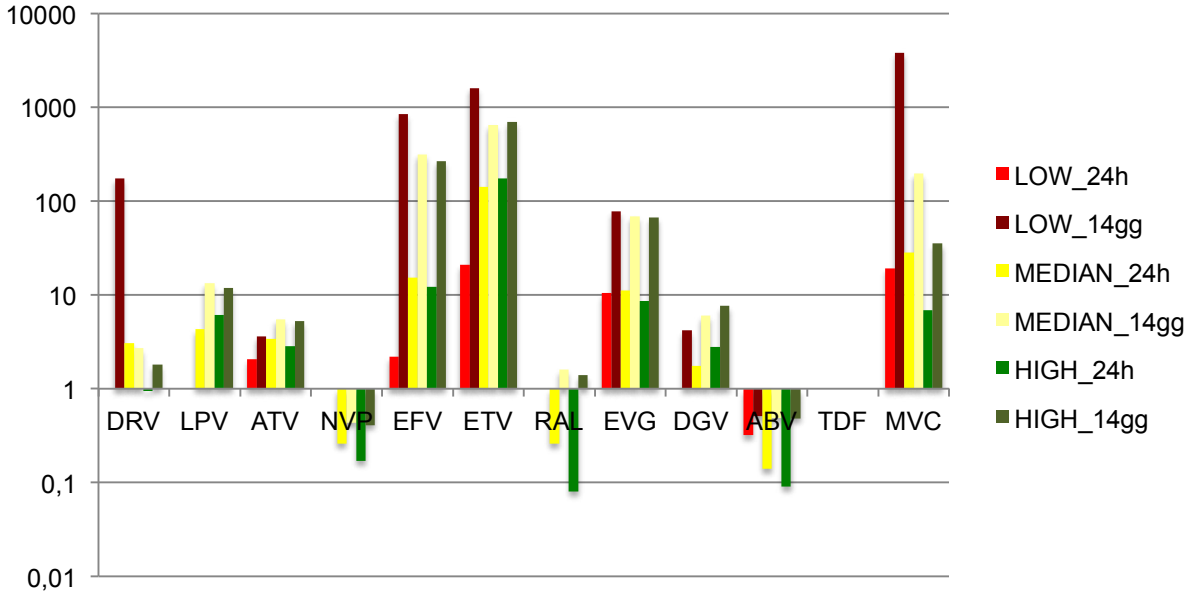
ABC and 3TC

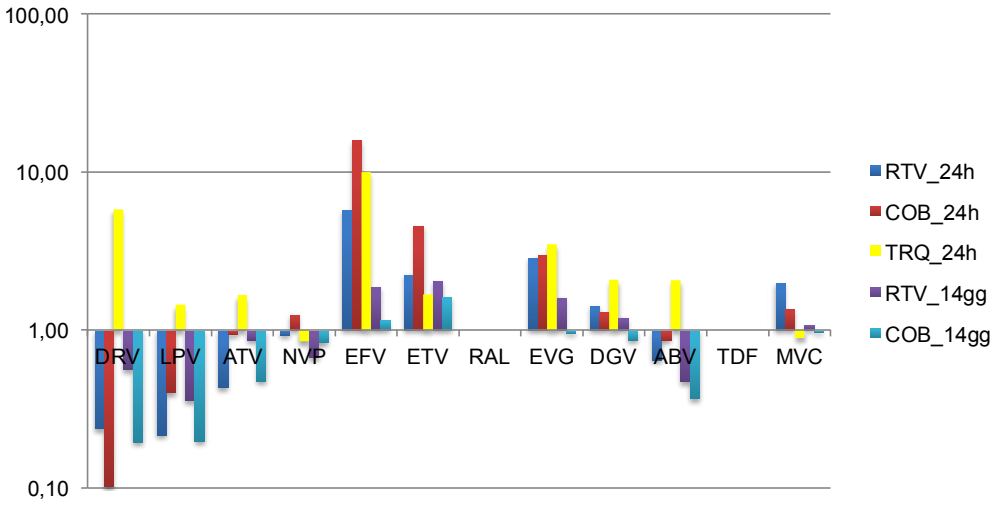
- Primary human astrocytes exposed to HIV-1 virions, inflammation and ARV drugs:
  - astrocyte elevated gene-1 (AEG-1), a novel HIV-1 inducible gene, along with ER stress markers
  - unfolded protein responses (UPRs)



Nooka S, et al. Cell Death Discovery 2017

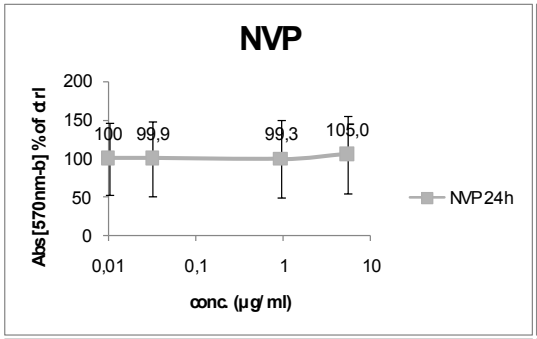
Cultured Rat astrocytes

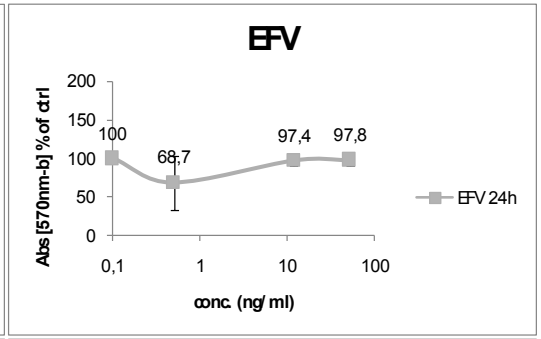


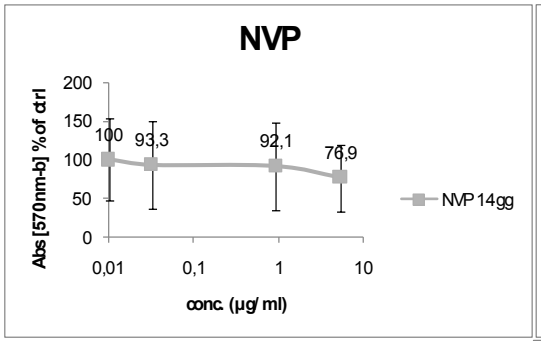


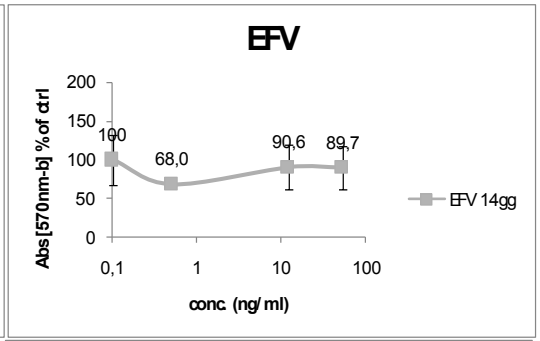
In preparation

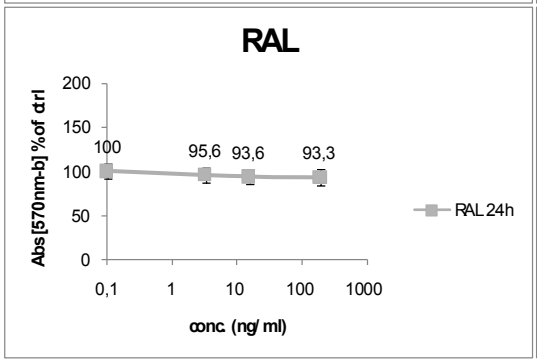
Cultured Rat astrocytes (2)

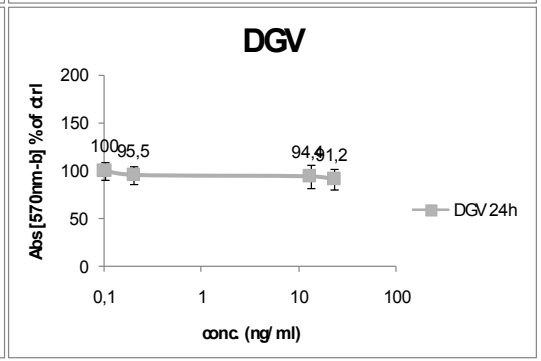


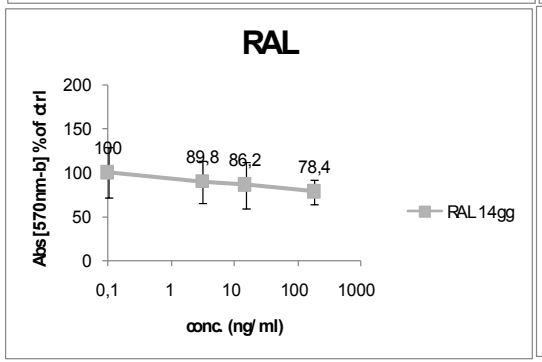


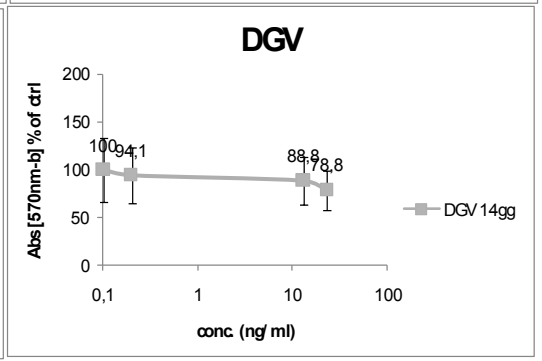












24 hours

14 days

In preparation

4. OLIGODENDROCYTES AND MYELIN

J Neuropathol Exp Neurol

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ORIGINAL ARTICLE

Altered Oligodendrocyte Maturation and Myelin Maintenance: The Role of Antiretrovirals in HIV-Associated Neurocognitive Disorders

Brigid K. Jensen, BS, Hubert Monnerie, PhD, Maggie V. Mannell, MS, Patrick J. Gannon, PhD, Cagla Akay Espinoza, MD, Michelle A. Erickson, PhD, Annadora J. Bruce-Keller, PhD, Benjamin B. Gelman, MD, PhD, Lisa A. Briand, PhD, R. Christopher Pierce, PhD, Kelly L. Jordan-Sciutto, PhD, and Judith B. Grinspan, PhD

Abstract

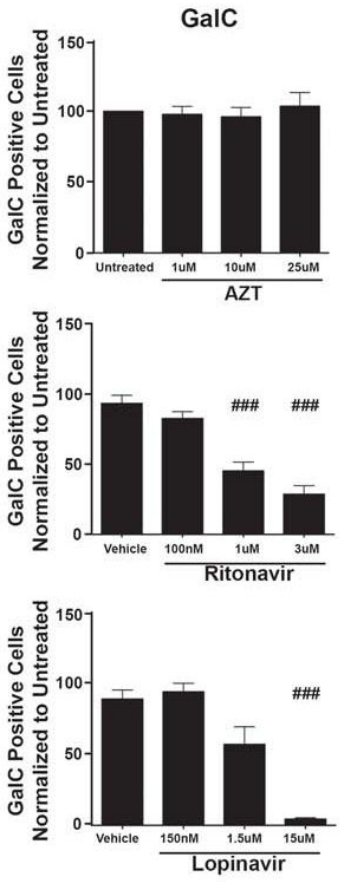
Despite effective viral suppression through combined antiretroviral therapy (cART), approximately half of HIV-positive individuals have HIV-associated neurocognitive disorders (HAND). Studies of antiretroviral-treated patients have revealed persistent white matter abnormalities including diffuse myelin pallor, diminished white matter tracts, and decreased myelin protein mRNAs. Loss of myelin can contribute to neurocognitive dysfunction because the myelin membrane generated by oligodendrocytes is essential for rapid signal transduction and axonal maintenance. We hypothesized that myelin changes in HAND are partly due to effects of antiretroviral drugs on oligodendrocyte survival and/or maturation. We showed that primary mouse oligodendrocyte precursor cell cultures treated with therapeutic concentrations of HIV protease inhibitors ritonavir or lopinavir displayed dose-dependent decreases in oligodendrocyte maturation; however, this effect was rapidly reversed after drug removal. Conversely, nucleoside reverse transcriptase inhibitor zidovudine had no effect. Furthermore, in vivo ritonavir administration to adult mice reduced frontal cortex myelin protein levels. Finally, prefrontal cortex tissue from HIV-positive individuals with HAND on cART showed a significant decrease in myelin basic protein compared with untreated HIV-positive individuals with HAND or HIV-negative controls. These findings demonstrate that antiretrovirals can impact myelin integrity and have implications for myelination in juvenile HIV patients and myelin maintenance in adults on lifelong therapy.

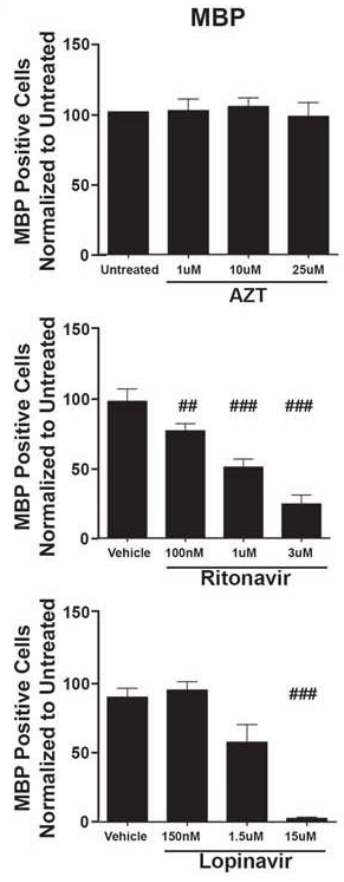
Key Words: Antiretroviral, Oligodendrocyte, Myelin, HIV, HIV-Associated Neurocognitive Disorders, Pediatric AIDS, Protease Inhibitor.

INTRODUCTION

Approximately 50% of patients infected with human immunodeficiency virus-1 (HIV) present with a broad spectrum of cognitive, motor, and behavioral disturbances collectively termed *HIV-associated neurocognitive disorders* (HAND) (1, 2) despite effective viral control through combined antiretroviral therapy (cART) (3–6). cART is designed to target multi-

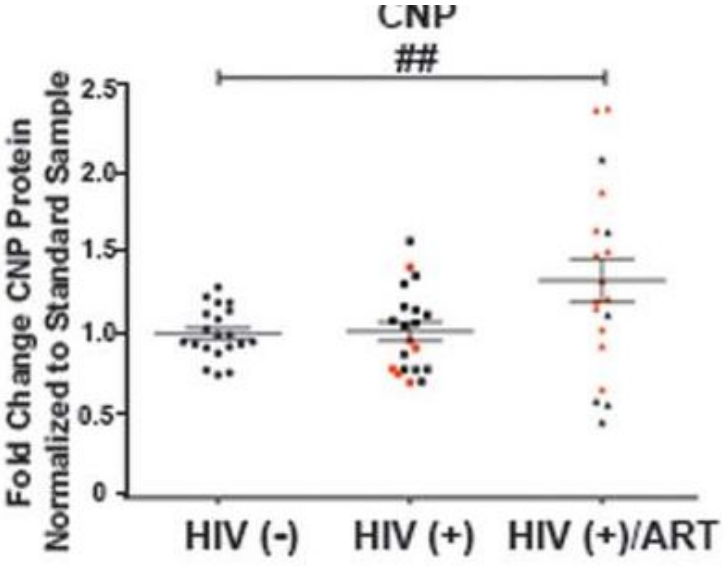
Oligodendrocyte maturation and myelin





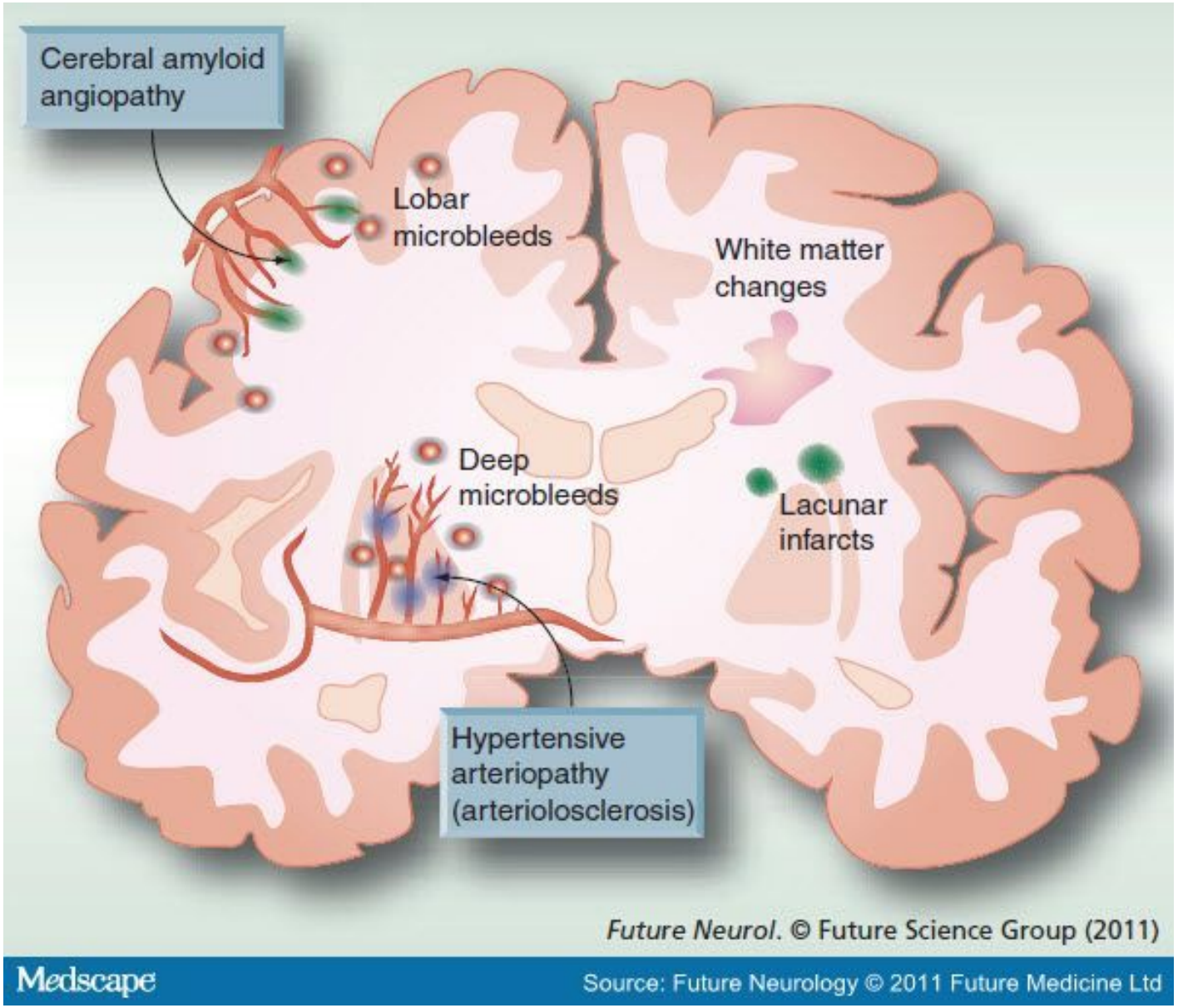
.. the immature oligodendrocyte stage marker GalC did not seem to correctly localize to the cell surface...

1. Rapidly reversible once drugs are removed
2. Oxidative stress
3. Recution in myein proteins in prefrontal cortex of patietns treated for more than 12 months before dying

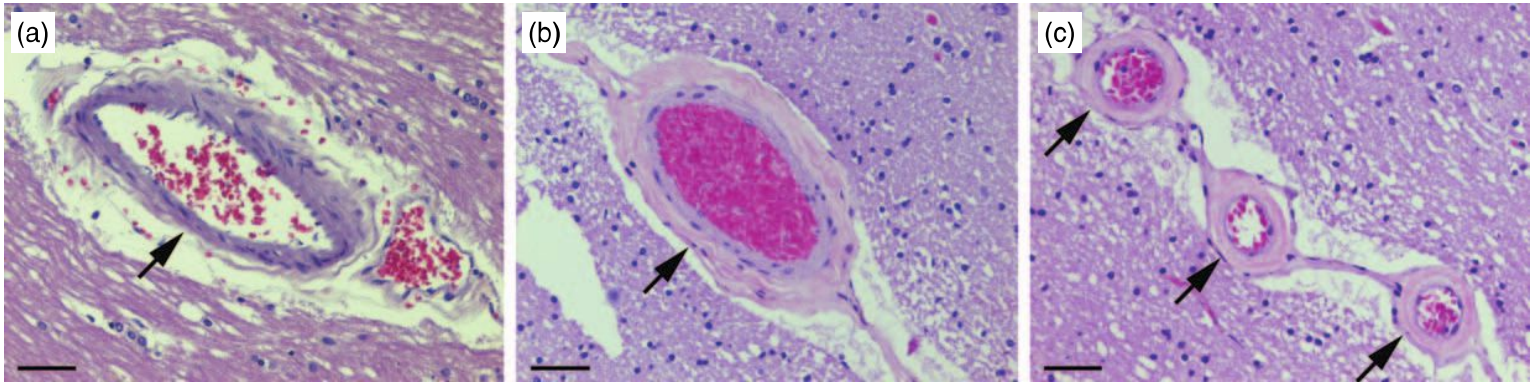


In preparation

5. INDIRECT EFFECT ON BLOOD VESSELS


Cerebral amyloid angiopathy
Lobar microbleeds
White matter changes
Deep microbleeds
Lacunar infarcts
Hypertensive arteriopathy (arteriolosclerosis)
Future Neurol. © Future Science Group (2011)
Medscape
Source: Future Neurology © 2011 Future Medicine Ltd

Cerebral Small Vessel Disease



(137 autopsies, 1999-2011)

Mild CSVD **24.8%** - moderate/severe CSVD **47.4%**

- associated with **PI-based HAARTs** and diabetes
- HAND associated with mild CSVD

Soontornniyomkij V, et al. AIDS 2014

6. EFAVIRENZ

Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients

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ABSTRACT

Background: Despite the availability of potent antiretroviral regimens (combination antiretroviral therapy [cART]), HIV-associated neurocognitive disorders (HAND) are increasingly recognized. Our aim was to investigate the prevalence and treatment-related correlates of HAND, exploring the potential neurotoxicity of antiretrovirals on cognitive functions.

Methods: We performed a cross-sectional single cohort study by consecutively enrolling asymptomatic HIV+ subjects during routine outpatient visits. Each patient was submitted to a comprehensive neuropsychological battery and was considered cognitively impaired on the basis of results obtained in matched healthy HIV-negative subjects. CNS penetration effectiveness (CPE) rank was calculated for cART regimens according to 2010 CHARTER criteria. Factors associated with cognitive impairment were investigated by linear or logistic regression analysis.

Results: A total of 146 patients were enrolled. Of these, 129 (88.4%) were on cART and 59.6% of them were on current regimen from ≥1 year. Sixty-nine patients (47%) were classified as cognitively impaired (35.6% asymptomatic and 11.6% mild neurocognitive impairment). In the multivariate analysis, efavirenz use (odds ratio [OR] = 4.00; $p = 0.008$) and non-Italian nationality (OR = 3.46; $p = 0.035$) were associated with increased risk of cognitive impairment, whereas higher education was associated with a lower risk (OR = 0.85; $p = 0.002$). Furthermore, efavirenz use and age ≥65 years independently predicted worse performance on the double barrage and the Stroop test (time). No association between CPE rank and cognitive impairment was observed.

Conclusions: A high prevalence of HAND was observed in apparently asymptomatic HIV+ individuals. HAND was associated with efavirenz use, suggesting the potential neurotoxicity of this drug. Routine neuropsychological examinations could help clinicians make correct diagnoses and manage mild, but clinically relevant, forms of HAND. *Neurology*® 2011;76:1403–1409

GLOSSARY

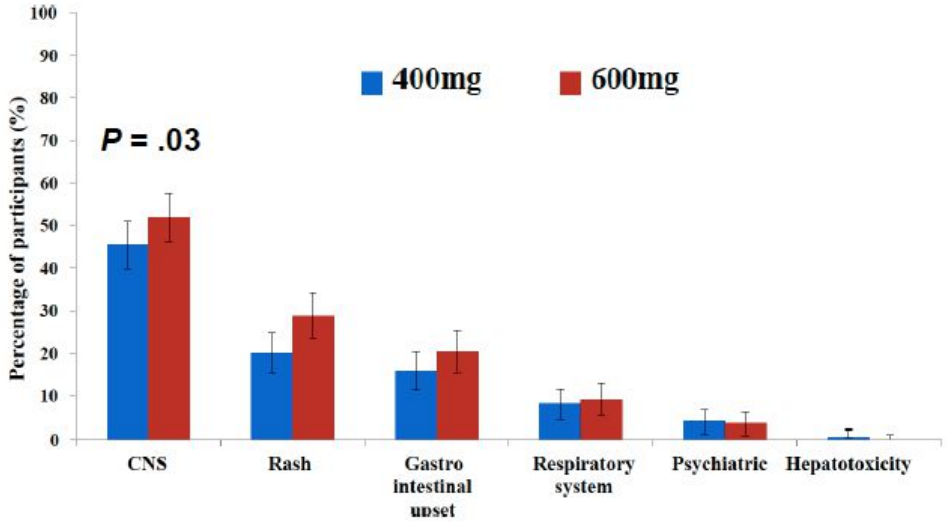
ANI = asymptomatic neurocognitive impairment; **cART** = combination antiretroviral therapy; **CI** = confidence interval; **CPE** = CNS penetration effectiveness; **HAD** = HIV-associated dementia; **HAND** = HIV-associated neurocognitive disorders; **HCV** = hepatitis C virus; **IADL** = Instrumental Activities of Daily Living; **MMSE** = Mini-Mental State Examination; **MND** = mild neurocognitive disorder; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **OR** = odds ratio; **WAIS** = Wechsler Adult Intelligence Scale.

Although the incidence of HIV-associated dementia (HAD) has significantly decreased in the era of potent combination antiretroviral therapy (cART),[1] the incidence and prevalence of milder forms of HAND have remained relatively stable,[2] suggesting that the treatment of CNS infections might be suboptimal in a high proportion of patients. Moreover, the longer lifespan of patients with HIV, as a consequence of cART, together with older age at seroconversion might contribute to increasing the risk of neurodegeneration.[3]

The sustained prevalence of HAND might also be due to drug resistance, poor adherence, and poor CNS penetration of some antiretroviral agents.[4] Several studies have shown that better penetration of antiretroviral drugs in the CNS, as estimated by the proposed CNS penetration effective-

EFV dose and NP symptoms

- Dose reductions (either TDM or PG/TDM based) were associated with improvements in neuropsychiatric symptoms
- PG (CYP2B6, CAR) associated with symptoms, drug discontinuation and suicidaility
- ENCORE1: 400 mg EFV associated with fewer CNS adverse events vs. 600 mg
- Single-dose EFV: PK and PG association with Grooved pegboard



Haas et al. AIDS 2004; Gatanaga et al., CID 2011; Wyen C et al J Antimicrob Chemother 2011; Ciccarelli et al., Neurology 2011; Johnson et al. BJCP 2012; Winston A, et al. CID 2015; Mollan KR, et al. IAS 2015; Johnson DH, et al. BJCP 2012

EFV/8-OH EFV and NC performances

8-OH EFV showed in vitro direct neurotoxicity

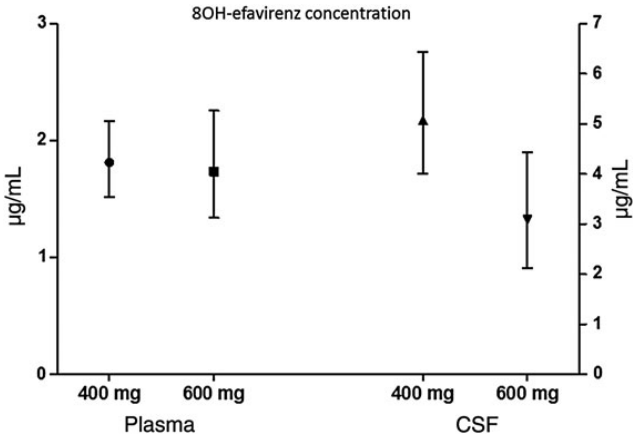
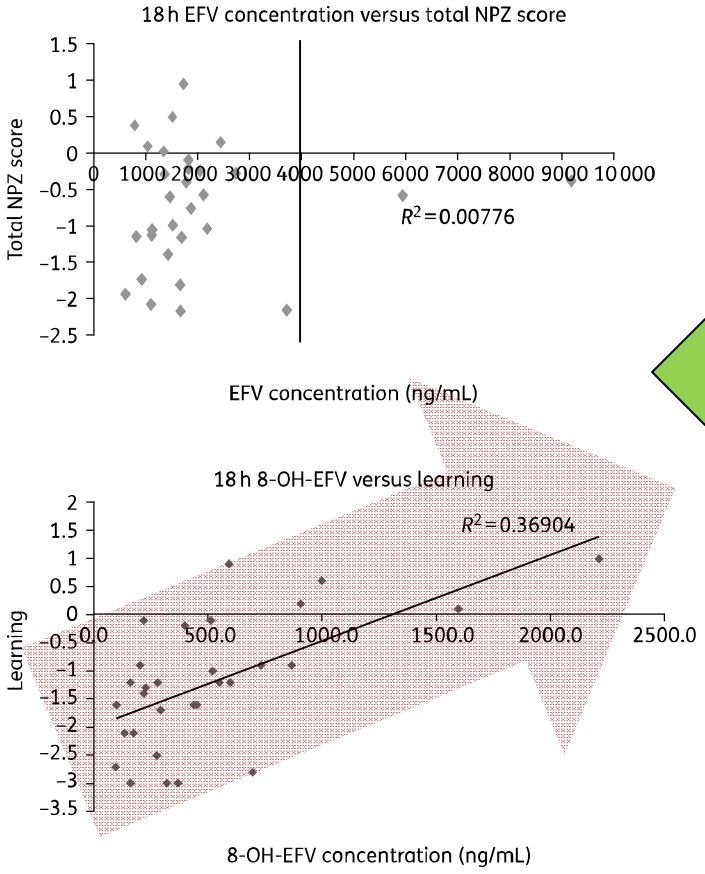


Table 4. Correlation Between Cerebrospinal Fluid 8-Hydroxy Efavirenz Exposure and Patient-Completed Questionnaires

Parameter	Week	Spearman Correlation Coefficient	*P* Value
DASS-Depression	48	0.20	.31
DASS-Anxiety	48	0.11	.58
DASS-Stress	48	0.38	.04
ESQ	4	−0.43	.02
ESQ	48	0.13	.05
SF-12-Physical score	48	0.13	.50
SF-12-Mental score	48	−0.38	.05

Abbreviations: DASS, Depression Anxiety Stress Scales; ESQ, efavirenz symptom questionnaire; SF-12, 12-item short form.

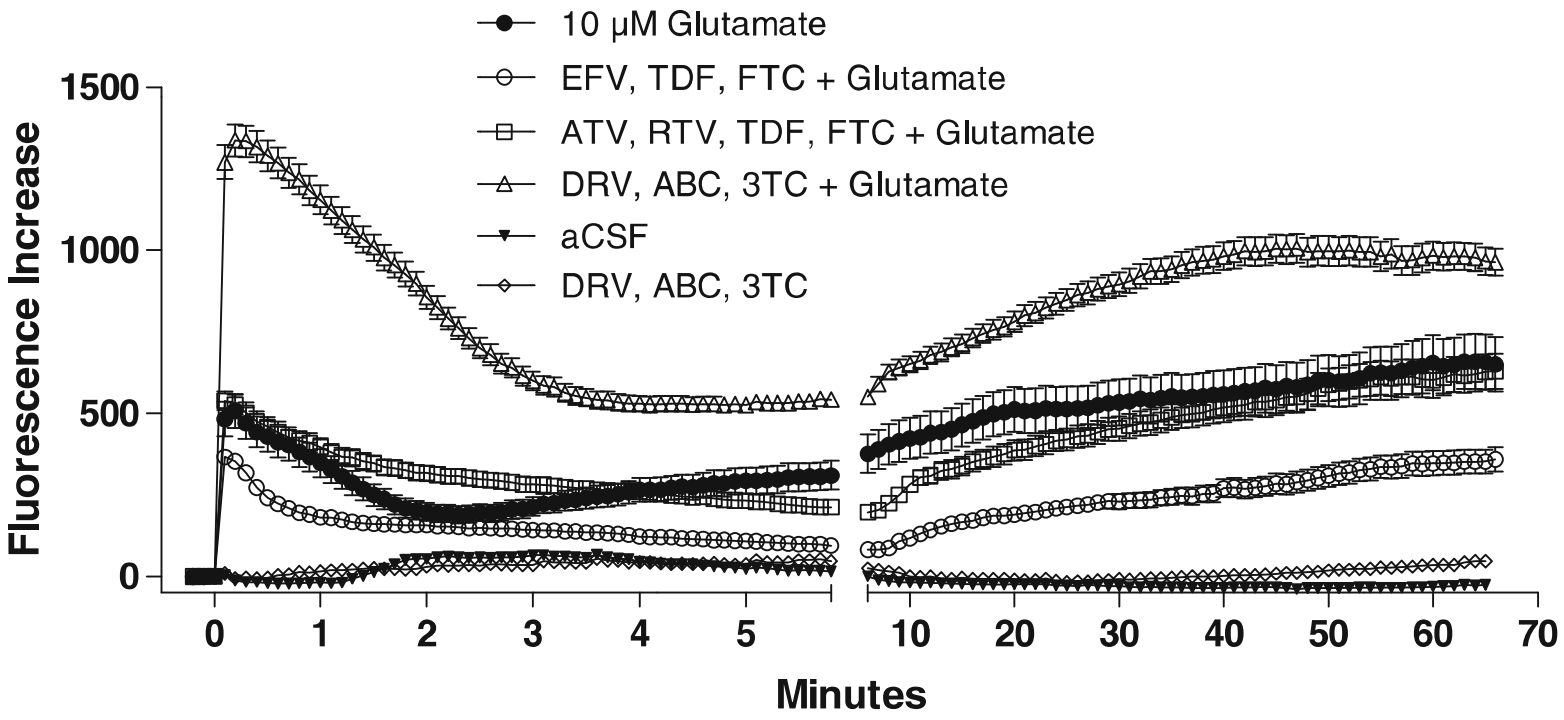


Differential expression of CYP 2B6 in liver and hippocampus in rats exposed to EFV

Tovar-y-Romo LB, et al. J Pharmacol Exp Ther 2012 ; Winston A, et al. CID 2015; Sandkovski U, et al. JAC 2017; Grilo NM, Eur J harm Sciences 2017

7. INTERFERENCE WITH NEUROTRANSMITTERS?

Sensitivity to glutamate effect?

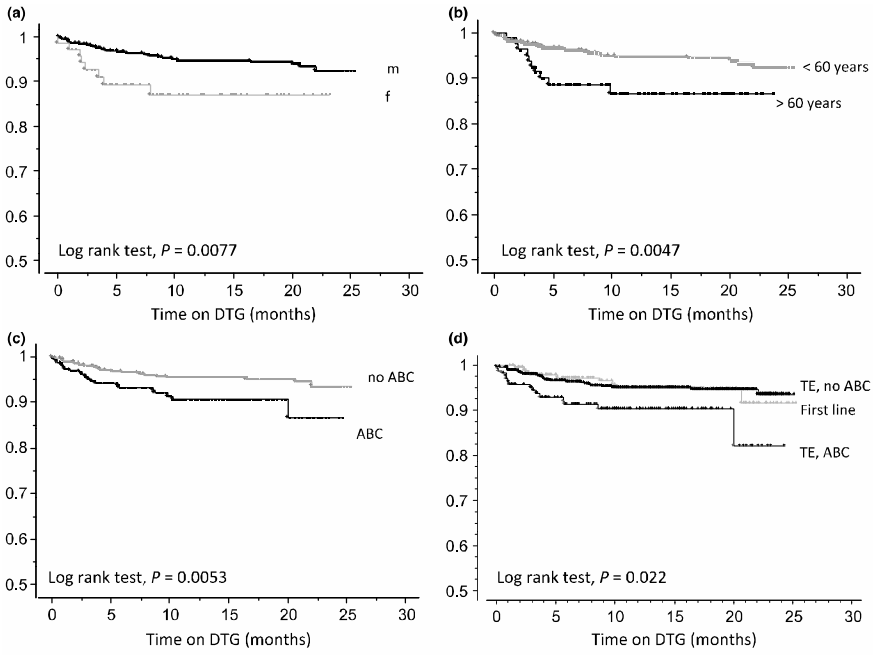


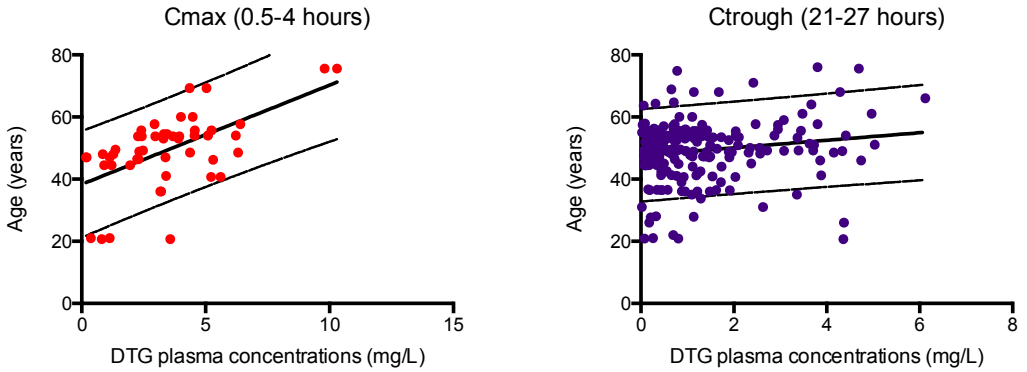
Robertson K, et al. JNV 2012

Dolutegravir and NP symptoms

- Contrasting data on DTG neuropsychiatric side effects
  - no signal in RCTs
  - higher incidence in SINGLE (vs. efavirenz)
  - higher incidence in some but not all observational studies: mild and reversible

- Higher incidence of CNS effects in patients on concomitant **abacavir, female and older subjects**

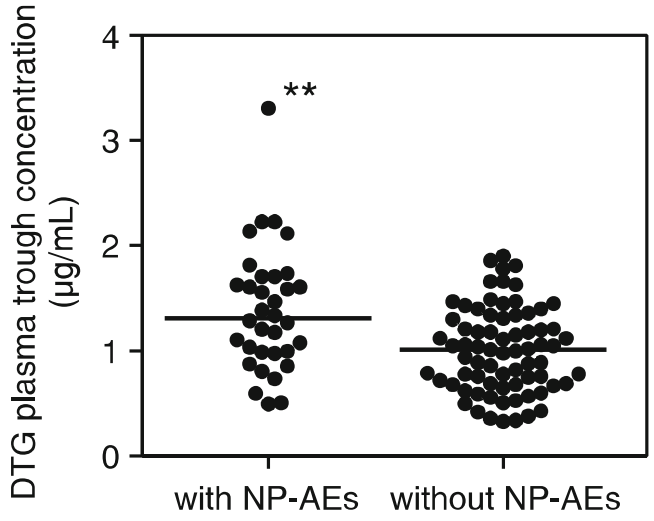




De Boer MG, AIDS 2016; Hoffman C, et al. HIV Medicine 2017; Fettiplace A, et al. JAIDS 2016; Bonfanti P, et al. AIDS 2017

Dolutegravir **PK** and NP symptoms

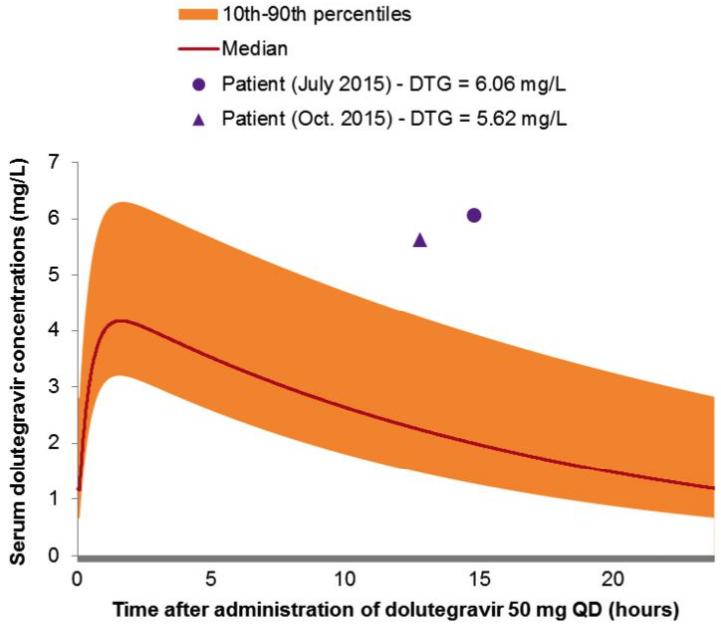
- ✓Higher DTG Ctrough in patients with symptoms
- ✓High DTG Ctrough in patients discontinuing (1719 ng/mL)



Yagura H, et al. BMC Inf Dis 2017; Menard A, et al. AIDS 2017; Parant F, et al. Current Drug Safety 2018; Elliot E, et al. IWCPHT 2017; Borghetti A, et al. ICAR 2017; Hoffmann C, et al. CROI 2018 #424

Dolutegravir PK and NP symptoms

- ✓Higher DTG Ctrough in patients with symptoms
- ✓High DTG Ctrough in patients discontinuing (1719 ng/mL)
- ✓Symptoms disappearance with DTG every other day (in a low BMI patient)



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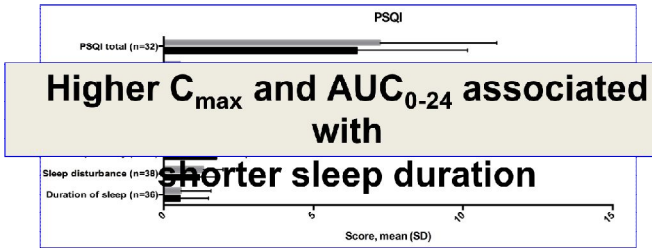
- ✓Symptoms disappearance with DTG every other day (in a low BMI patient)
- ✓Higher DTG Cmax and AUC in older subjects associated to shorter sleep duration

Results: Pittsburgh Sleep Quality Index



Higher C_{max} and AUC_{0-24} associated with shorter sleep duration

PSQI	Spearman correlation coefficient, p-value		
	C_{max}	C_{min}	AUC_{0-24}
Duration of sleep (n=36)	**0.330 (0.05)**	0.065 (0.71)	**0.353 (0.03)**
Sleep disturbance (n=38)	-0.100 (0.55)	0.077 (0.65)	-0.121 (0.47)
Sleep latency (n=37)	-0.247 (0.14)	0.036 (0.83)	-0.053 (0.75)
Day dysfunction (n=37)	-0.181 (0.28)	-0.200 (0.24)	-0.205 (0.22)
Sleep efficiency (n=35)	0.120 (0.49)	-0.136 (0.44)	0.032 (0.86)
Sleep quality (n=38)	-0.212 (0.20)	-0.153 (0.36)	0.207 (0.21)
Medication (n=37)	0.016 (0.92)	0.036 (0.83)	0.021 (0.90)
PSQI total (n=32)	0.074 (0.69)	-0.207 (0.26)	-0.042 (0.82)

Yagura H, et al. BMC Inf Dis 2017; Menard A, et al. AIDS 2017; Parant F, et al. Current Drug Safety 2018; Elliot E, et al. IWCPHT 2017; Borghetti A, et al. ICAR 2017; Hoffmann C, et al. CROI 2018 #424

Dolutegravir **PK** and NP symptoms

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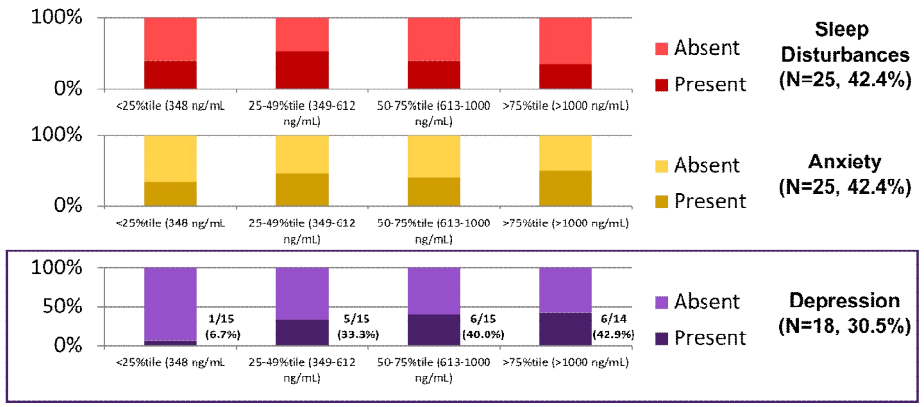
- ✓High DTG Ctrough in patients discontinuing (1719 ng/mL)
- ✓Symptoms disappearance with DTG every other day (in a low BMI patient)
- ✓Higher DTG Cmax and AUC in older subjects associated to shorter sleep duration
- ✓More depressive symptoms in the highest DTG Ctrough quartile



Yagura H, et al. BMC Inf Dis 2017; Menard A, et al. AIDS 2017; Parant F, et al. Current Drug Safety 2018; Elliot E, et al. IWCPHT 2017; Borghetti A, et al. ICAR 2017; Hoffmann C, et al. CROI 2018 #424

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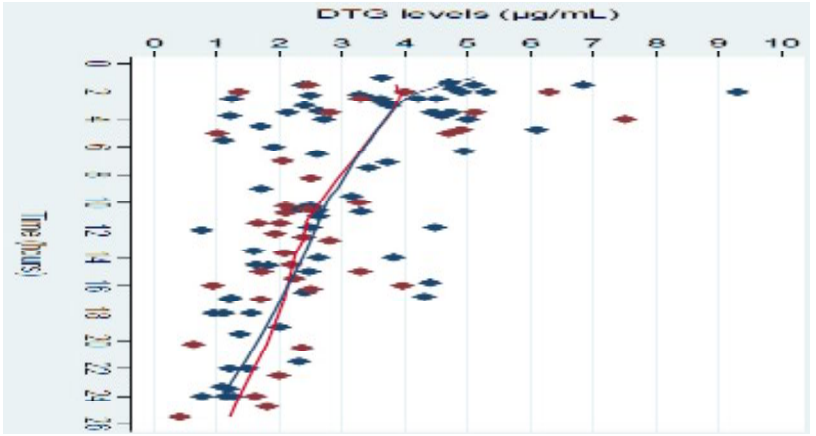
- ✓High DTG Ctrough in patients discontinuing (1719 ng/mL)
- ✓Symptoms disappearance with DTG every other day (in a low BMI patient)
- ✓Higher DTG Cmax and AUC in older subjects associated to shorter sleep duration
- ✓More depressive symptoms in the highest DTG Ctrough quartile
- ⤮ No effect of PK on DTG discontinuation for NPAEs



Yagura H, et al. BMC Inf Dis 2017; Menard A, et al. AIDS 2017; Parant F, et al. Current Drug Safety 2018; Elliot E, et al. IWCPHT 2017; Borghetti A, et al. ICAR 2017; Hoffmann C, et al. CROI 2018 #424

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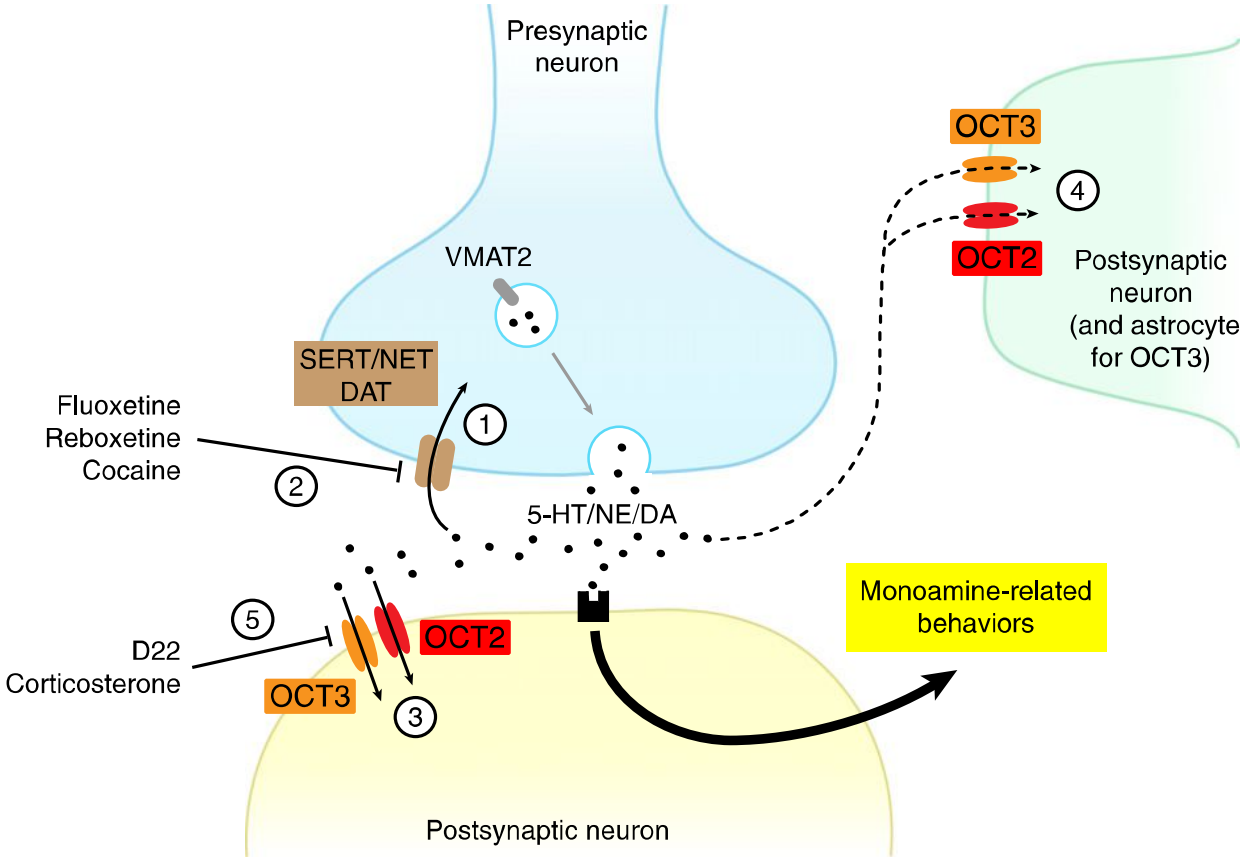
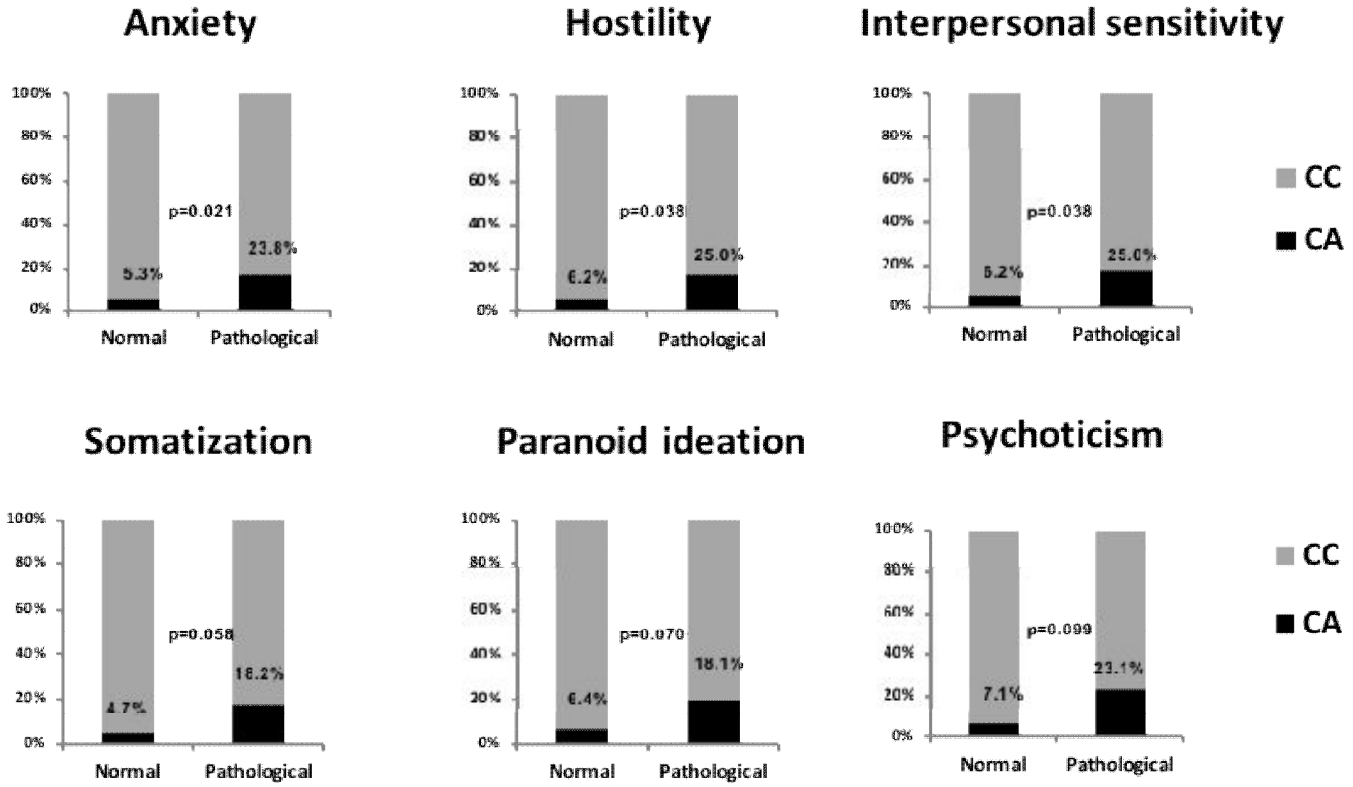


Couroussè T and Gautron S, Pharmacology and Therapeutics 2015

Dolutegravir PG and NP symptoms

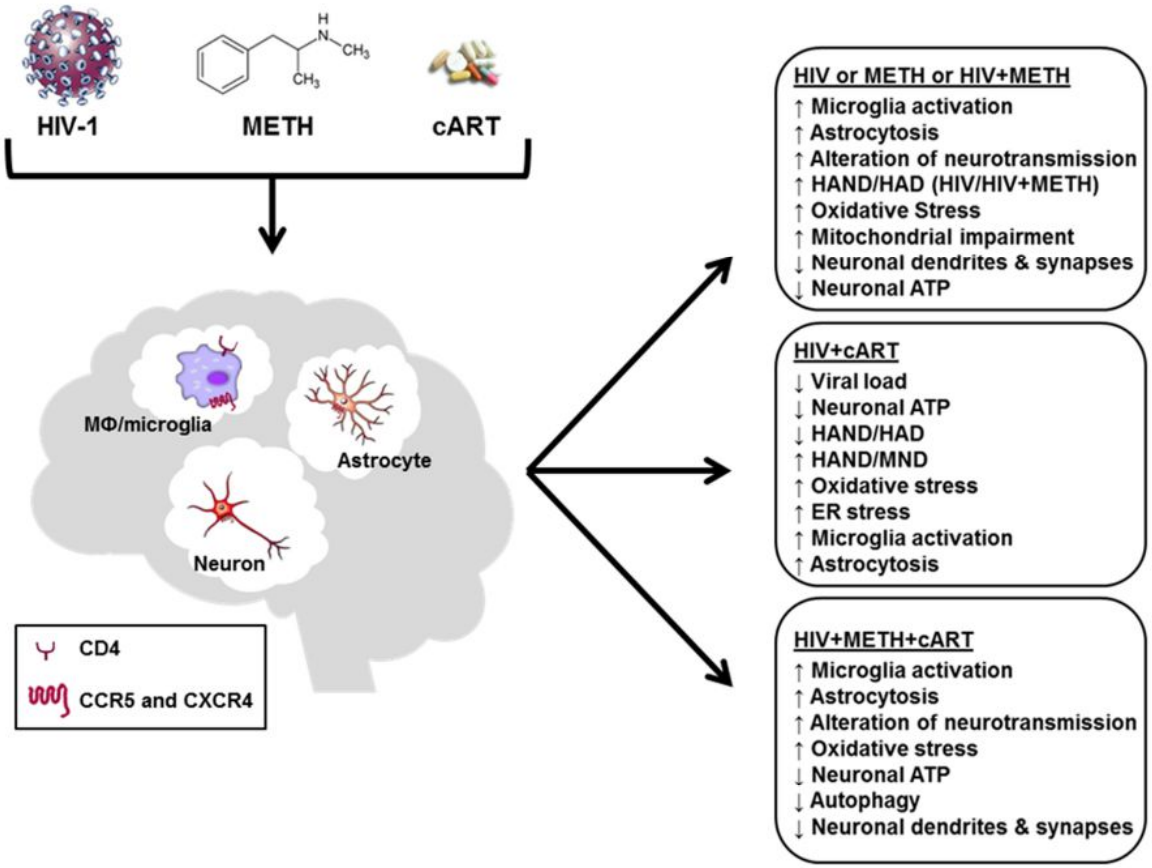
- No effect of DTG Cmax
- DTG Ctrough and *SLC22A2* C/A variants associated with NP symptoms at multivariate analysis



Borghetti A, et al. IWCPHT 2018

*. OTHER AFFECTING VARIABLES

Modifiers

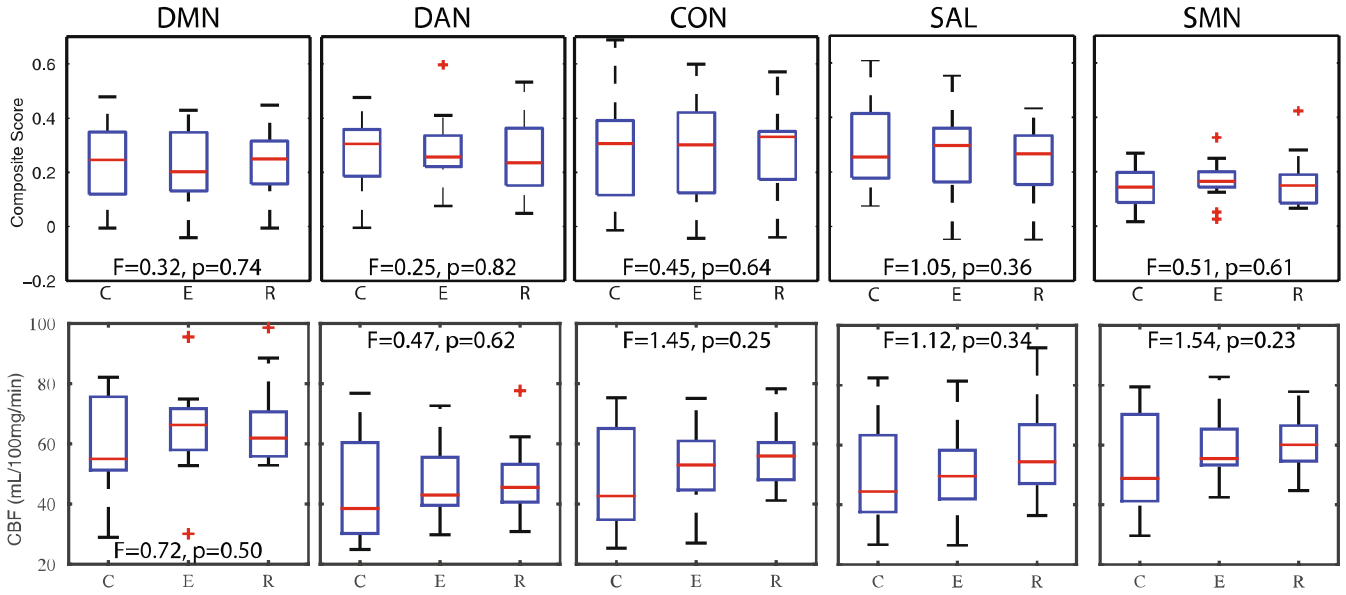


- Age effect (PK, BBB, Vascular)
- Viral proteins
- Concomitant drugs → effect
- PgP inhibitors: dose?
- Genetics

Sanchez AB and Kaul M, Brain Sci 2017

Neurotoxicity in HIV- patients?

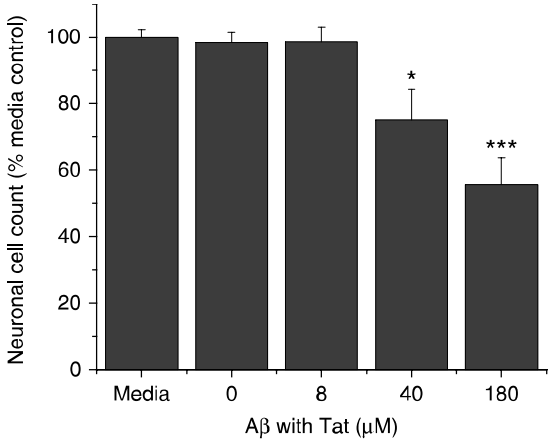
- 11 healthy volunteers
- three days of RTV or EFV (3 weeks washout)
- rs-fMRI: no effect on functional connectivity and cerebral blood flow

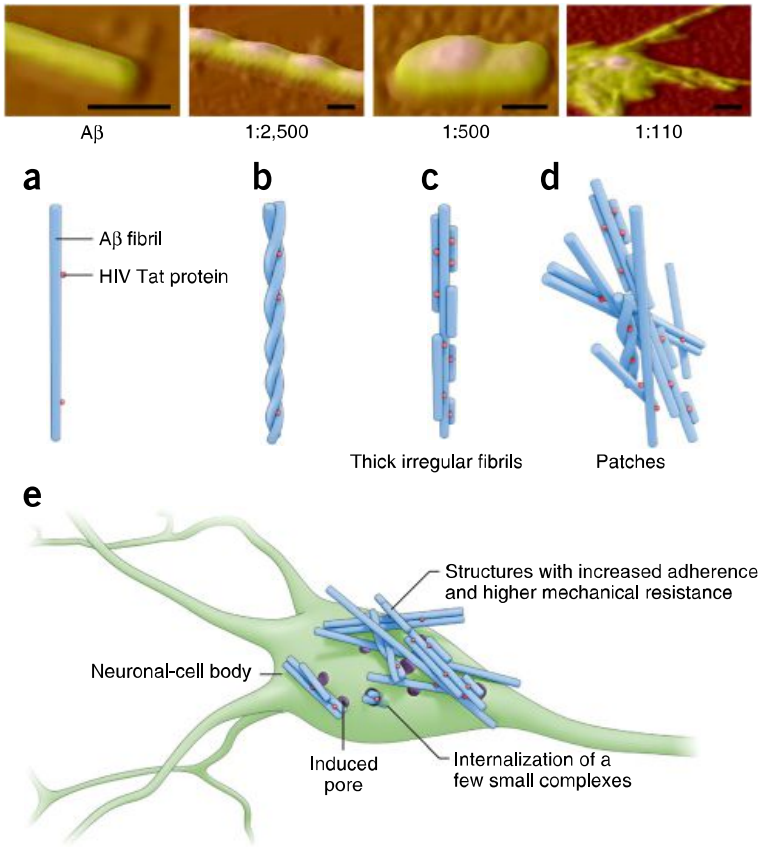


Brier MR, et al. JNP 2015

TAT and amyloid fibrils

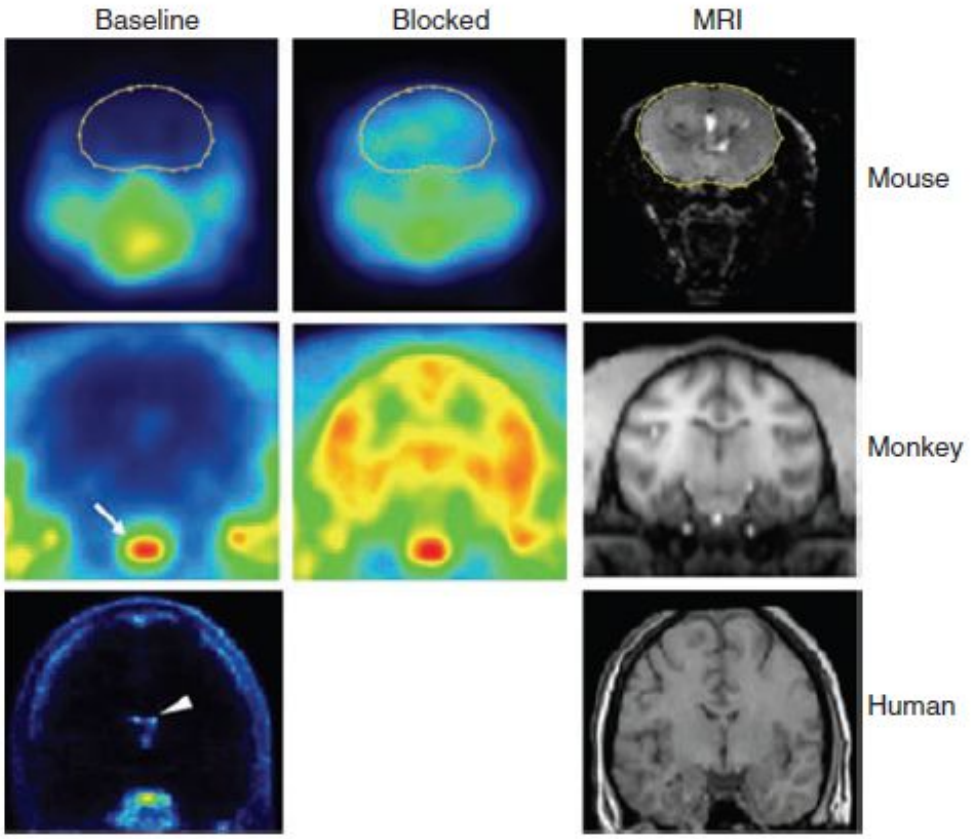
- **TAT increases:**
  - beta-sheets formation
  - fibrils aggregation
  - Alpha fibrils rigidity
  - **TAT/fibrils neuronal toxicity**

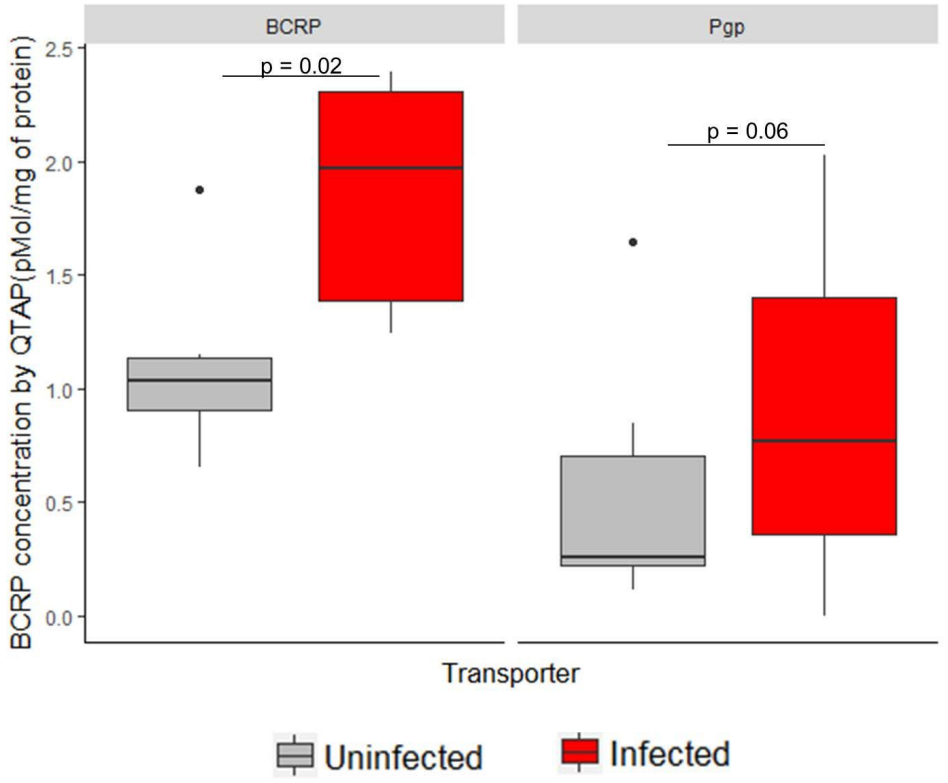




Hategan A, et al. Nature Struct & Molec Biology 2017

Brain parenchyma concentrations





Kannan P, et al. Clinical Pharm and Ther 2009; Srinivas et al, IAS 2017, Abstract WEAB0105

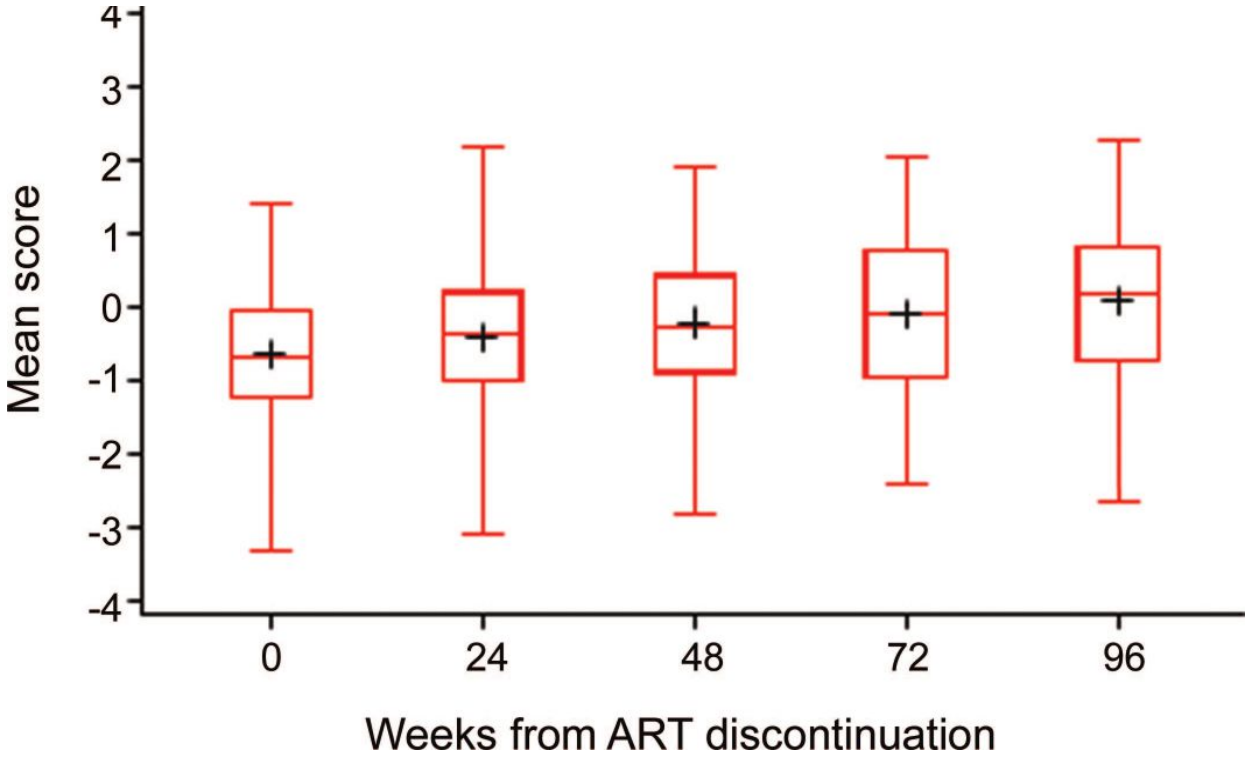
Polypharmacy and P-glycoprotein

Substrates	Inhibitors	Inducers
actinomycin D	amiodarone	ASA
aldosterone	atorvastatin	cisplatin
alpha-methyldigoxin	azithromycin /clarithromycin	cyclosporine
amiloride	carbamazepine	dexamethasone
amitriptyline	carvedilol	erythromycin
amoxicillin	chloroquine	insulin
amprenavir	Tacrolimus/cyclosporin ++	nifedipine
atorvastatin	verapamil ++/diltiazem	phenobarbital
beta-acetyldigoxin	fenofibrate	phenytoin
bisantrene	fluoxetine /paroxetina	rifampin
bunitrolol	grapefruit juice	St. John's Wort
carbamazepine	garlic	tacrolimus
celiprolol	green t ea (catechins)	tamoxifen
cetirizine	ivermectin	verapamil
chloroquine	Lanso/ome/pantoprazolo	
chlorpromazine	loperamide	
cimetidine	progesterone	
citalopram	tamoxifen ++	

*. CLINICAL DATA AND MANAGEMENT

NP improvement in treatment discontinuation

- 167 pts with CD4>350, HIV RNA <55000 copies/mL
- Elected to discontinue HAART
- Trail Making (A/B) and Digit Symbol mostly
- Greater benefit in those stopping EFV

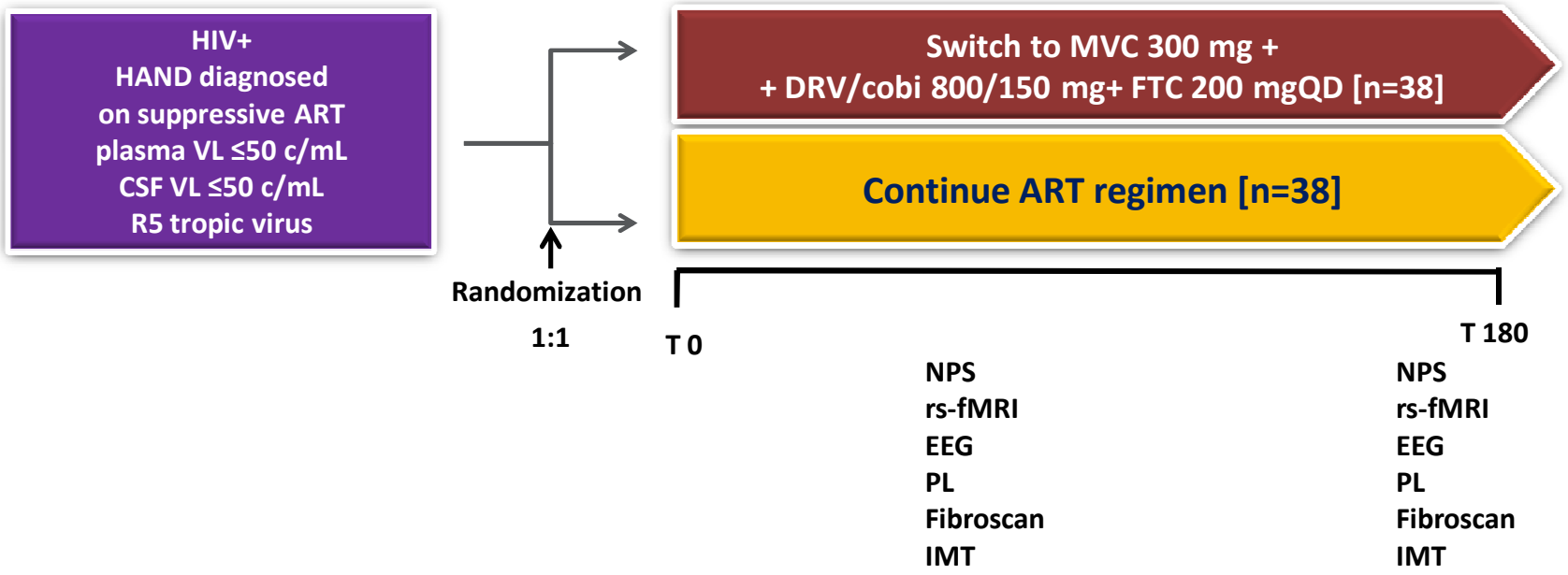


Robertson K, et al. Neurology 2010


BAD
Well, that's not
a good sign.

MARAND X

Single-centre, open-label, randomised pilot study of 180 days duration



Conclusions

- The benefits of HAART on CNS HIV infection are predominant
- Potential harm of certain drugs
  - So far tenofovir (TAF?), emtricitabine, darunavir (but boosters may have some effect) and maraviroc are the drugs with the least neurotoxic profile *in vitro*
- Different mechanisms to be studied and also different ways of assessing/monitoring
- The clinical relevance of neurotoxicity of “modern” Arvs needs to be accurately assessed

Thanks for your attention!