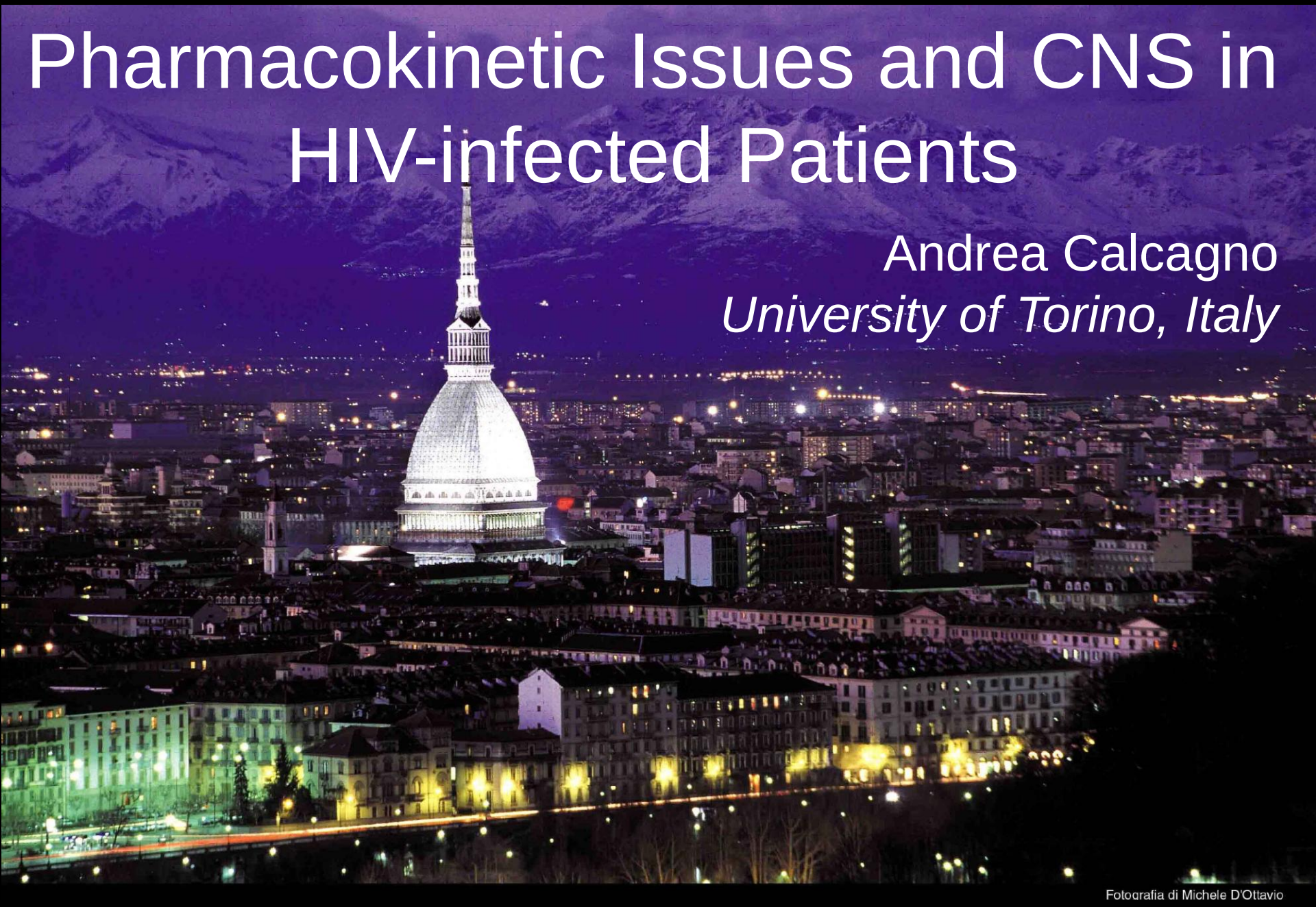
Pharmacokinetic Issues and CNS in HIV-infected Patients

Andrea Calcagno
University of Torino, Italy

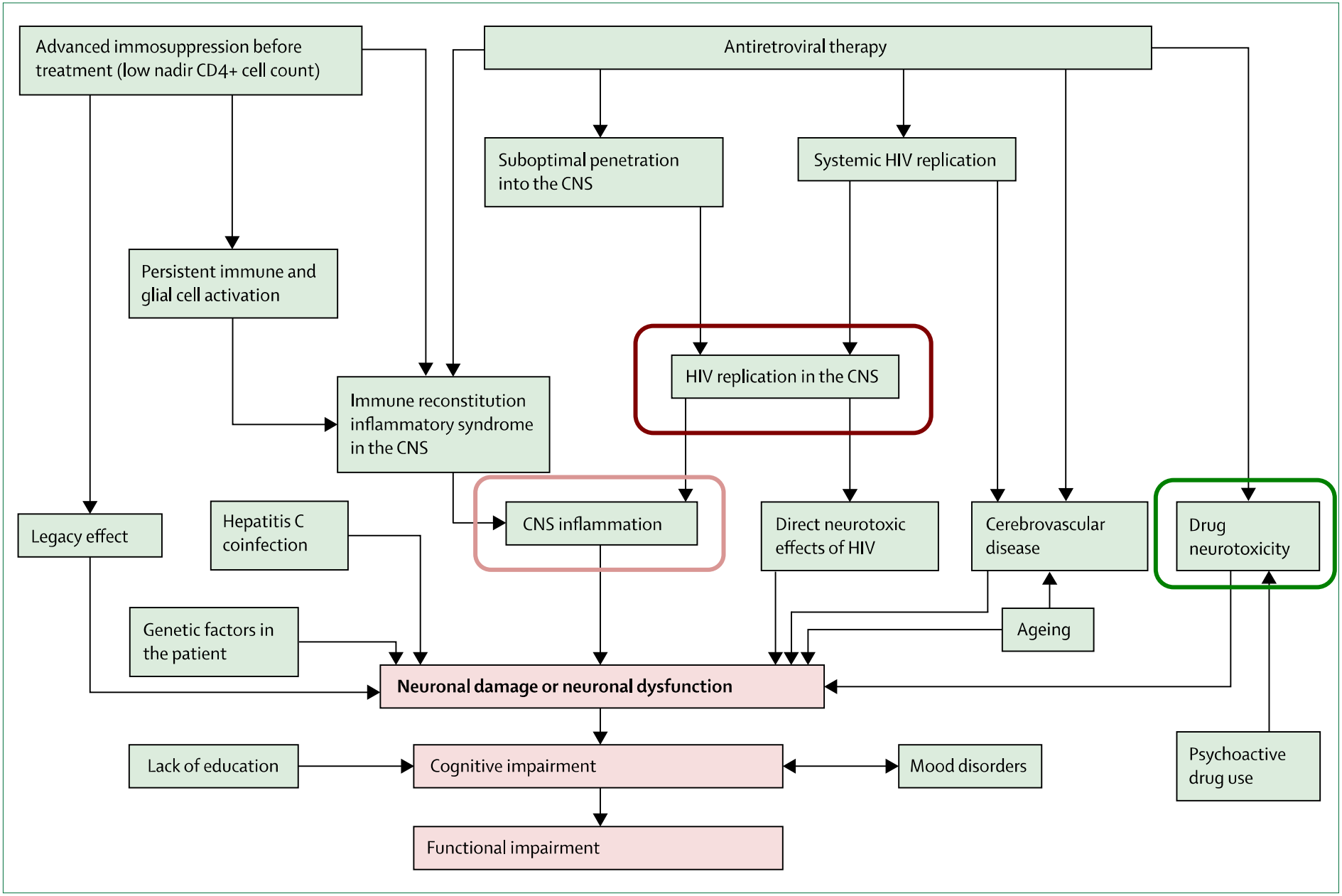


Fotografia di Michele D'Ottavio

10th Symposium on Neuropsychiatry and HIV – Barcelona 26-28 May 2017

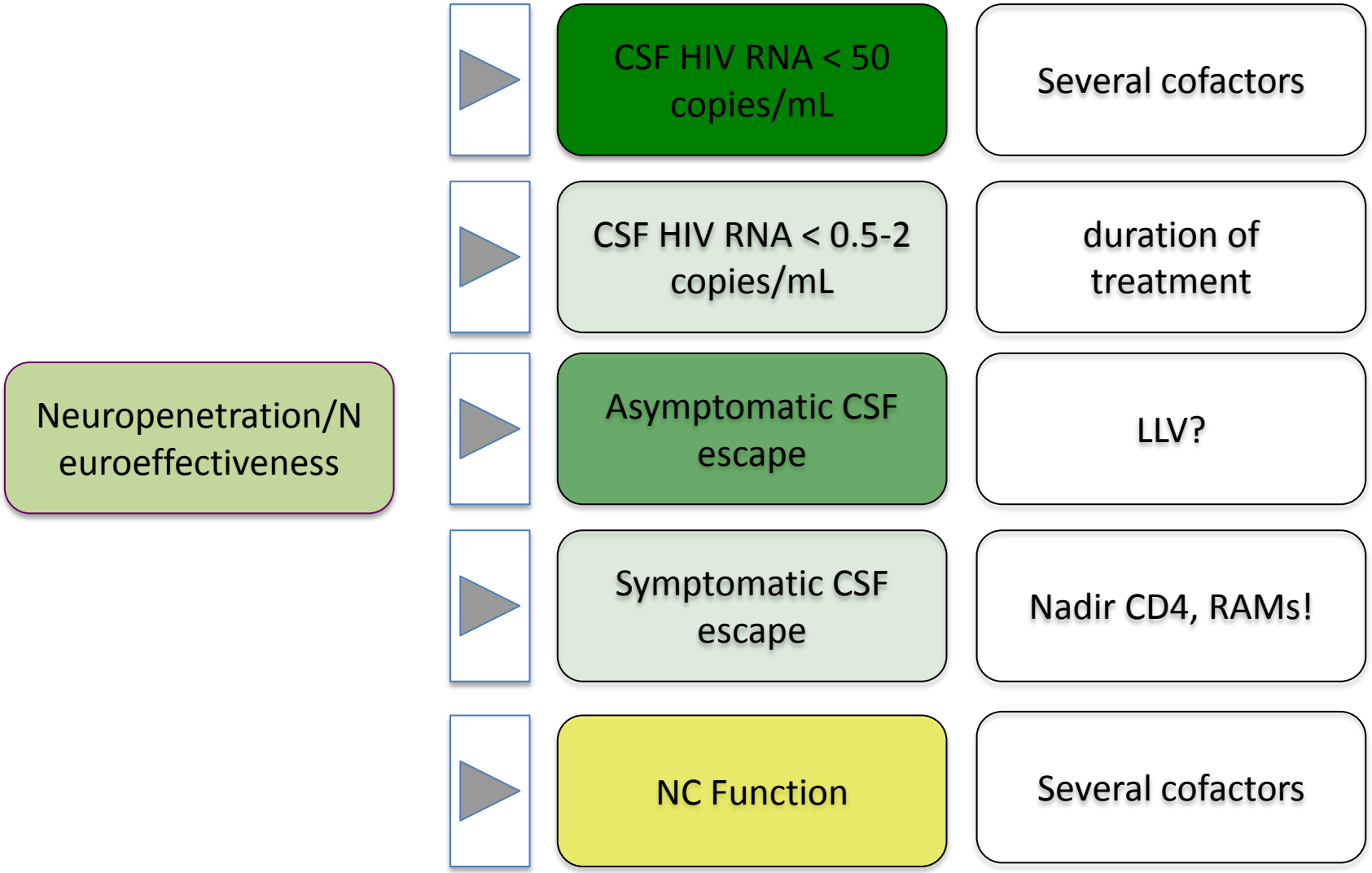
Outline

1. Pharmacokinetics and the CNS
   - The CSF/brain PK?
   - Determinants of ARVs' passage into the CSF
   - New drugs
2. PK and antiretrovirals' efficacy in the CNS
   - CPE and other "scores" → CSF HIV RNA/NC
   - ARVs' strategies→CSF HIV RNA/NC
3. PK and Neurotoxicity?

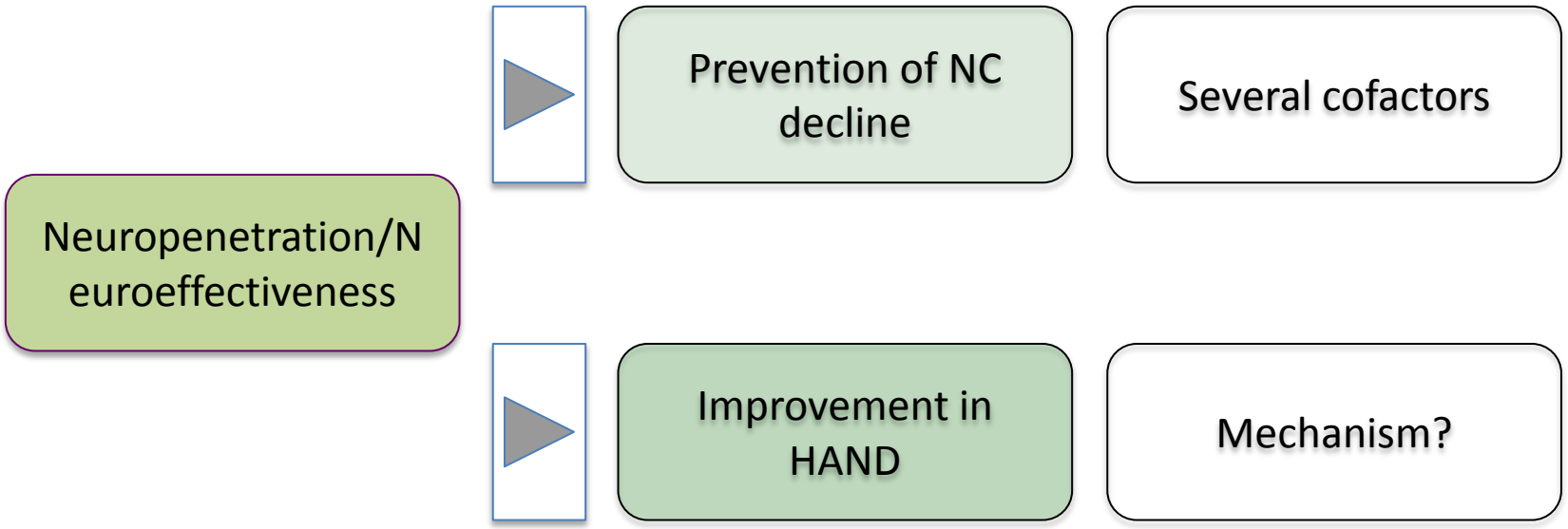


Nightingale S, et al. Lancet Neurology 2014

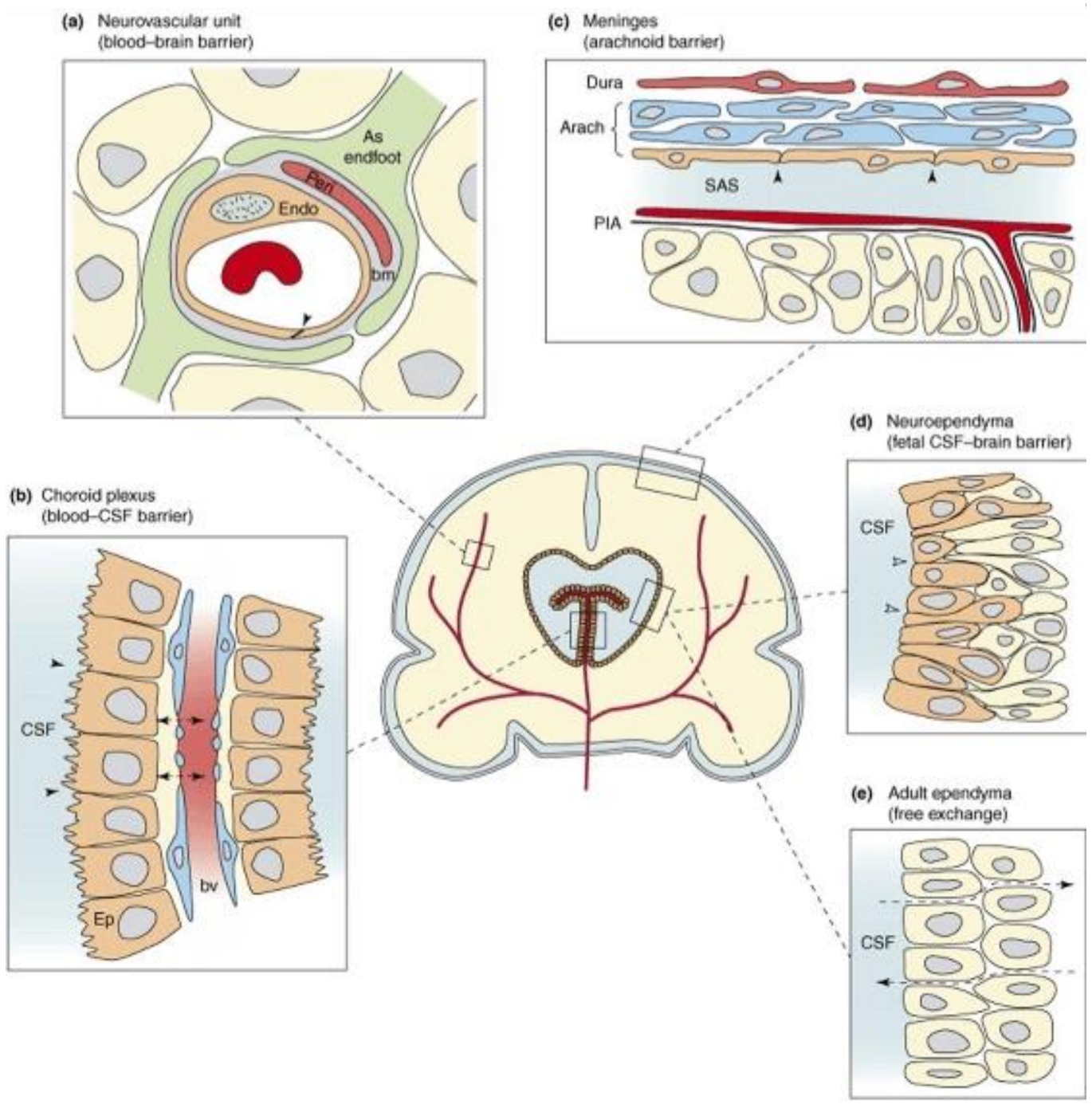
Summary of PK and CSF/CNS outcomes



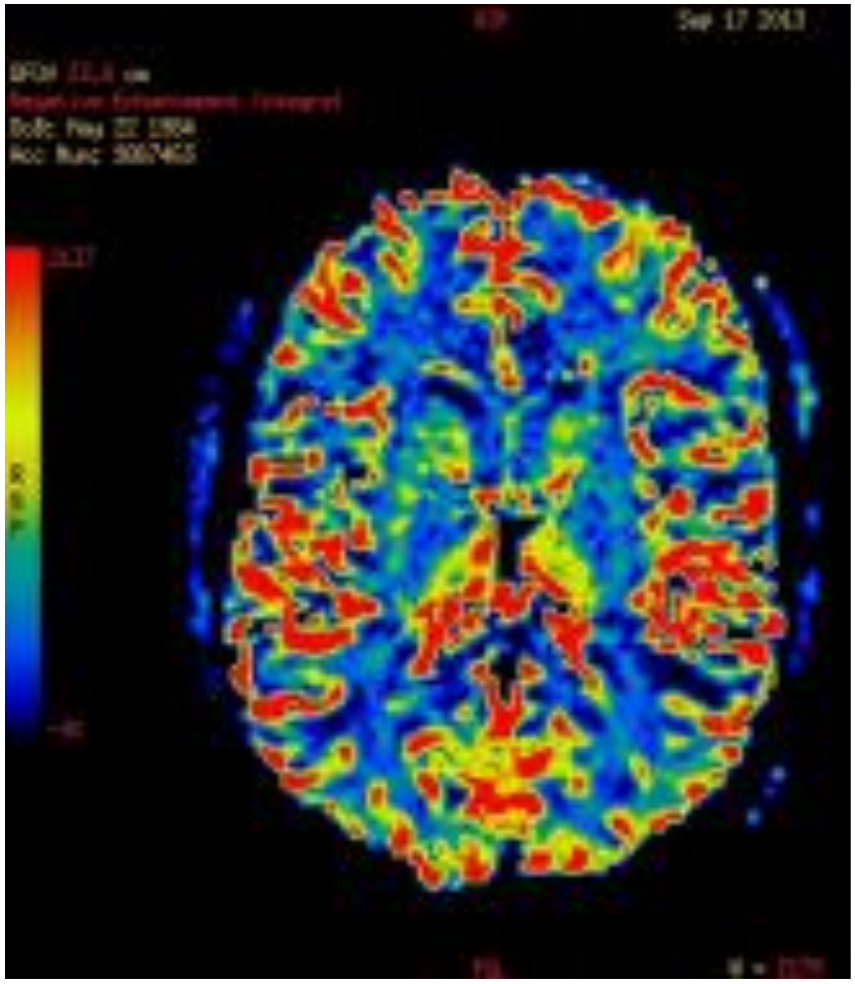
Summary of PK and CSF/CNS outcomes

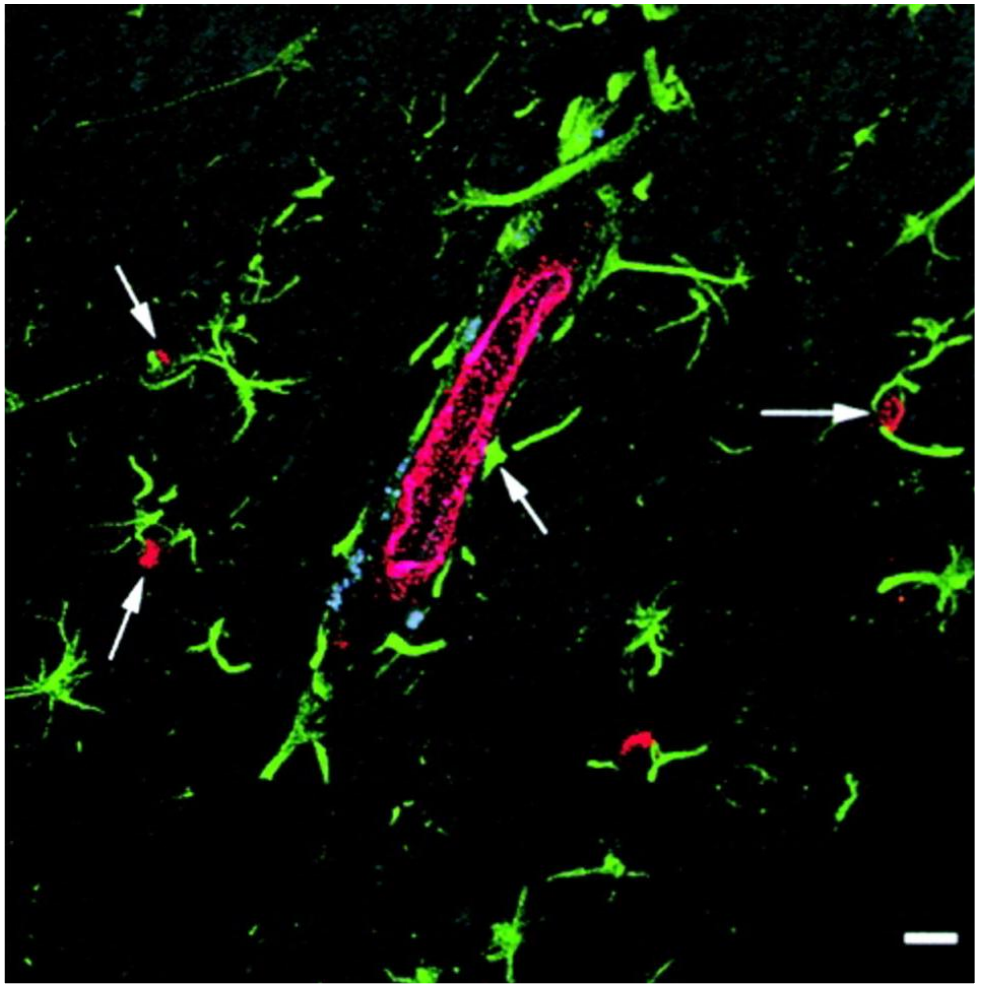


PK and the CNS


(a) Neurovascular unit
(blood–brain barrier)
As
endfoot
Peri
Endo
bm
(c) Meninges
(arachnoid barrier)
Dura
Arach
SAS
PIA
(b) Choroid plexus
(blood–CSF barrier)
CSF
bv
Ep
(d) Neuroependyma
(fetal CSF–brain barrier)
CSF
(e) Adult ependyma
(free exchange)
CSF

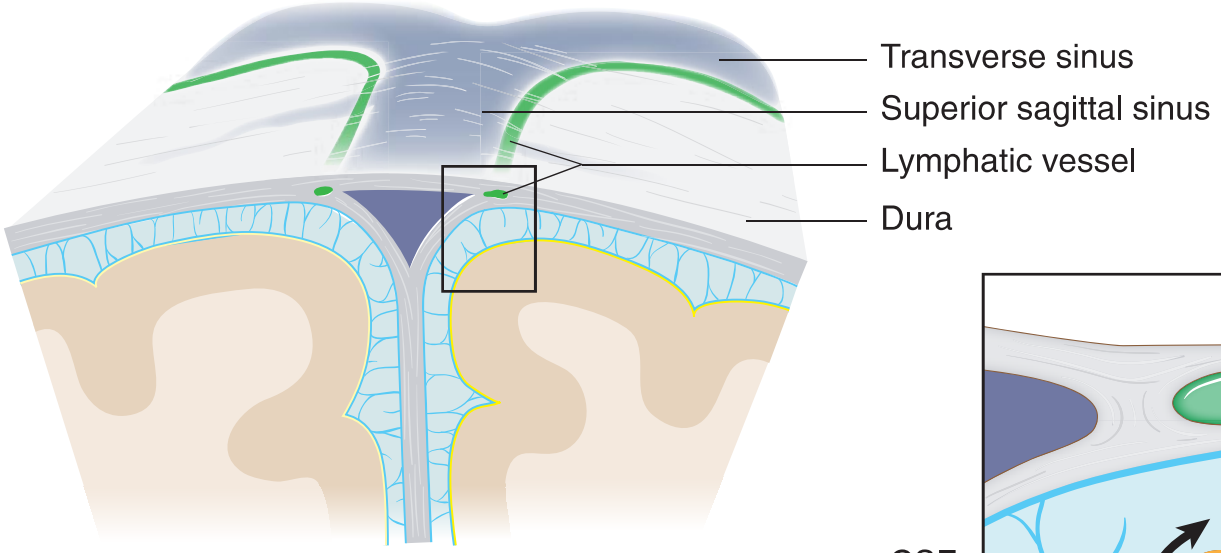
Penetrazione omogenea?

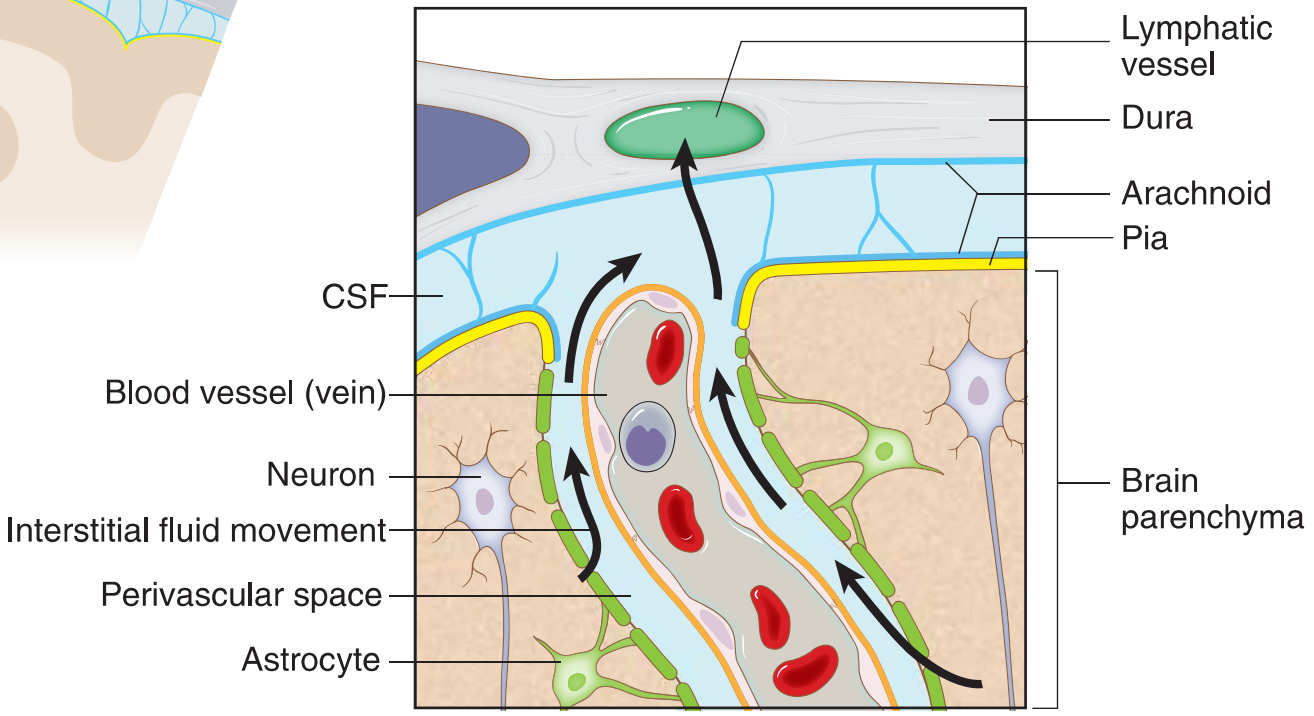




1. www.istockphoto.com 2. Williams K C et al. J Exp Med 2001.

Brain “Functional” Lymphatic Vessels



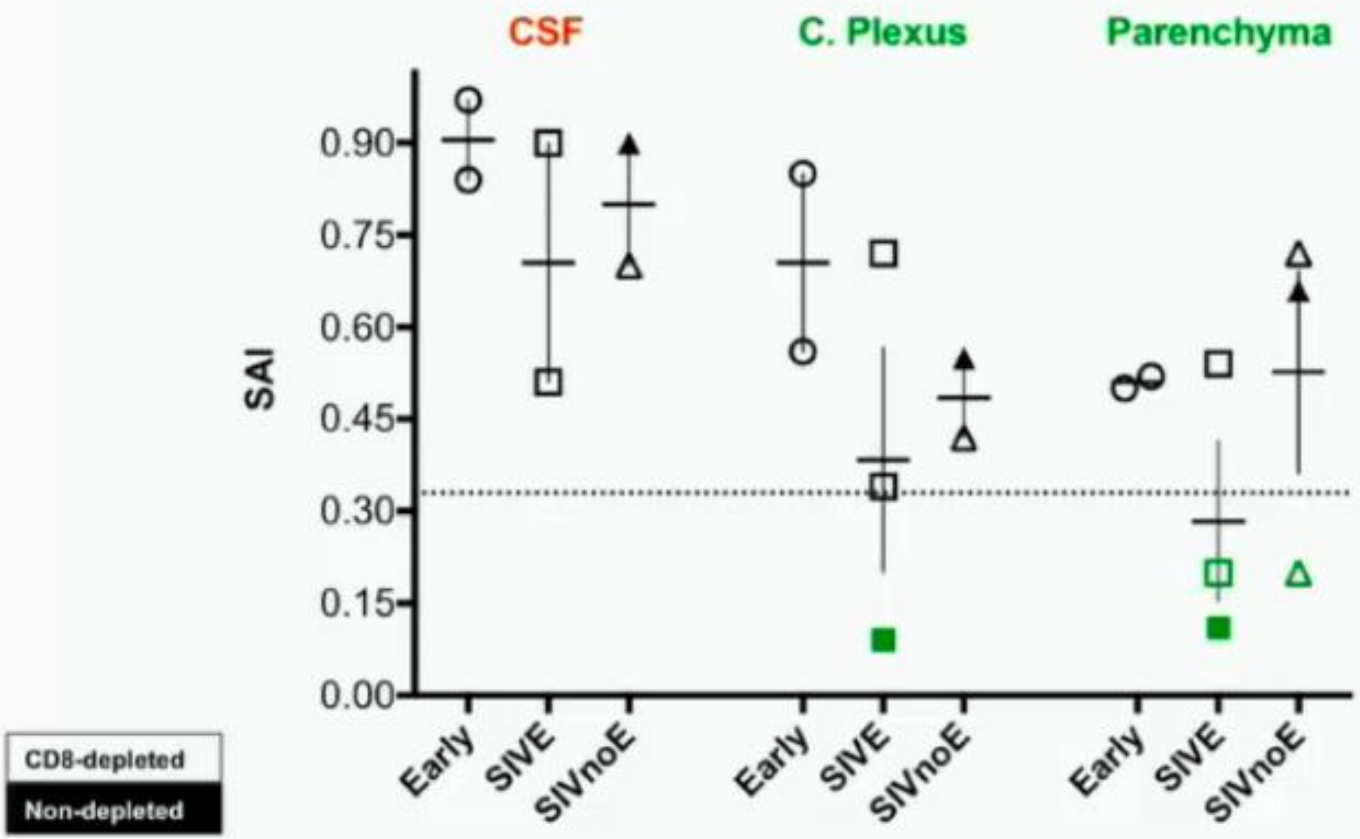


RRansohoff RM, et al. Nat Rev Immunol. 2003, Louveau et al. Nature 2015

Cerebrospinal fluid vs. brain tissue

Brain and Choroid P vs. CSF

- Simmons Association Index (SAI) – Degree of a phylogenetic population structure
  - SAI ≤ 0.33 ⟶ compartmentalized population [Wang, *et al., J. Virol* 2001]



Mallard J, et al. CROI 2017 O69

Methodological issues in measuring CNS PK

1. Drug concentration in tissue homogenates: average conc in different CNS compartments→ preparation and measurments

2. Microdialysis: extracellular space (but availability and differences with different molecules)

CSF PK → Brain PK

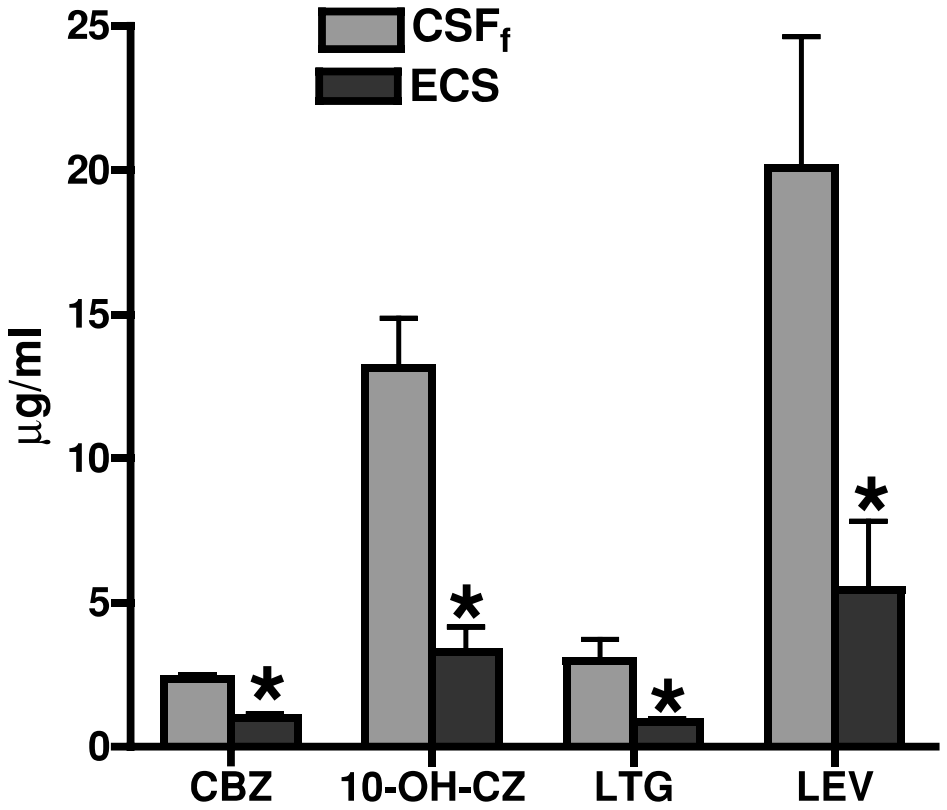
Compound	Homogen	*CSF*	*Plasma UNB*
Carbamazepine	**2**	**1**	**1**
Citalopram	**1**	**1**	**1**
Ganciclovir	**2**	**1**	**14**
Metoclopramide	**1**	**1**	**3**
Desmethylclozapine	**1**	**1**	**6**
Quinidine	**3**	**2**	**6**
Risperidone	**2**	**2**	**2**
9-OH-Risperidone	**2**	**5**	**9**
Thiopental	**4**	**1**	**1**

Liu, X., et al. Drug Metab. Dispos 2009. 37:787–793.

CSF PK → ECF PK

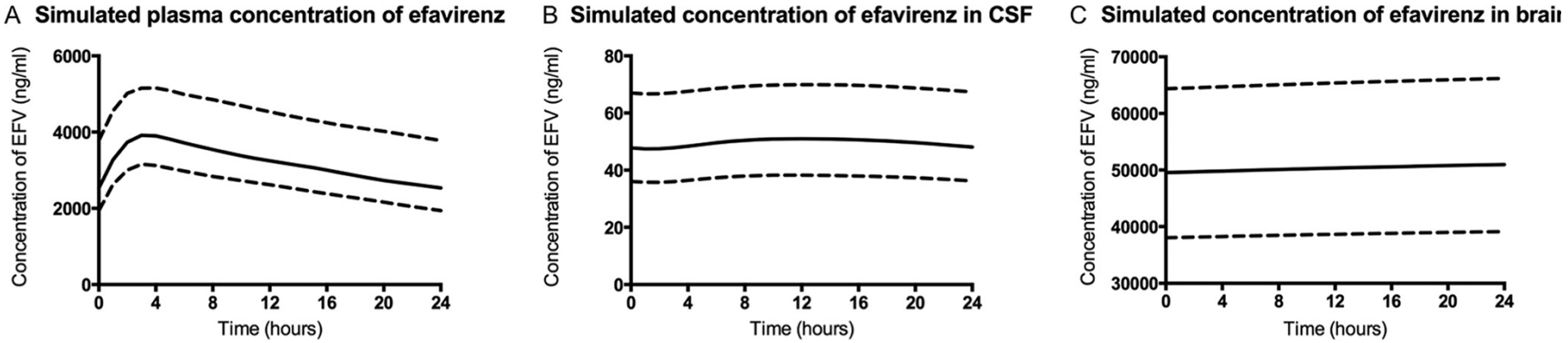
22 pharmacoresistant epilepsy patients (nine male, 13 female patients; age 15–54 years) with complex partial seizures or secondarily generalized seizures were involved.

Concentrations of carbamazepine (CBZ), 10-hydroxy-carbazepine (10-OH-CZ, metabolite of oxcar-bazepine), lamotrigine (LTG), levetiracetam (LEV), topiramate, or phenytoin were determined by using one to four catheters during IOMD in the medial temporal gyrus.



Rambeck B, et al. Epilepsy 2006

Brain tissue concentrations



Predicted Cmax

plasma 3184 ng/mL (2219 - 485)

CSF 49.9 ng/mL (36.6 - 69.7)

brainT 50343 ng/mL (38351 - 65799)

tissue to plasma ratio = 15.8

Observed Cmax - rats

plasma 69.7 ng/mL (44.9 – 130.6)

brainT 702.9 ng/mL (475.5 - 1018)

tissue to plasma ratio = 9.5 (7-10.9)

Curley P, et al. AAC 2016

Determinants of ARVs' passage into the CSF

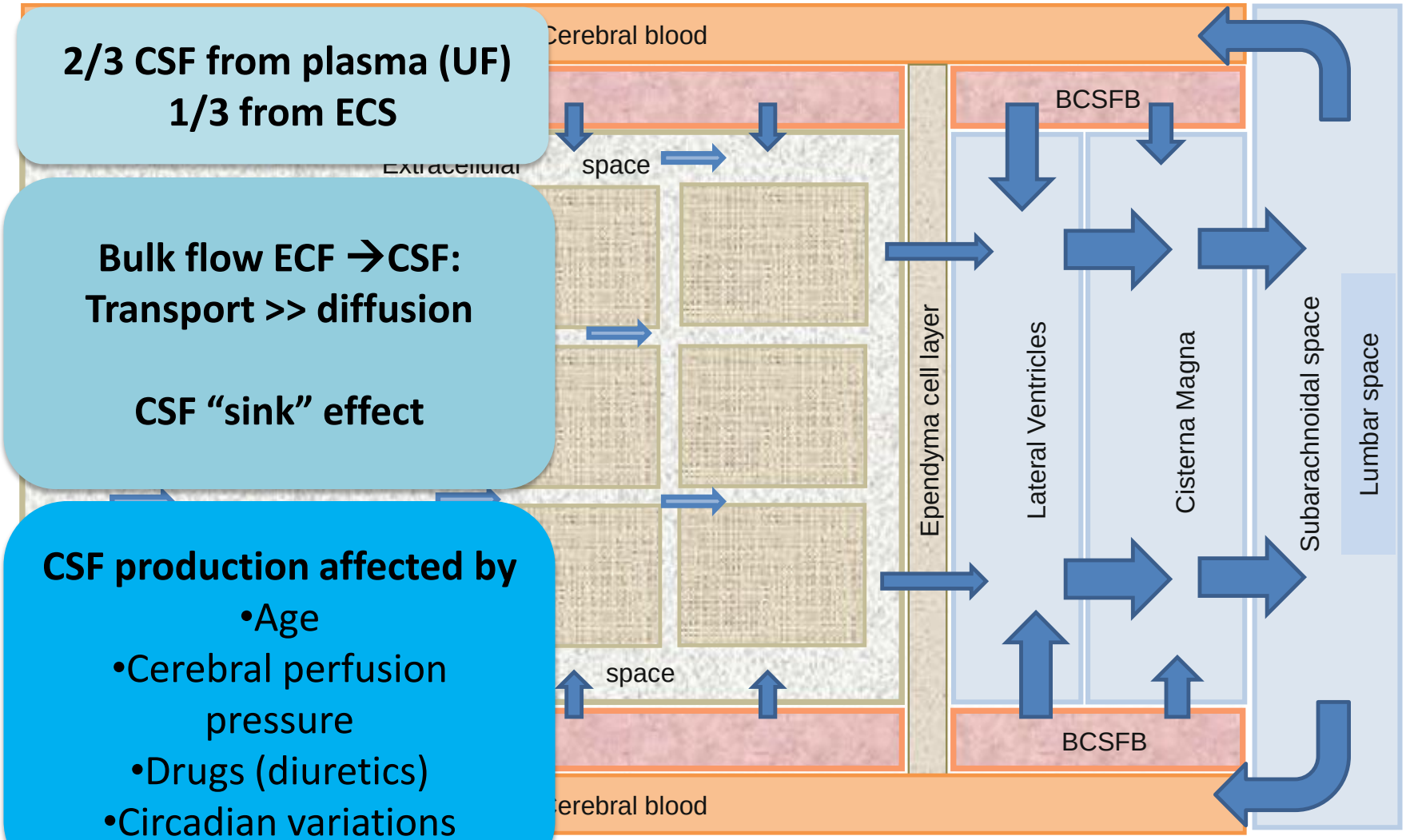
CSF flow and exchange

2/3 CSF from plasma (UF)
1/3 from ECS

Bulk flow ECF →CSF:
Transport >> diffusion

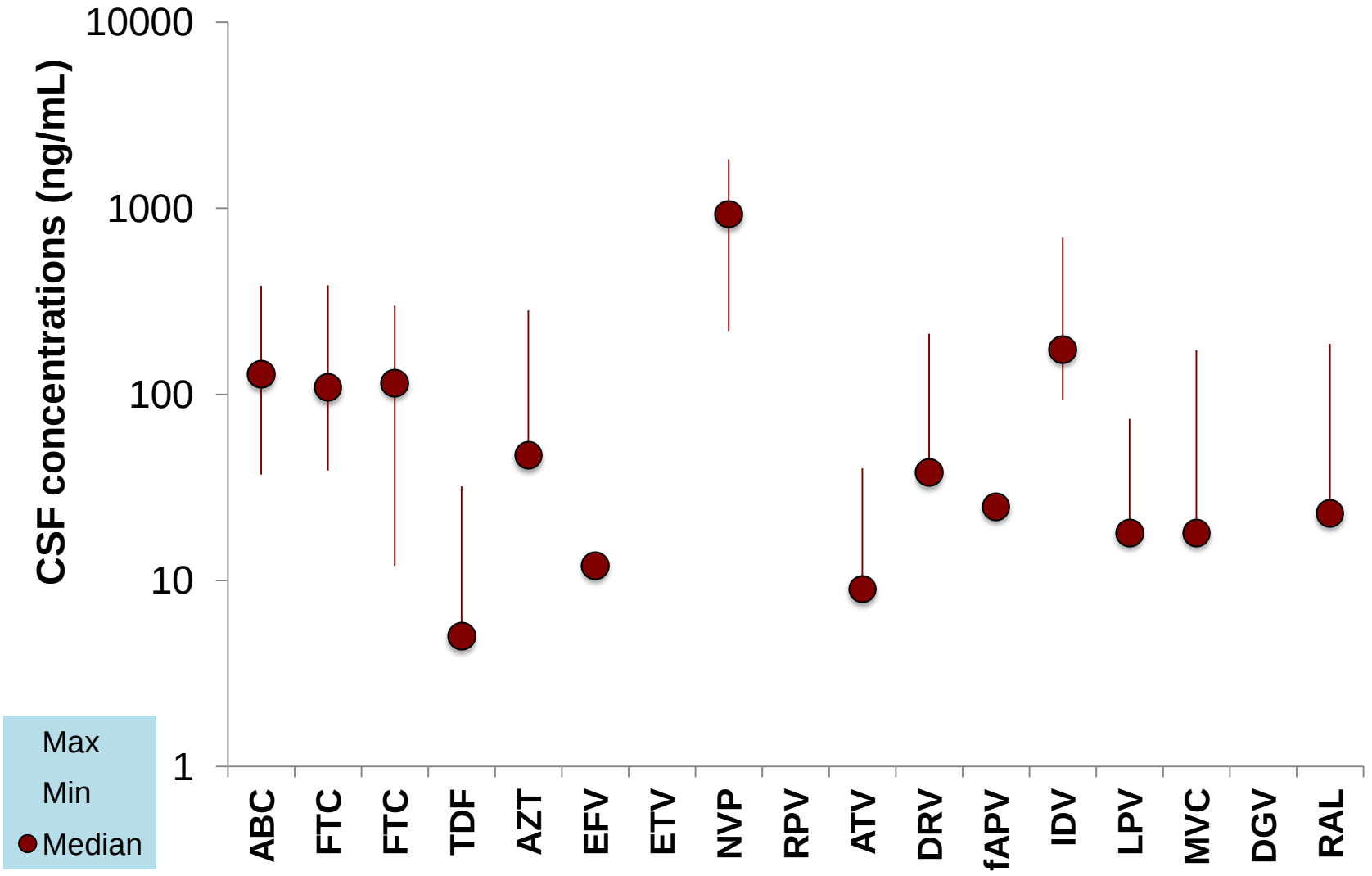
CSF "sink" effect

CSF production affected by
- Age
- Cerebral perfusion pressure
- Drugs (diuretics)
- Circadian variations



de Lange ECM, J Pharmacokinet Pharmacodyn (2013) 40:315–326

High variability in CSF exposure

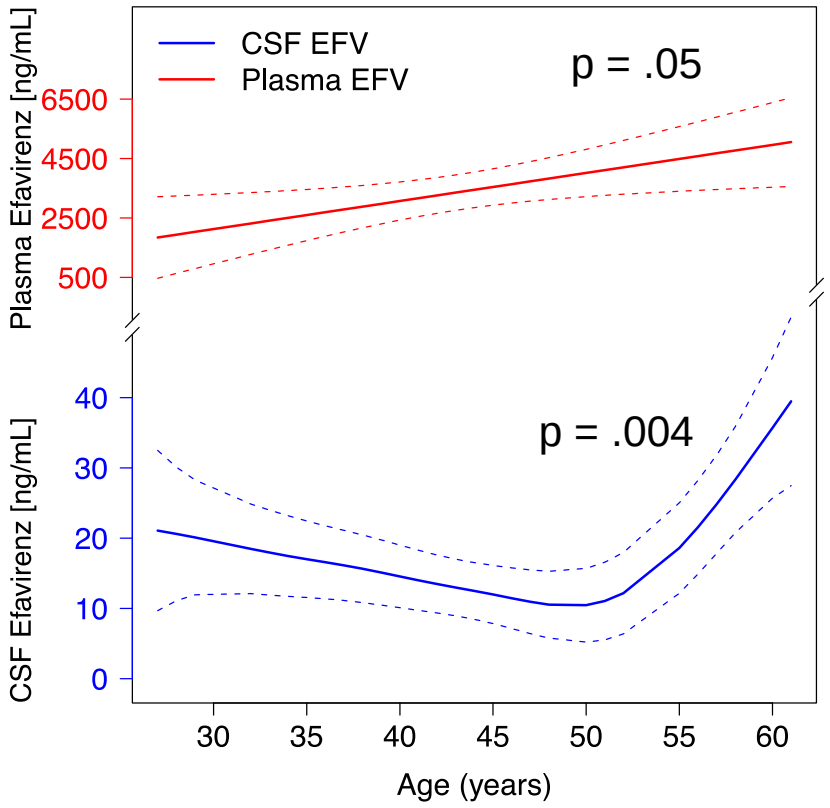


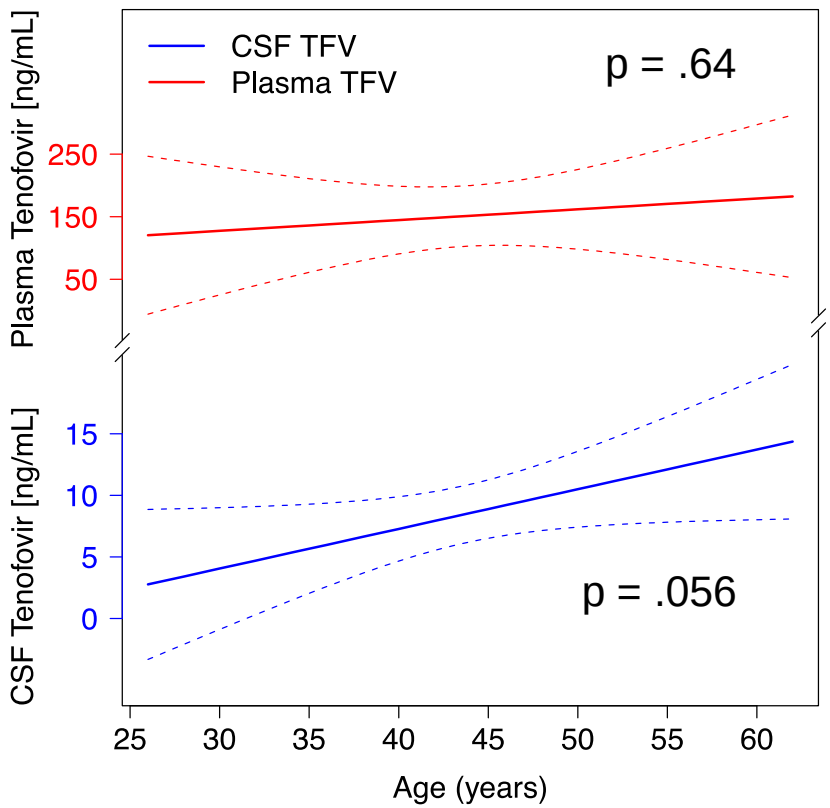
Calcagno A, et al. Clin Pharmac 2014

Determinants of CSF PK

- Patient:
  - Δ Age (↑infants and older persons: ↓ turnover?)
  - Δ Meningeal inflammation
  - Δ CSF flow alterations
- Drug:
  - Ω **Molecular Size**
  - Ω **Lipophilicity**
  - Ω **Plasma Protein Binding**
  - Ω **Ionization**
  - Ω **Active Transport**

Age

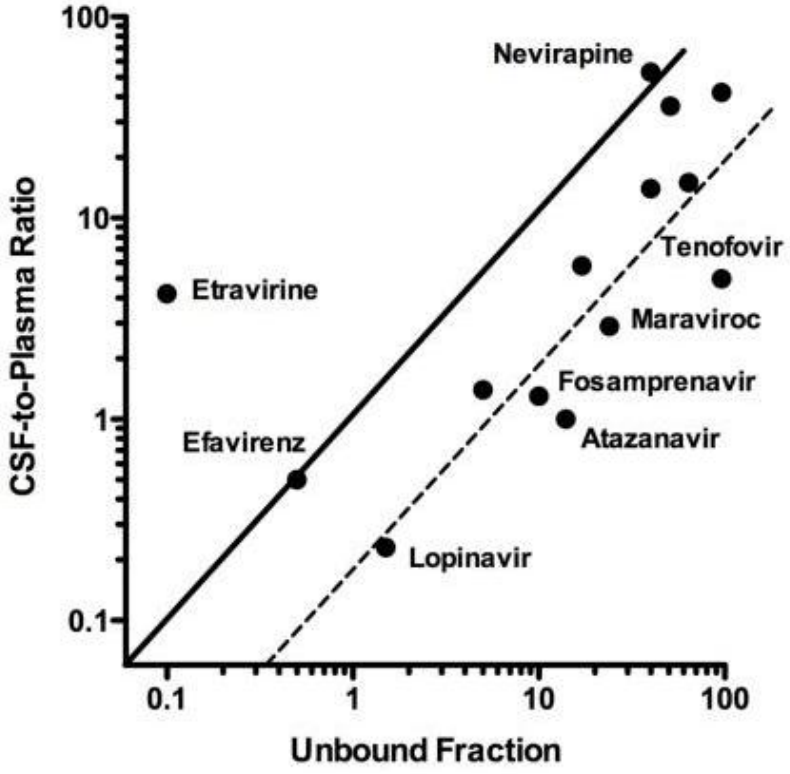




Croteau D, et al. CROI2012

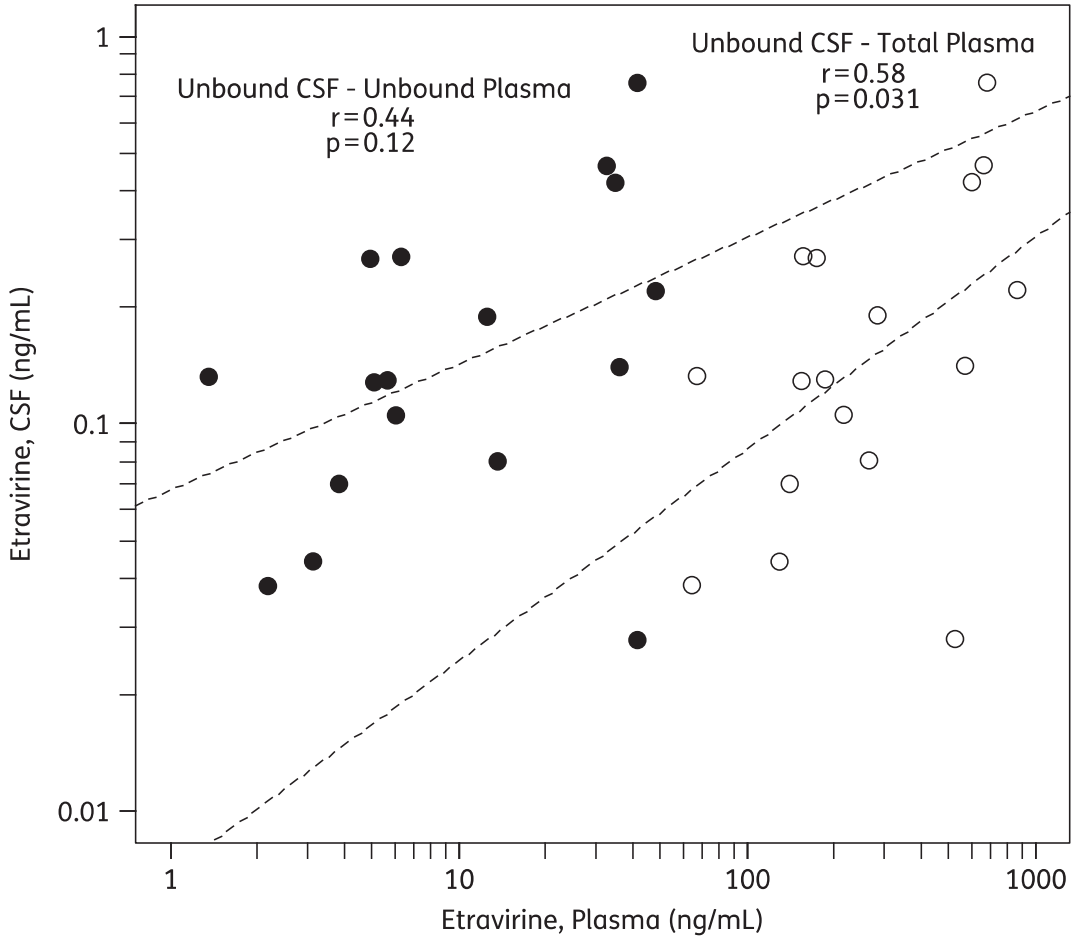
Protein binding and penetration

Drug	Published Unbound Fraction	CSF: Plasma Ratio	Ratio
Nevirapine	40%	46%	**115%**
Efavirenz	0.5%	0.5%	**100%**
Abacavir	51%	36%	**71%**
Emtricitabine	96%	42%	**44%**
Etravirine	0,1%	4%	**40%**
Indinavir	40%	14%	**35%**
Raltegravir	17%	5.8%	**34%**
Darunavir	5%	1.4%	**28%**
Lamivudine	64%	15%	**23%**
Lopinavir	1-2%	0.23%	**23%**
Fosamprenavir	10%	1.3%	**13%**
Maraviroc	24%	2.9%	**12%**
Atazanavir	14%	1%	**7%**
Tenofovir	93-99%	5%	**5%**

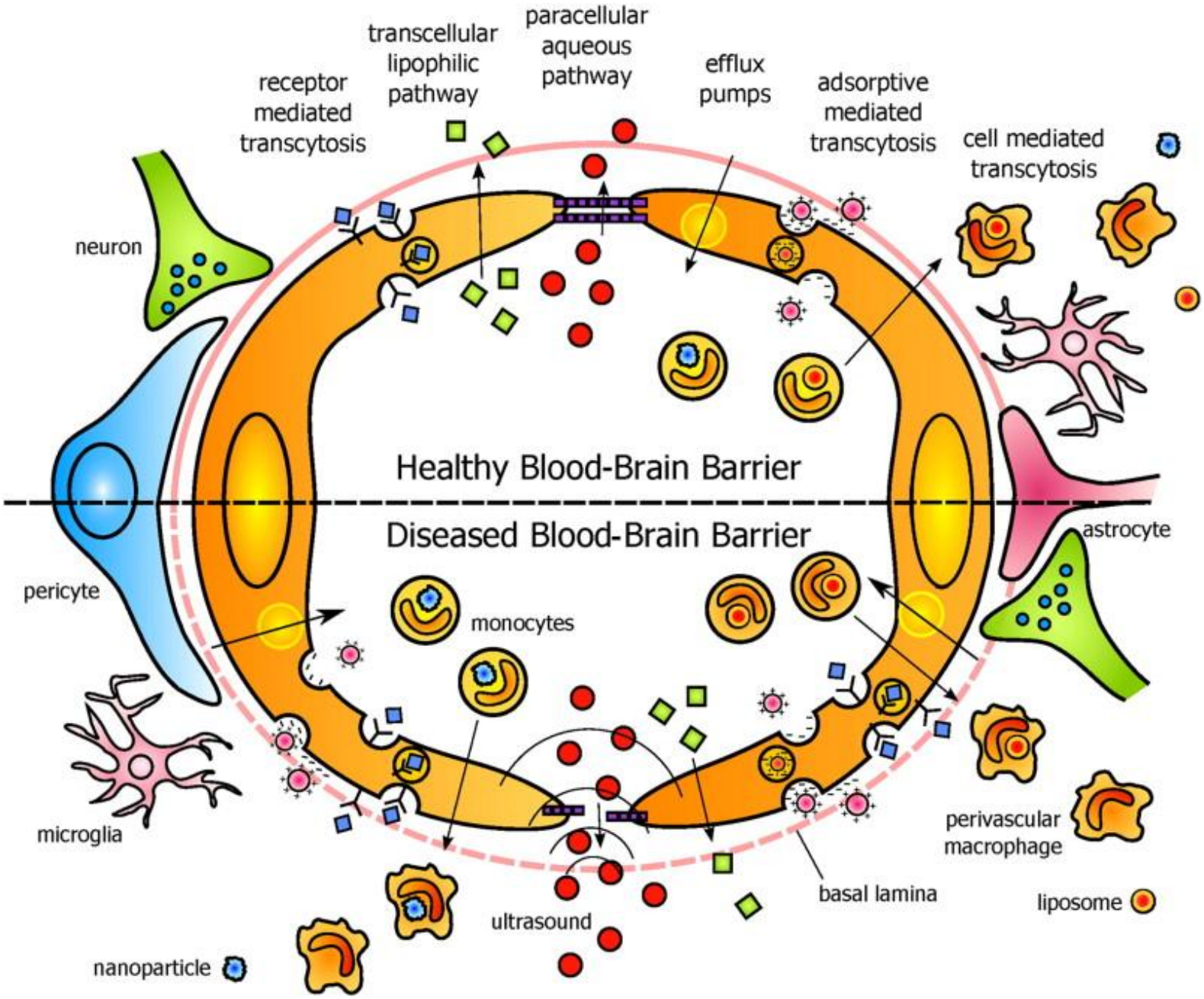


Etravirine in CSF is highly protein bound

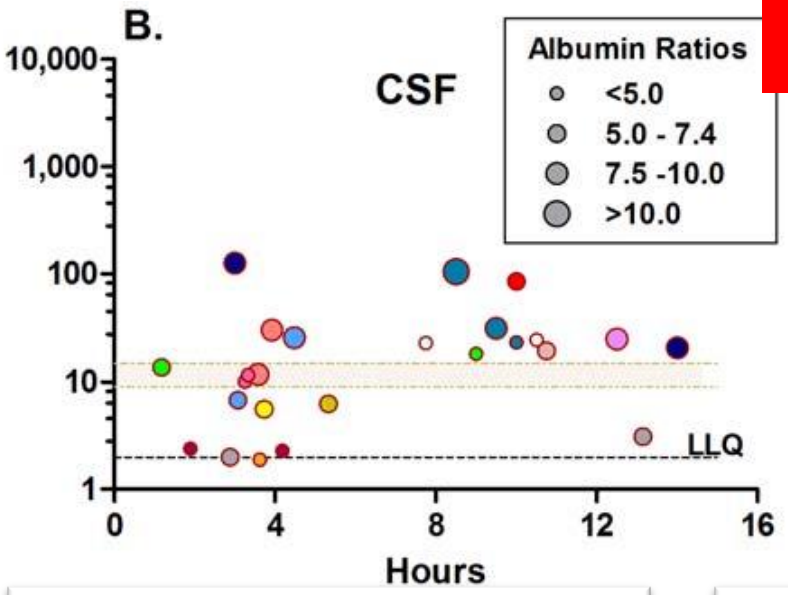
Anh Nguyen[1], Steven Rossi[1], David Croteau[2]*, Brookie M. Best[1,3], David Clifford[4], Ann C. Collier[5], Benjamin Gelman[6], Christina Marra[5], Justin McArthur[7], J. Allen McCutchan[8], Susan Morgello[9], David Simpson[10], Ronald J. Ellis[2], Igor Grant[11], Edmund Capparelli[1] and Scott Letendre[8] on behalf of the CHARTER Group†



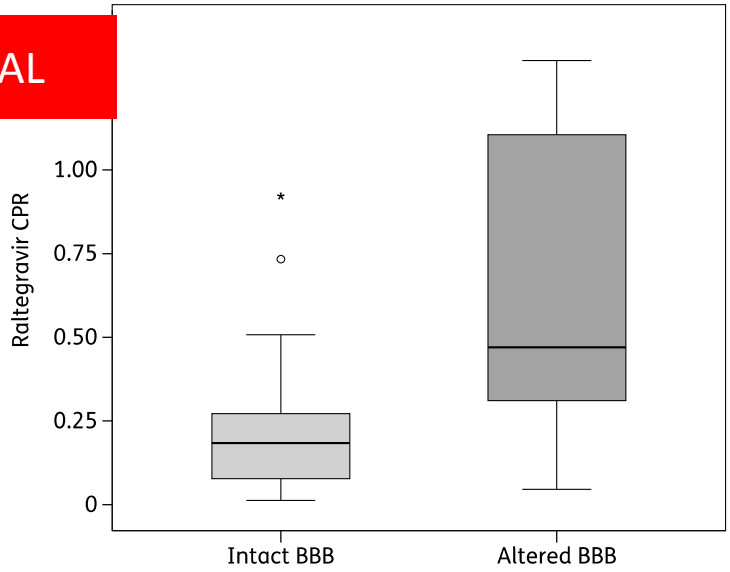
Nguyen A, et al. JAC 2013

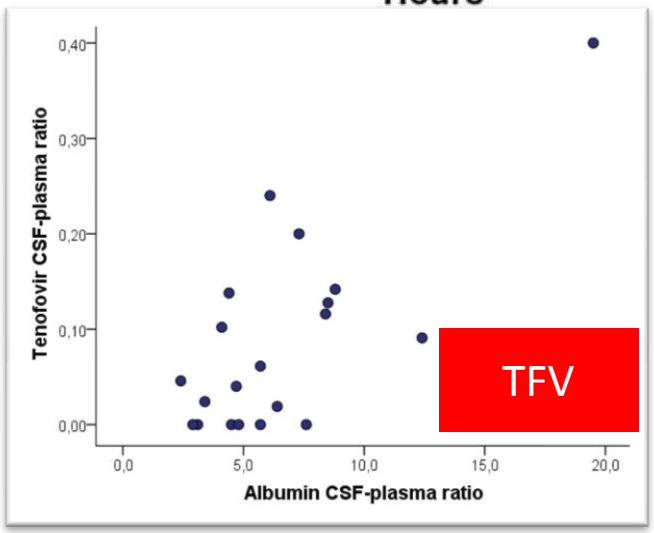

receptor mediated transcytosis
transcellular lipophilic pathway
paracellular aqueous pathway
efflux pumps
adsorptive mediated transcytosis
cell mediated transcytosis
neuron
Healthy Blood-Brain Barrier
Diseased Blood-Brain Barrier
astrocyte
pericyte
monocytes
microglia
perivascular macrophage
basal lamina
liposome
ultrasound
nanoparticle

BBB and CSF concentrations

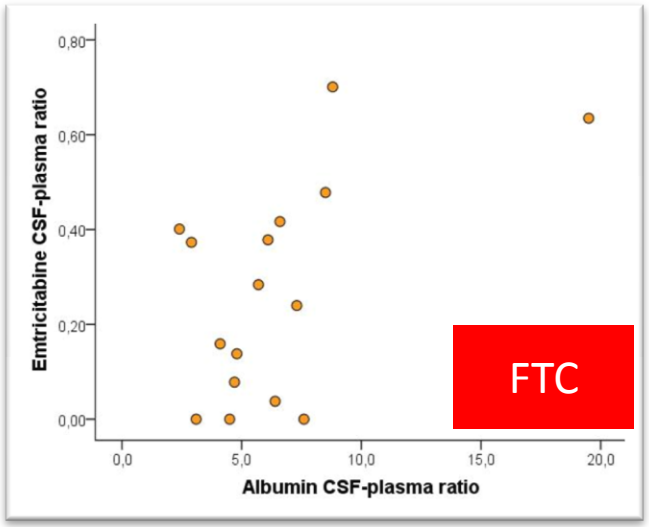


RAL





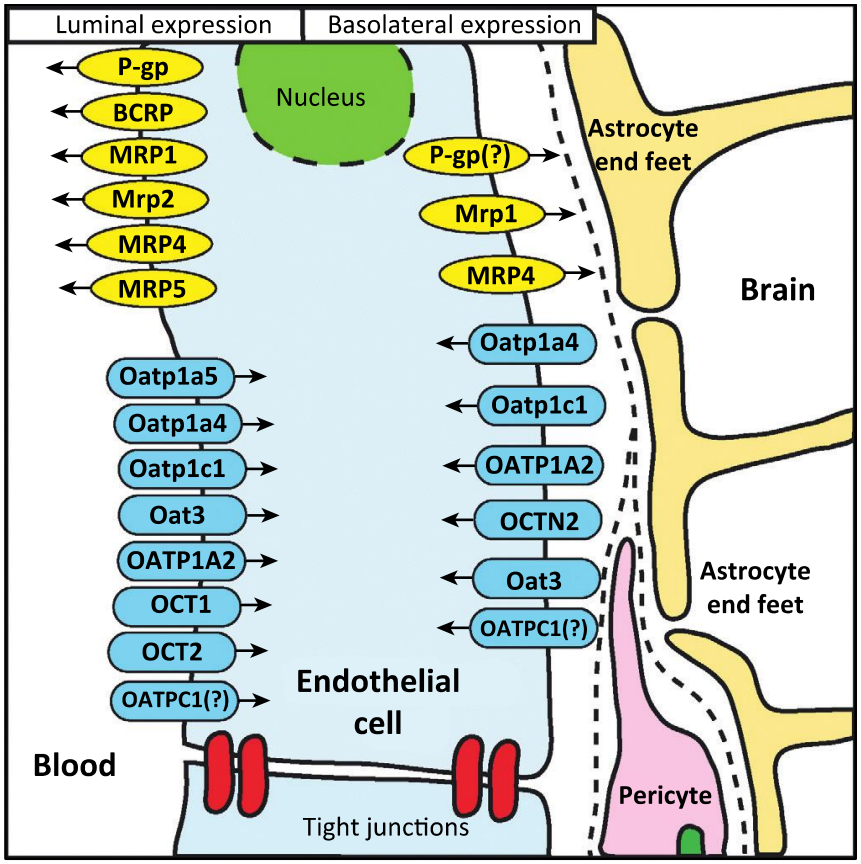
TFV

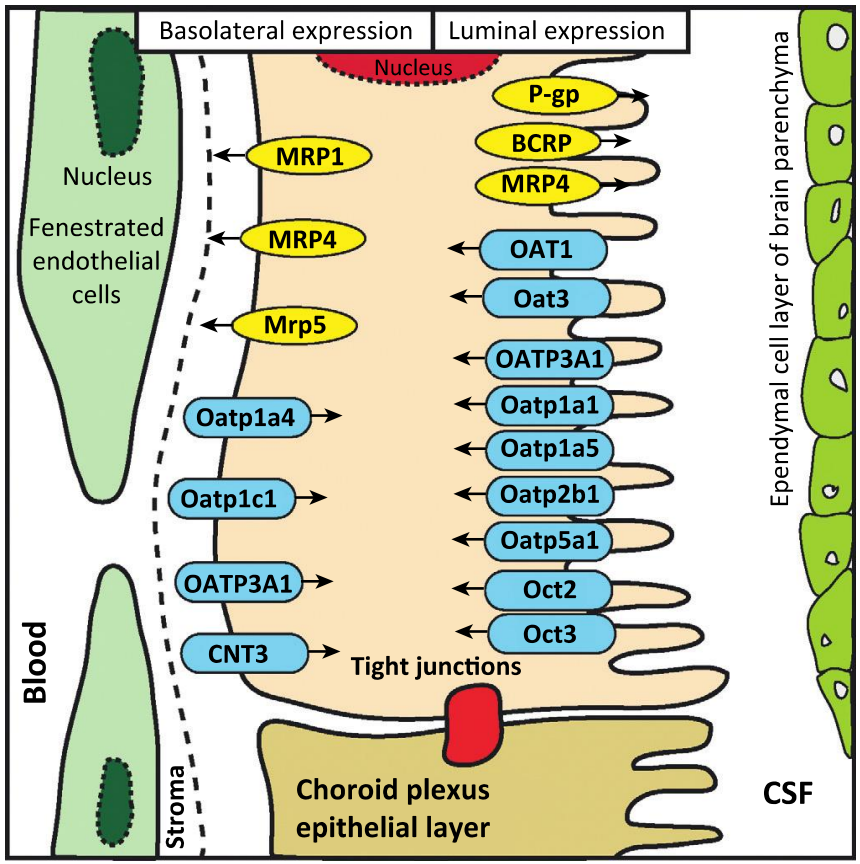


FTC

Yilmaz A, et al. PlosOne 2009;
Calcagno A, et al. AIDS 2011
and JAC 2013

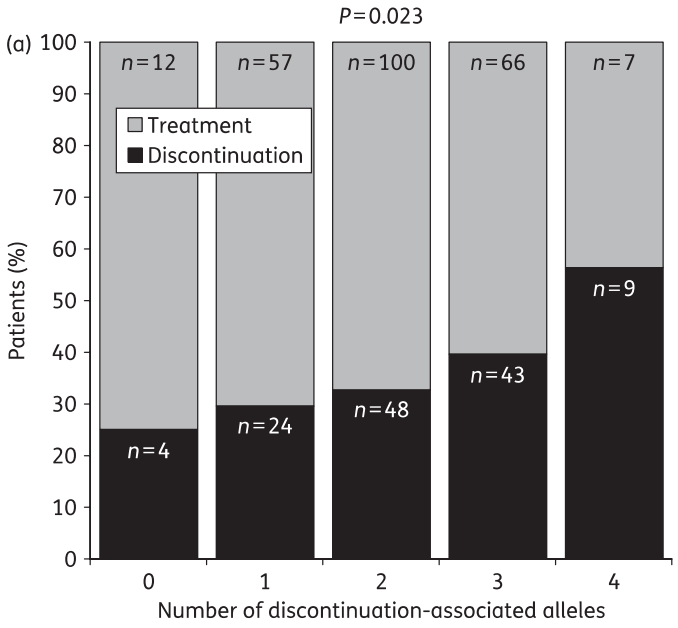
Transporters at the BBB and BCB



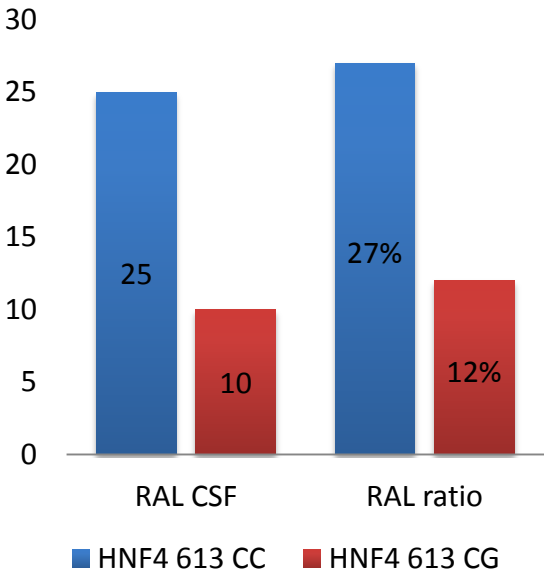


Chan GNY, et al. Trends in Pharmacological Sciences 2013

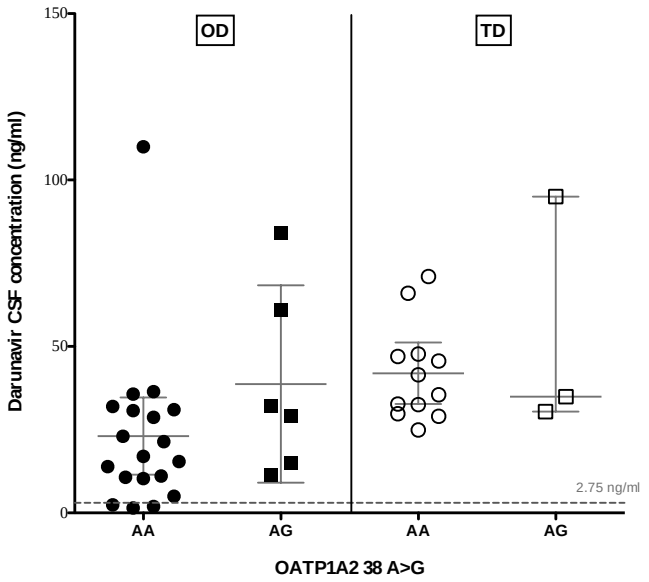
PG and CSF concentrations



EFV



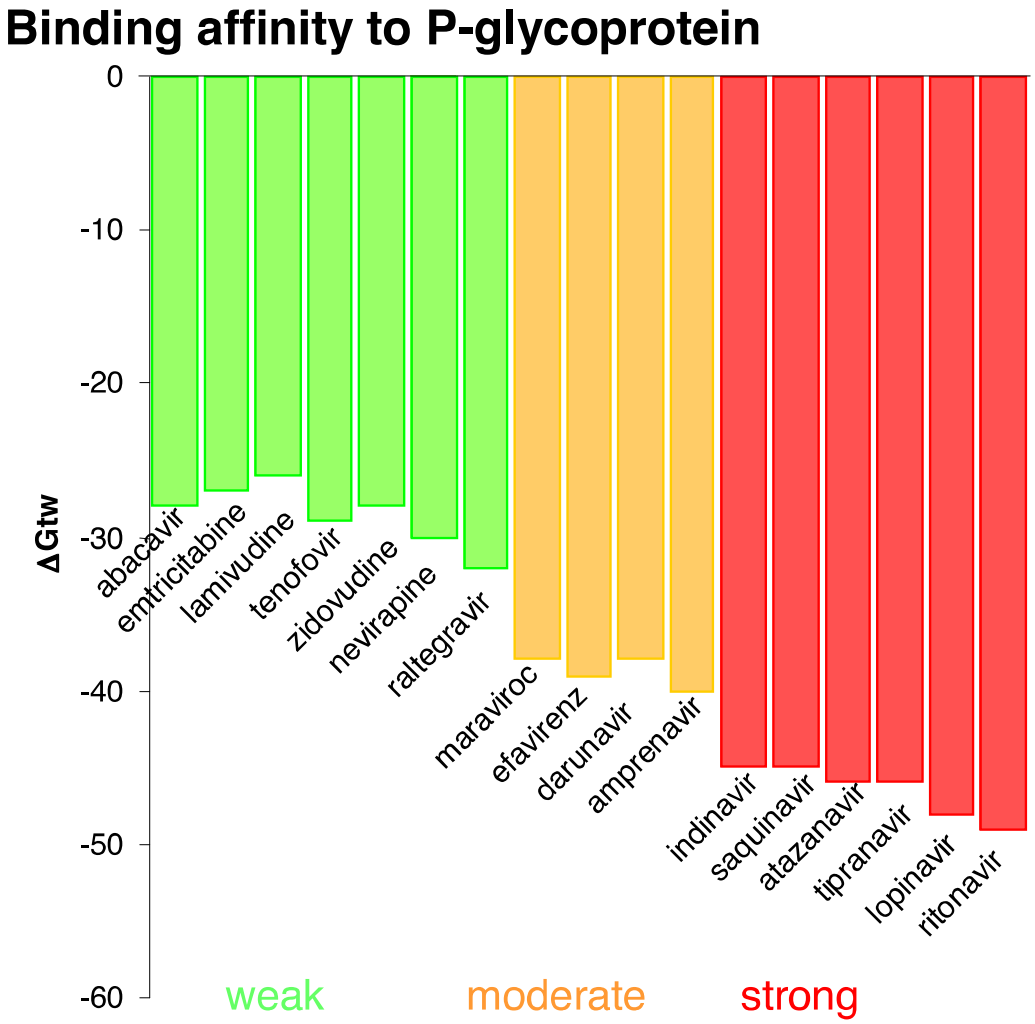
RAL



DRV/r

Wyen C, et al. JAC 2011, Calcagno A, et al. AIDS 2012 and JAC 2013

Permeation of antiretroviral agents across the blood-brain barrier and interactions with efflux drug transporters



Most NRTIs are predicted to cross the blood-brain barrier due to their high passive influx.

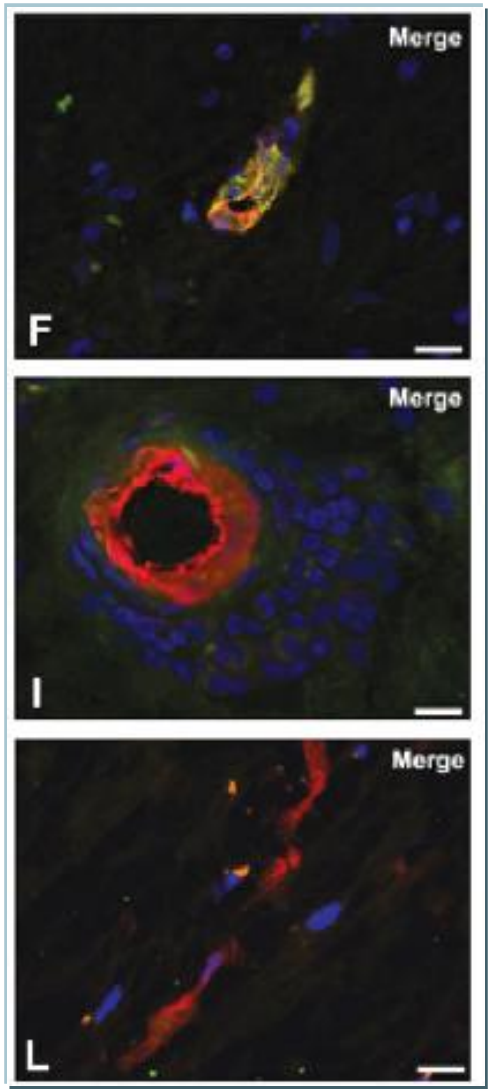
PIs are unlikely to cross the blood-brain barrier but may modulate the activity of efflux transporters and increase the brain permeation of co-administered drugs.

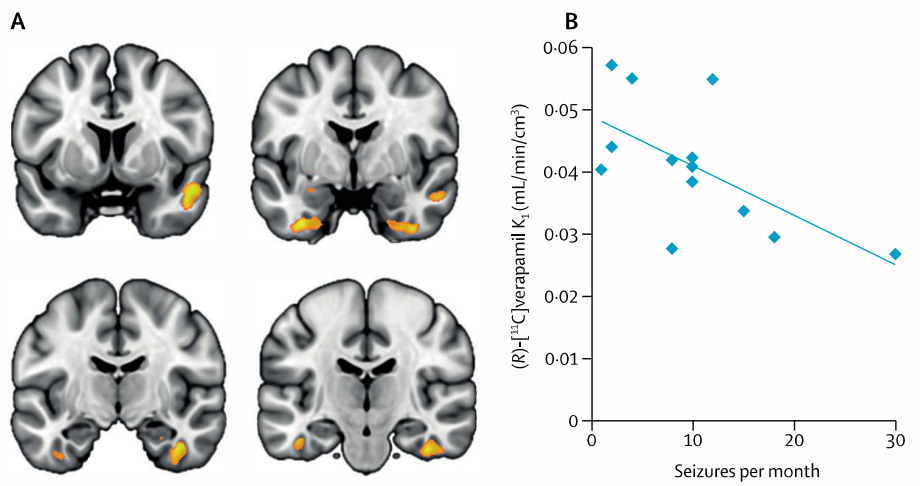
Marzolini C, et al. Molecular Pharmaceutics 2013

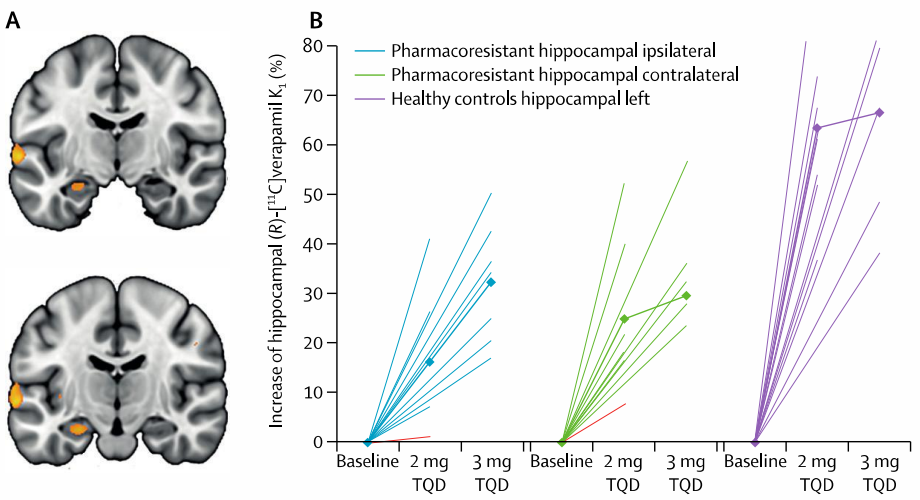
PgP in MS and temporal lobe epilepsy

Loss of vascular P-gp expression in MS lesions

Increased expression of P-gp in hypertrophic GFAP-positive astrocytes







Kooij G, et al. Journal of Autoimmunity 2010; Feldmann M, et al. Lancet Neurol 2013

Inflammation and cART

Taylor & Francis
Taylor & Francis Group

Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

Inflammation and pharmacokinetics: potential implications for HIV-infection

Sharon M. Seifert, Jose R. Castillo-Mancilla, Kristine M. Erlandson & Peter L. Anderson

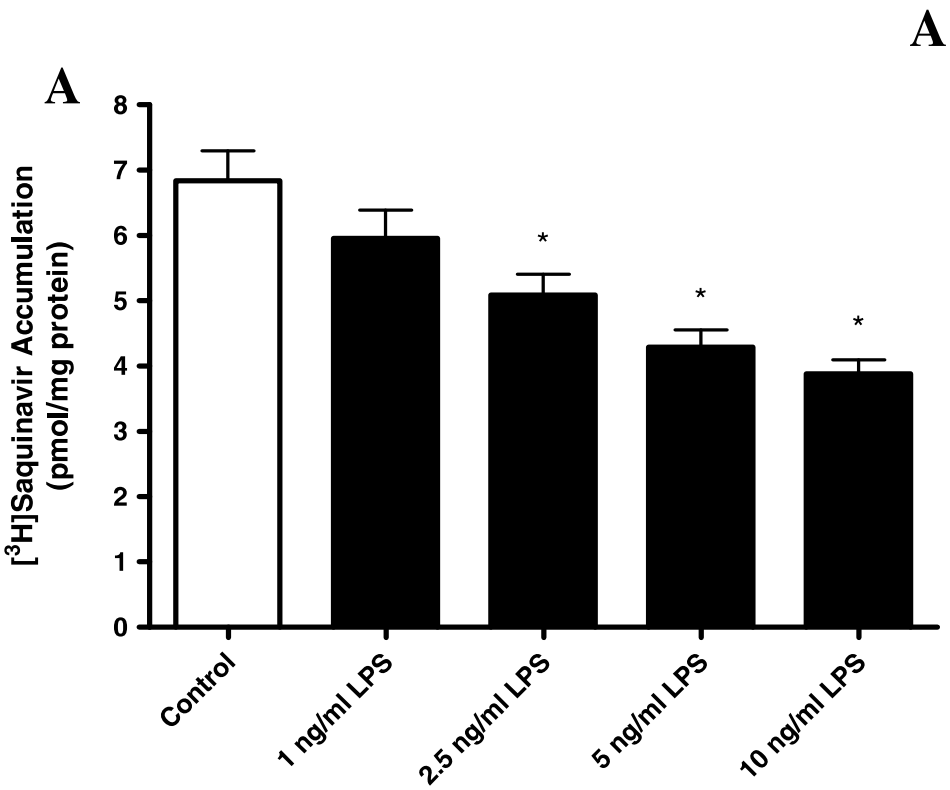
Inflammation and cART

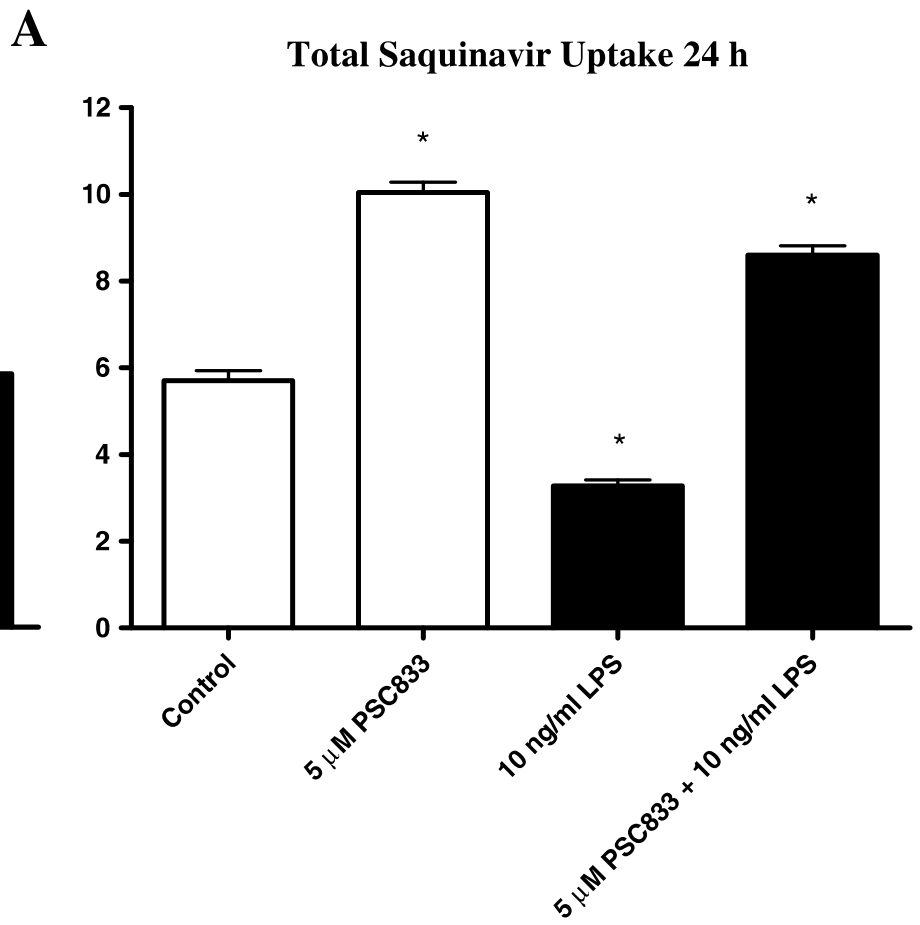
Table 1. Potential effects of inflammation on HIV antiretroviral pharmacology.

Absorption	Pharmacokinetic effect	Example drugs
Inflammatory effect		
Decreased gastric acidity	Increase or decrease in bioavailability	↓Atazanavir[151], rilpivirine[152], elvitegravir[153]
Distribution		
Increased alpha-1-acid glycoprotein	Increased total drug concentration	↑PIs[154]
Decreased albumin	Decreased total drug concentration	↓PIs, efavirenz [154]
Increased P-gp	Increase or decrease in bioavailability and/or access to target site	PIs[155]
Metabolism		
Decreased hepatic CYP3A4	Decreased clearance	↑PIs[156], NNRTIs [156], maraviroc [157], elvitegravir [153]
Decreased hepatic UGT	Decreased clearance	↑INSTI[158]
Elimination		
Decreased hepatic ENT1 (SLC29a1)	Unknown	NRTIs[159]
Decreased renal MRP2 (ABCC2)	Increased plasma concentration	↑Tenofovir[160]

PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; arrows denote potential effects on plasma concentrations of indicated antiretroviral classes/agents.

LPS on Purified cultures of rodent microglia



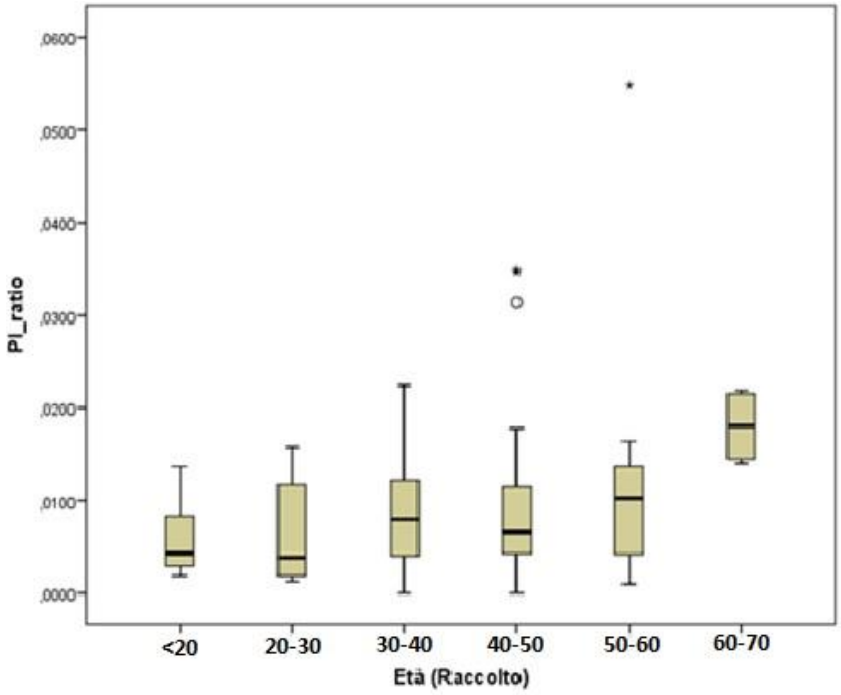


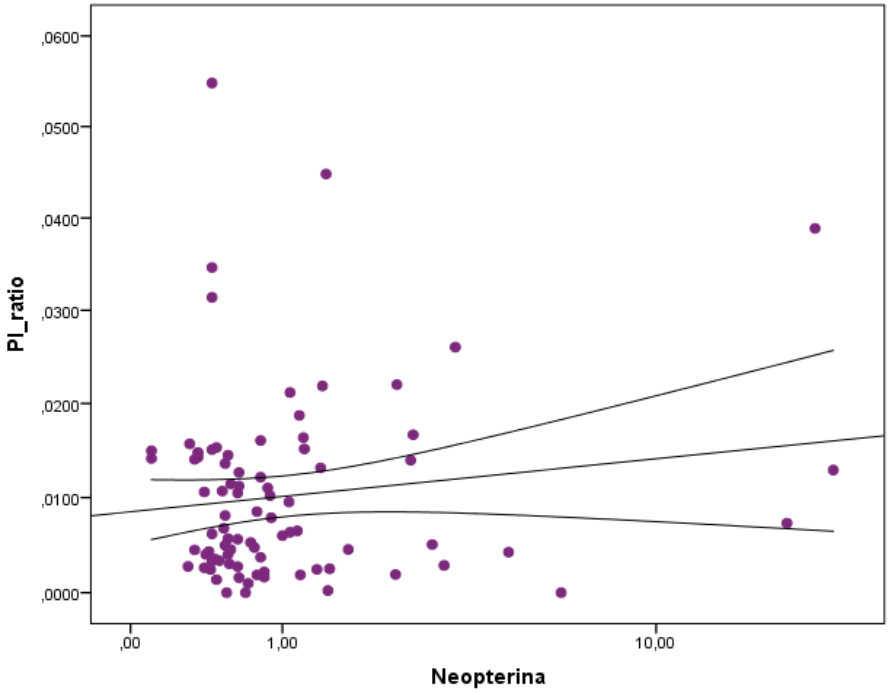
De Rosa MF, et al. JCP 2013; Ellis K, JPP 2015; Kis O, et al. AAC 2016; Roy U, et al. PlosOne 2013; Turriziani O, et al. JMV 2008; Zhang JC, et al. Int J Mol Med 2014; Maffeo A, New Microbiologica 2004; Chaillou S, et al. HIV Clin Trials 2002; Dallas S, et al. J Neuroinflammation 2013

Determinants of PI CSF to plasma ratios

n=137 (79 DRV/r, 31 ATV/r e 27 LPV/r)

- Multivariate linear regression analysis adjusted for age, CSAR, time after dose and *ABCB1* 3435C>T
- **Age (p=0.01) and CSF neopterin (p=0.05)**



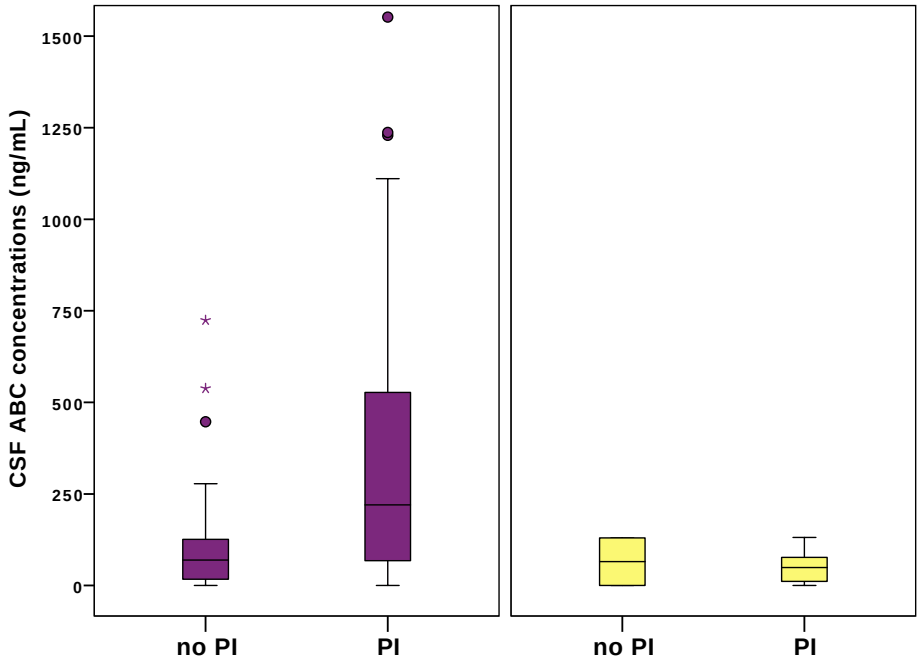


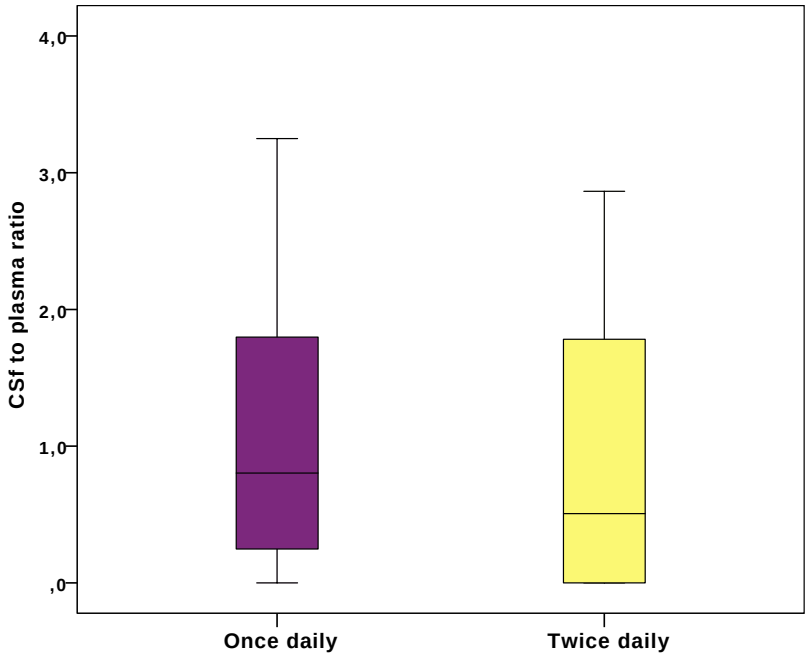
Scarvaglieri E, et al. In preparation

New drugs

Once-daily abacavir

- 70 patients (61 on qd and 9 on bid)
- No significant difference, comparable to Capparelli AAC 2005 (higher ratios)

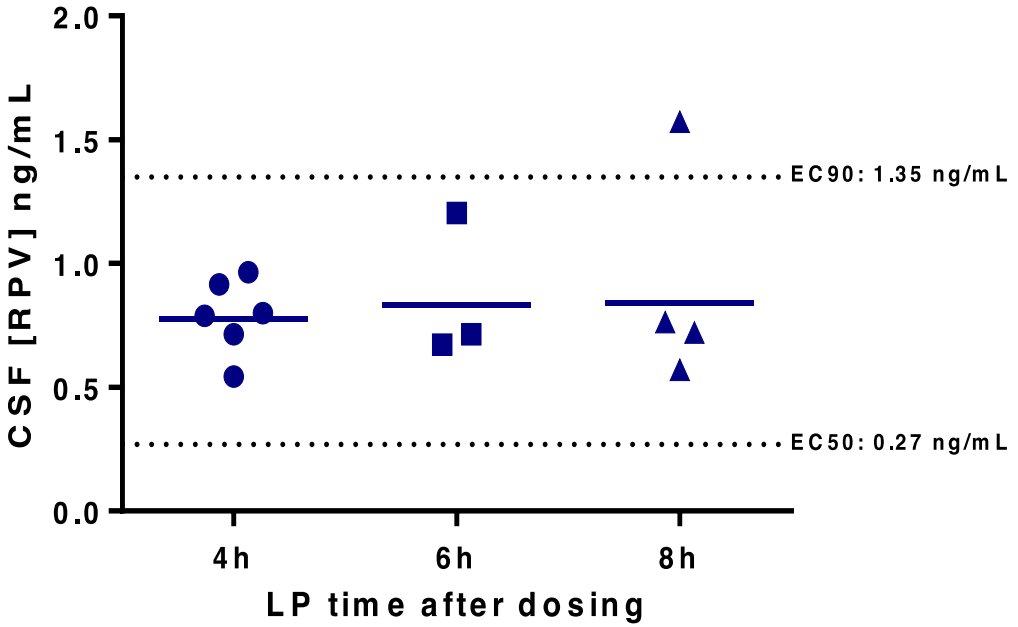




Calcagno A, et al. ICAR 2017

Rilpivirine

- 13 patients
- from NVP-containing regimens
- ratio= 1.4%
- CSF PK correlated with plasma PK and glucose/protein CSF levels
- No changes in cerebral metabolites



GM (95% CI)	Total n=13	Time elapsed from RPV dosing to LP			p-value
		4h n=6	6h n=3	8h n=4	
RPV concentration in CSF (ng/mL)	0.8(0.7-1.0)	0.8(0.6-1.0)	0.8(0.4-1.8)	0.8 (0.4-1.7)	**0.96**
RPV CSF:Plasma ratio (%)	1.4 (1.2-1.6)	1.25 (1-1.6)	1.5 (0.8-2.7)	1.5 (0.8-2.8)	**0.08**

Mora-Peris B, et al. JAC 2014

Dolutegravir

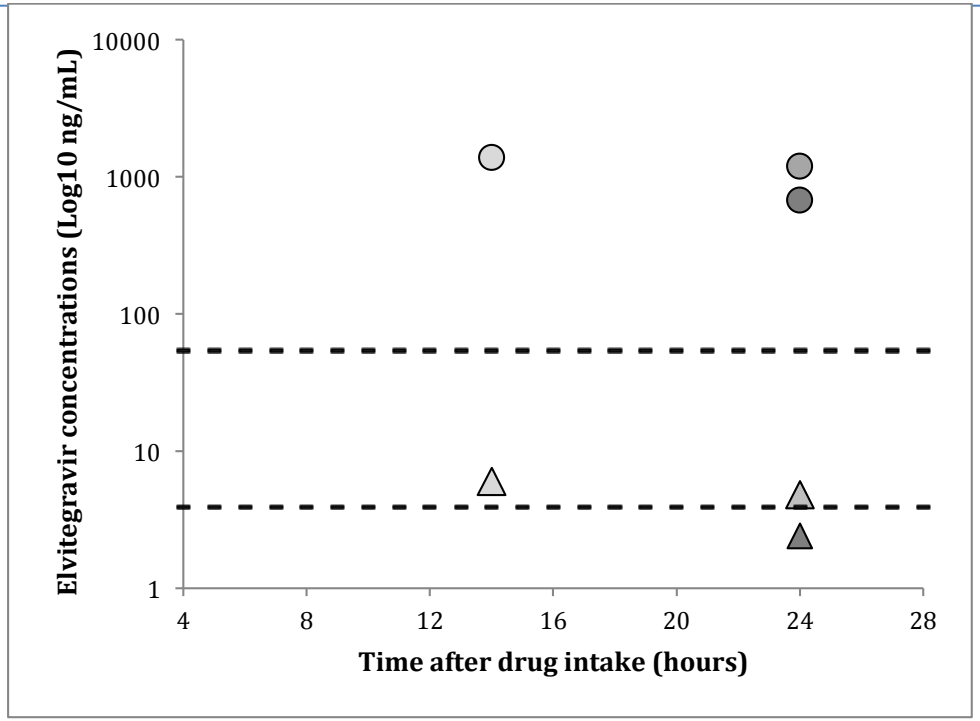
- 12 patients
- naive
- DGV + ABC/3TC
- ratio 0.51%
- at week 16 all patients had a CSF VL<50 copies/mL

Subject	Plasma DTG (μg/mL)	Plasma DTG Unbound (ng/mL)	Plasma DTG Unbound Fraction (%)	CSF DTG (μg/mL)	DTG CSF/Plasma Ratio (%)	Plasma HIV-1 RNA			CSF HIV-1 RNA			CD4+ Cell Count		
						Baseline Absolute Value (c/mL)	Week 16 Absolute Value (c/mL)	Change from Baseline (log_{10} c/mL)	Baseline Absolute Value (c/mL)	Week 16 Absolute Value (c/mL)	Change from Baseline (log_{10} c/mL)	Baseline Absolute Value (cells/mm³)	Week 16 Absolute Value (cells/mm³)	Change from Baseline (cells/mm³)
A	3.14	23.79	0.76	0.0139	0.44	38,697	<50	-3.00	2,600	<2	-3.41	527	1156	+629
B	3.65	30.38	0.83	0.0150	0.41	232,844	<50	-3.78	6,400	<2	-3.81	577	853	+276
C	4.92	23.96	0.49	0.0183	0.37	18,483	<50	-2.68	29,000	<2	-4.46	320	485	+165
D	3.27	17.95	0.55	0.0098	0.30	47,061	<50	-3.08	450	<2	-2.65	549	1147	+598
E	2.04	14.16	0.69	0.0128	0.62	24,222	<50	-2.79	29	<2	-1.46	404	511	+107
F	3.39	31.16	0.92	0.0115	0.34	137,948	<50	-3.55	1,000	<2	-3.00	345	713	+368
G	0.67	28.92	4.30	0.0137	2.04	11,712	<50	-2.48	4,400	<2	-3.64	457	627	+170
H	3.69	27.99	0.76	0.0152	0.41	3,976	<50	-2.01	140	<2[a]	-2.15[a]	863	615	-248
I	2.95	19.98	0.68	0.0123	0.42	3,684,952	236	-4.19	400,000	<2	-5.60	487	462	+175
J	4.83	32.09	0.66	0.0146	0.30	301,078	<50	-3.89	57,000	<2	-4.76	152	436	+284
K	3.13	22.17	0.71	0.0103	0.33	53,272	<50	-3.14	460	<2	-2.66	360	448	+88
L	0.64	3.81	0.59	0.0037	0.57	74,301	77	-2.98	9,000	5	-3.26	226	531	+305

[a] CSF HIV-1 RNA assessment performed on Day 141 (within the Week 24 time window)

Letendre S, et al. CID 2014

Elvitegravir



	Time (hours)	Elvitegravir			Cobicistat		
		plasma (ng/mL)	CSF (ng/mL)	ratio	plasma (ng/mL)	CSF (ng/mL)	ratio
Patient A	14	1389	11.7	0.0084	344	8.4	0.0244
Patient B	24	676	2.4	0.0035	38	5.8	0.1526
Patient C	24	1197	4.8	0.0040	23	7.3	0.3174

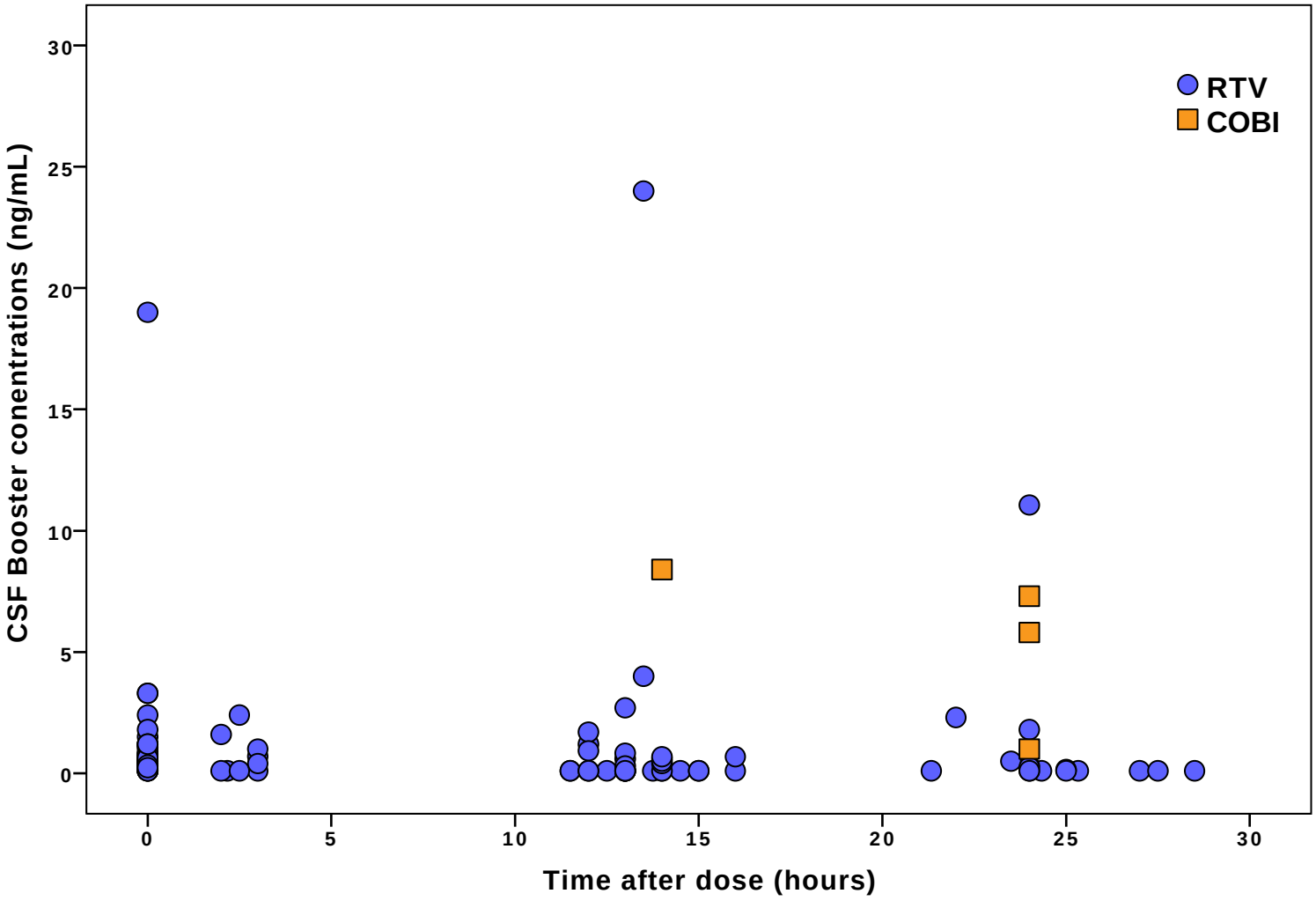
Calcagno A, et al. AIDS Res and Human Retrov 2016

TAF

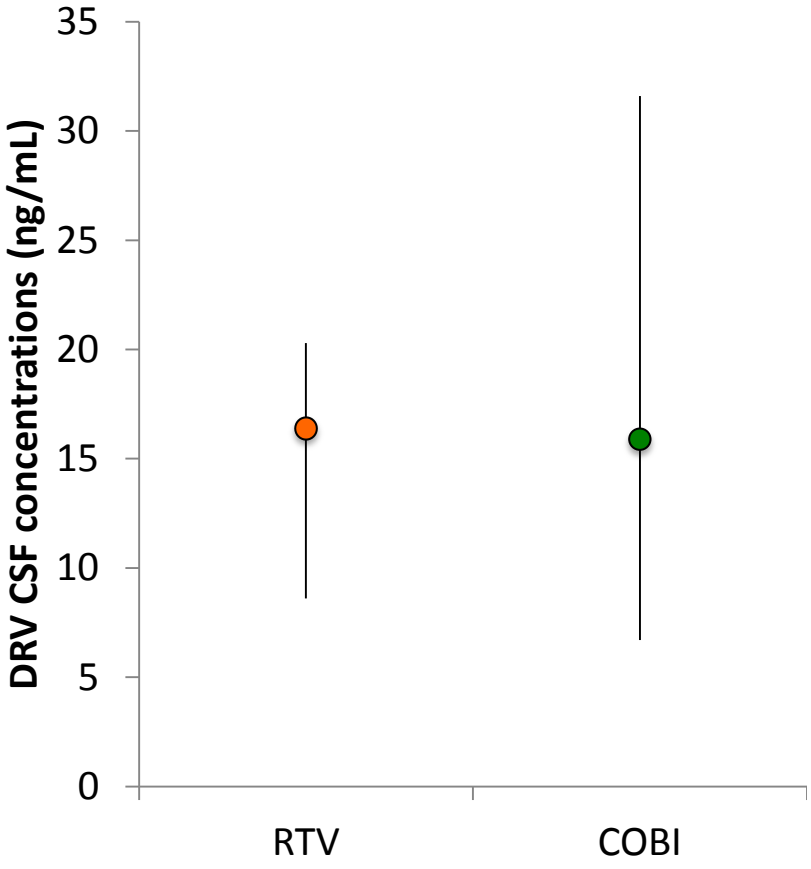
Tissue or fluid	Tenofovir DF		GS 7340		Tissue concn ratio of GS 7340 to tenofovir DF
	% Dose	Concn (μg-eq/g)[b]	% Dose	Concn (μg-eq/g)[b]	
Liver	12.40	38.3 ± 14.3	16.45	52.9 ± 4.7	1.4
Kidney	4.58	87.9 ± 38.4	3.78	80.2 ± 3.4	0.9
Lungs	0.03	0.53 ± 0.06	0.34	4.34 ± 0.15	8.2
Iliac lymph nodes	<0.01	0.51 ± 0.14	0.01	5.42 ± 0.86	10.6
Axillary lymph nodes	<0.01	0.37 ± 0.25	0.01	5.54 ± 0.42	14.8
Inguinal lymph nodes	<0.01	0.28 ± 0.28	<0.01	4.12 ± 0.44	15.0
Mesenteric lymph nodes	<0.01	1.20 ± 0.64	0.04	6.88 ± 0.78	5.7
Thyroid gland	<0.01	0.30 ± 0.20	<0.01	4.78 ± 1.31	15.8
Pituitary gland	<0.01	0.23 ± 0.07	<0.01	1.80 ± 0.13	7.8
Salivary gland (left + right)	<0.01	0.45 ± 0.1	0.03	5.54 ± 0.10	12.3
Adrenal gland	<0.01	1.9 ± 0.79	<0.01	3.47 ± 0.13	1.8
Spleen	<0.01	0.63 ± 0.11	0.17	8.13 ± 0.19	12.8
Pancreas	<0.01	0.57 ± 0.62	0.01	3.51 ± 0.57	6.2
Prostate	<0.01	0.24 ± 0.03	<0.01	2.14 ± 0.38	9.1
Testes (left + right)	0.02	1.95 ± 0.84	0.02	1.99 ± 0.74	1.0
Skeletal muscle	<0.01	0.11 ± 0.00	0.01	1.12 ± 0.17	10.1
Heart	0.03	0.46 ± 0.17	0.15	1.97 ± 0.03	4.3
Femoral bone	<0.01	0.08 ± 0.03	<0.01	0.28 ± 0.05	3.5
Bone marrow	<0.01	0.2 ± 0.08	<0.01	2.05 ± 0.92	10.2
Skin	<0.01	0.13 ± 0.06	<0.01	0.95 ± 0.17	7.2
Abdominal fat	<0.01	0.16 ± 0.01	<0.01	0.90 ± 0.07	5.8
Eye (left + right)	<0.01	0.06 ± 0.03	<0.01	0.24 ± 0.00	3.7
Brain	<0.01	<LOD	<0.01	<LOD	ND
Cerebrospinal fluid	<0.01	<LOD	<0.01	<LOD	ND
Spinal cord	<0.01	<LOD	<0.01	0.04 ± 0.00	ND
Stomach	0.11	1.93 ± 1.03	0.26	2.68 ± 0.27	1.4
Jejunum	1.34	3.01 ± 1.37	0.79	4.16 ± 0.73	1.4
Duodenum	0.49	4.96 ± 0.54	0.44	8.77 ± 1.13	1.8
Ileum	0.01	0.50 ± 0.19	0.16	4.61 ± 1.91	9.2
Large intestine	1.63	2.57 ± 0.33	2.65	47.2 ± 42.2	7.9
Gall bladder	<0.01	3.58 ± 1.99	0.04	25.0 ± 4.7	7.0
Bile	<0.01	9.63 ± 9.42	0.22	40.5 ± 4.9	4.2
Feces	40.96	ND	0.19	ND	NA
Total GI tract contents	5.61	ND	21.64	ND	NA
Urine	23.72	ND	14.73	91.9 ± 34.0	NA
Plasma at 24 h	<0.01	0.20 ± 0.09	<0.01	0.20 ± 0.02	1.0
PBMCs at 24 h[c]	<0.01	ND	<0.01	63.2 ± 15.5	ND
Whole blood at 24 h	<0.01	0.85 ± 0.20	0.16	0.20 ± 0.00	0.2

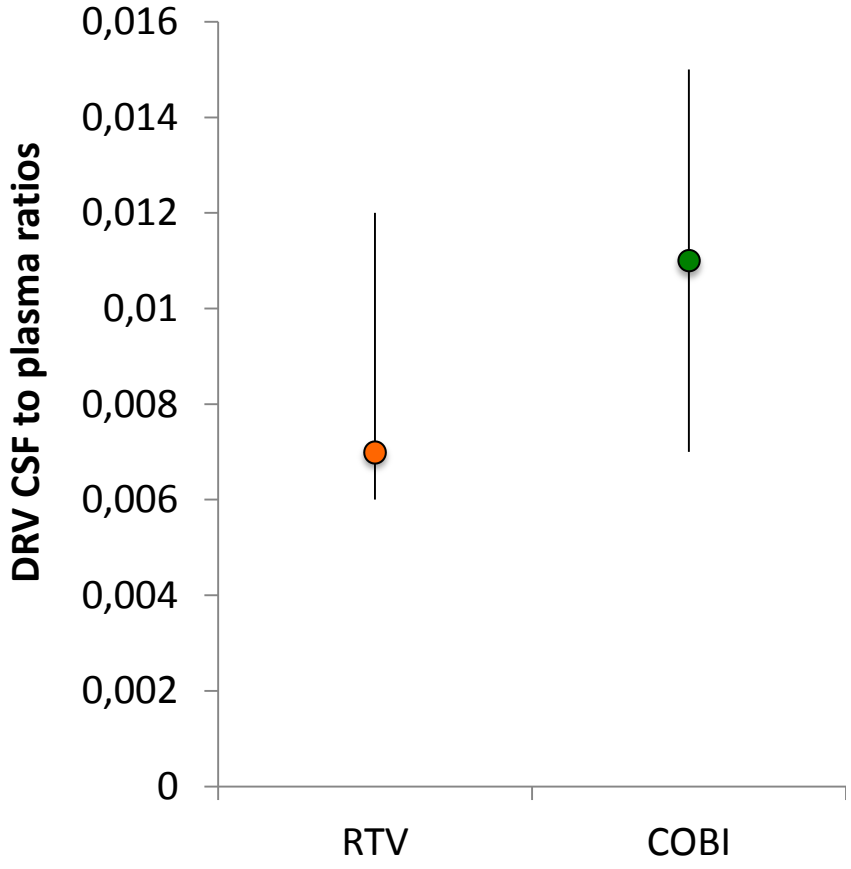
Lee WA, et al. AAC 2005

RTV vs. COBI in the CSF?



DRV/cobi vs. DRV/r
n=7





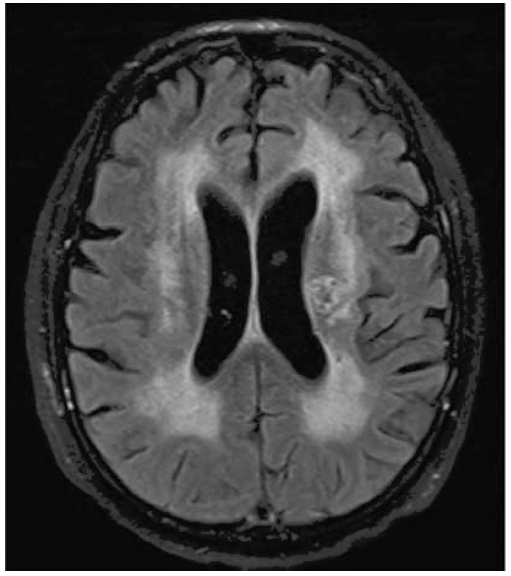
PK and Antiretrovirals' efficacy in the CNS

Symptomatic CSF escape

Two case series and few case reports

n=30

- Acute neurological symptoms
- **Resistance associated mutations**
- MRI alterations
- **Strong immune response**
- Reversibility



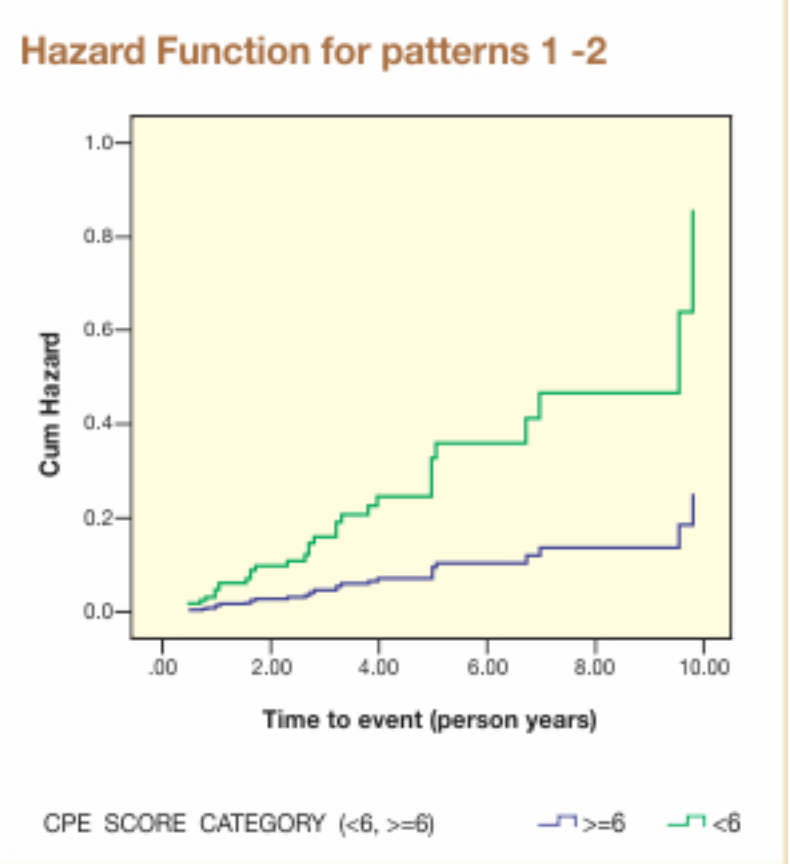
Canestri A, et al. CID 2010; Peluso MJ, et al. AIDS 2012; Wendel KA, et al. CID 2003; Bogoch II, et al. J Infect 2011; Binhgam MR, et al. J Int AIDS Soc 2011; Khouri MN, et al. JNV 2013; Imaz A, AIDS Res and Human Retrov 2014; Beguelin C, J Int AIDS Soc 2014, Spudich S. Curr Opin HIV/AIDS 2016.

Symptomatic CSF escape - India

- 1427 HIV+ patients in India
- 6 months of ART and HIV RNA <1000 copies/mL
- 9.7% with neurological disease at baseline
- Median ART duration 66 months (36-105)
- 79.4% on NNRTIs and 19.8% on PIs
- gait ataxia and tremolousness

31 cases of incident neurological disorders with
20 patients with HIV-encephalitis

Symptomatic CSF escape – India (2)

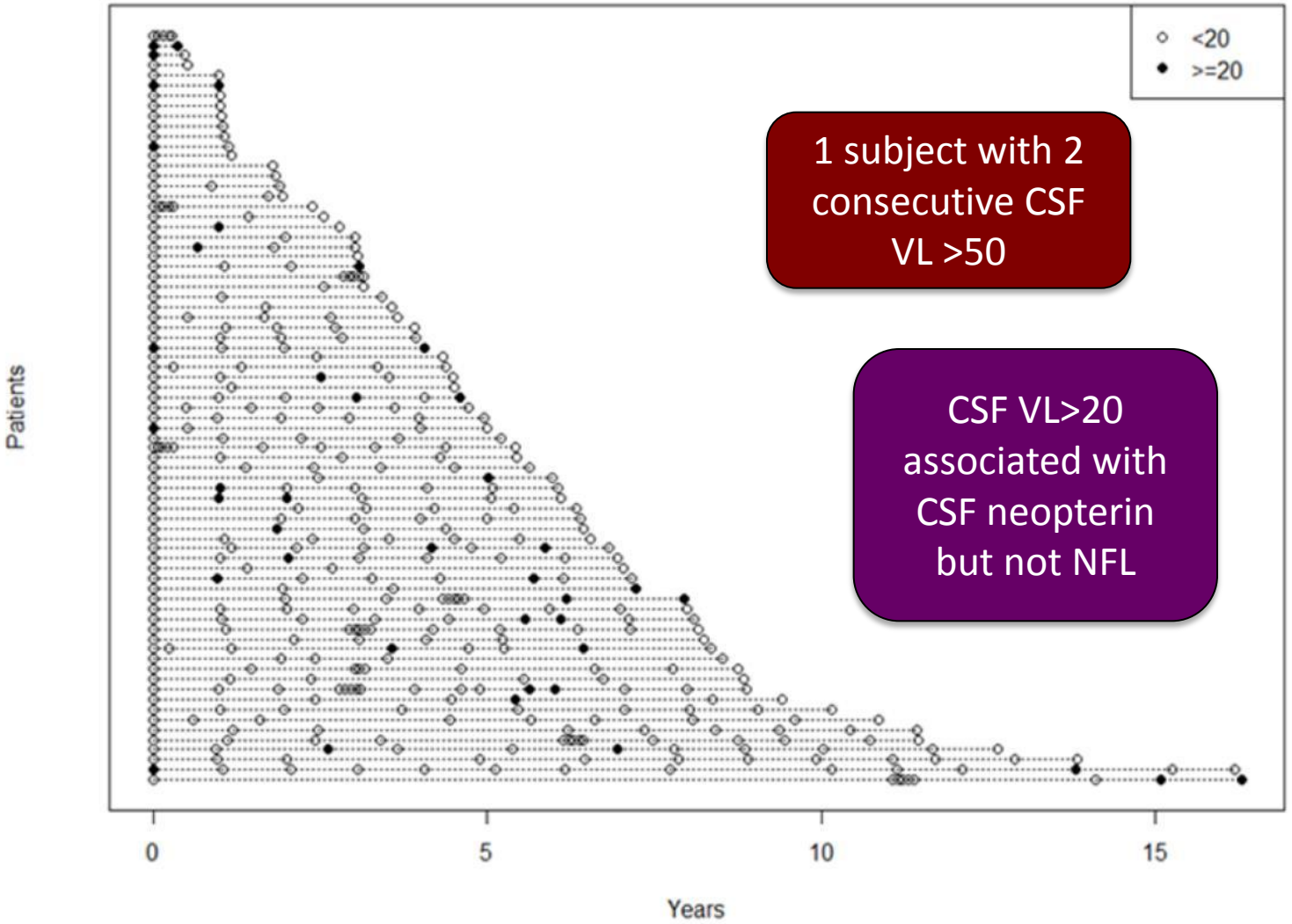


10	TDF/FTC + ATV/r	K65R, M184V	Y181C, Y188L	NS	NS

First line EFV, HIV RNA once a year, HAART change to PI/r (mostly ATV/r) with recycled NRTIs, very low CD4 nadir

Longitudinal - Eden

Twenty-seven (36%) patients had ≥1 CSF-HIV-RNA >20 copies/ml (23% >50), in median 50 (IQR 32-77) copies/ml.

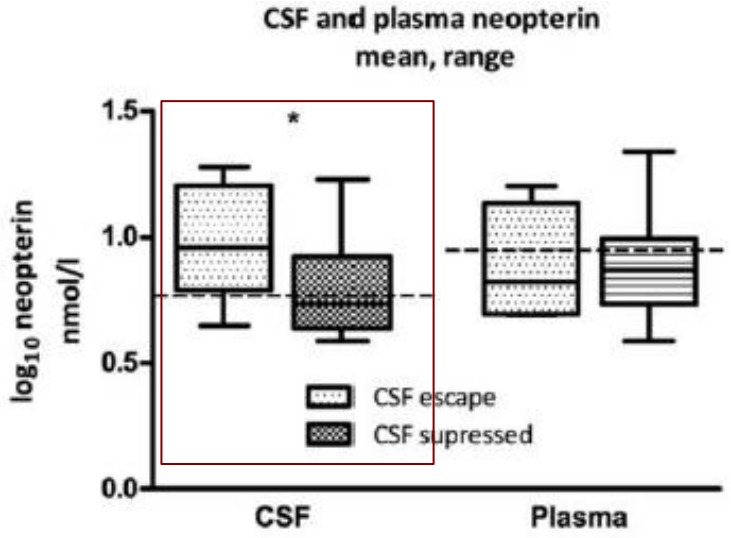


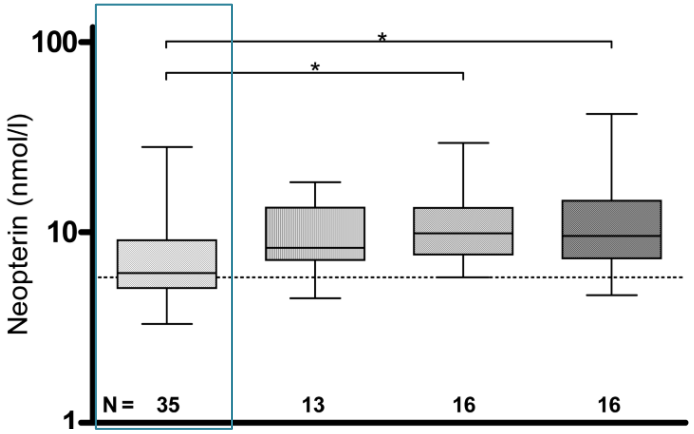
1 subject with 2 consecutive CSF VL >50

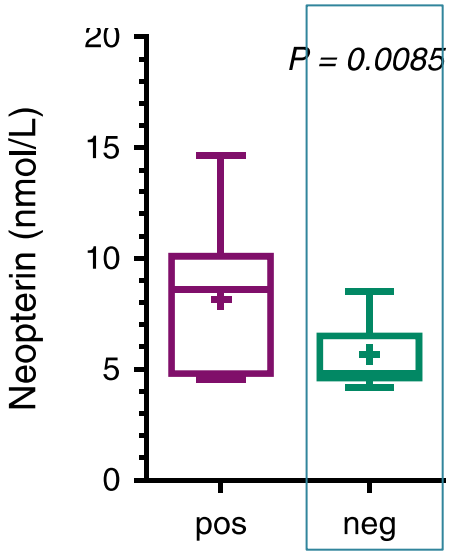
CSF VL>20 associated with CSF neopterin but not NFL

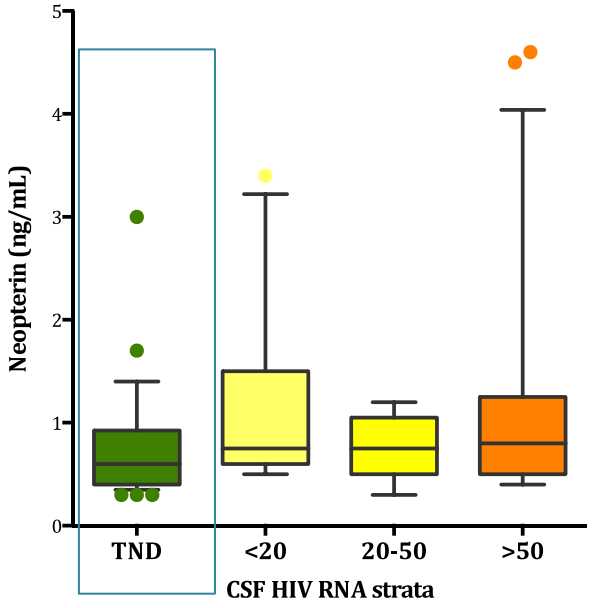
Eden A, et al. JID 2016

CSF low level replication & neopterin





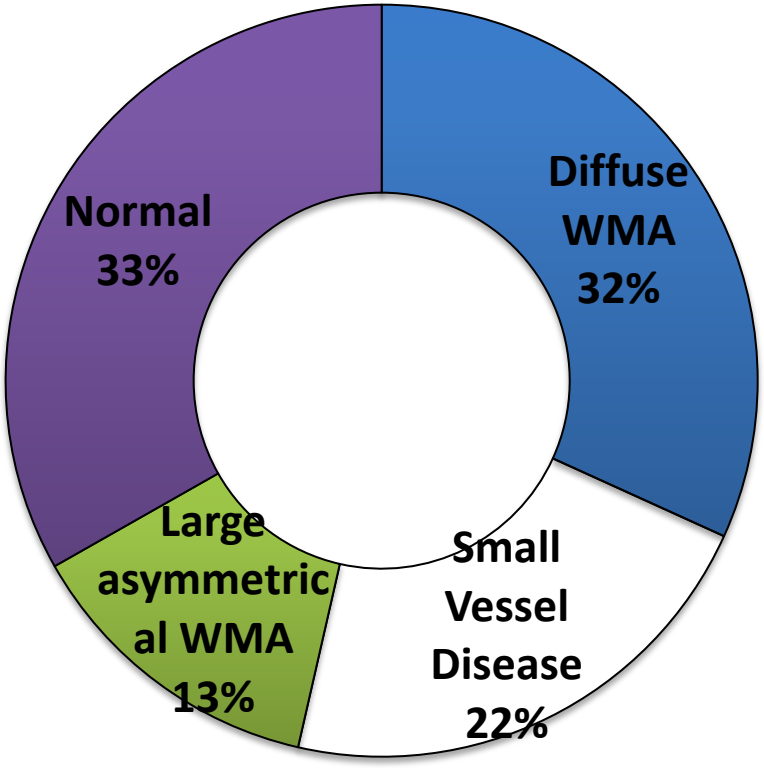




Eden A, et al. JID 2010; Yilmaz A, et al. JAIDS 2008; Dahl V, et al. AIDS 2014; Motta I, et al. *Under review*

Determinants WMA in HIV

- retrospective, cross-sectional study
- 254 patients: 70% male, 53% white, mean age 42 years, median current CD4 count 240 cells/mm3, and 41% not taking antiretroviral therapy (ART)



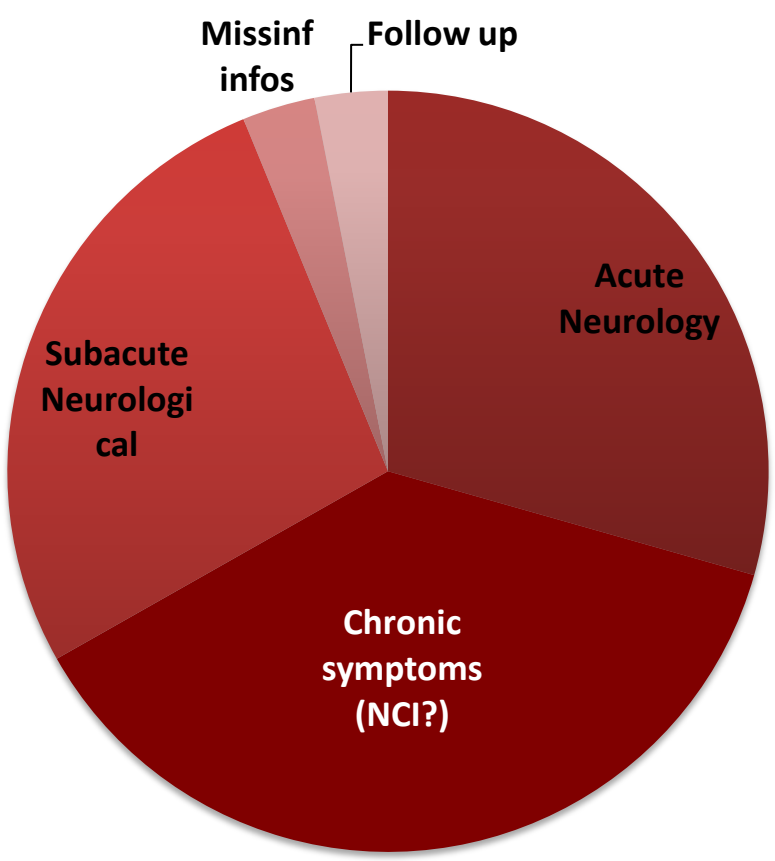
- Black Ethnicity

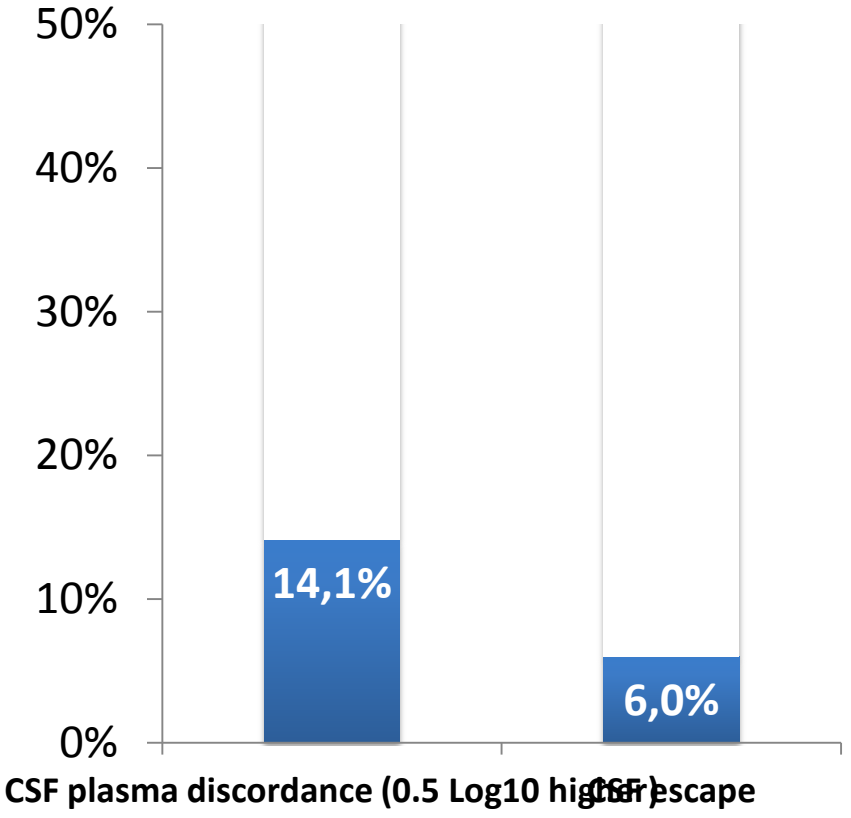
- Age
- CV risk factors

Haddow LJ, et al. AIDS care and STDs 2014

WMA and CSF escape

- 163 LPs





CPE and other scores

Studies on the CPE score

Reference	n	Design		⬆ CPE ⬇ CSF VL	⬆ CPE ⬆ NC testing	Areas NC	CPE cut off
Cysique et al.	37	prospective	single arm	**lower CSF VL**	**better**	6	≥2
Tozzi et al.	185	prospective	single arm	not done	**better**	4 and 8	no
Marra et al.	26	prospective	single arm	**lower CSF VL**	**worse**	8	≥2
Winston et al.	30	prospective	randomized	not done	**better**	Cogstate	no
Smurzynski et al.	2636	prospective	single arm	not done	**better >3 drugs**	3	no
Arendt et al.	3883	prospective	single arm	**lower CSF VL**	**better**	2	no
Garvey et al.	101	retrospective	single arm	not done	**no effect**	Cogstate	no
Rourke et al.	545	prospective	single arm	not done	**better**	4	≥1.5 (2008)
Robertson et al.	860	prospective	randomized	not done	**no effect**	4	no
Ciccarelli et al.	101	prospective	single arm	not done	**better**	8	≥6
Kahouadji et al.	54	prospective	single arm	not done	**worse**	2	no
Ellis et al.	49	prospective	randomized	**no effect**	**no effect – trend to lower**	8	(2.5 vs. 1)
Vassallo et al.	246	prospective	controlled	not done	**stable or better**	8	(8.1 vs. 6.9)
Baker et al.	64	prospective	single arm	not done	**no effect**	4	7
Carvahal	417	prospective	single arm	not done	**better**	4	no

Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions

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ABSTRACT

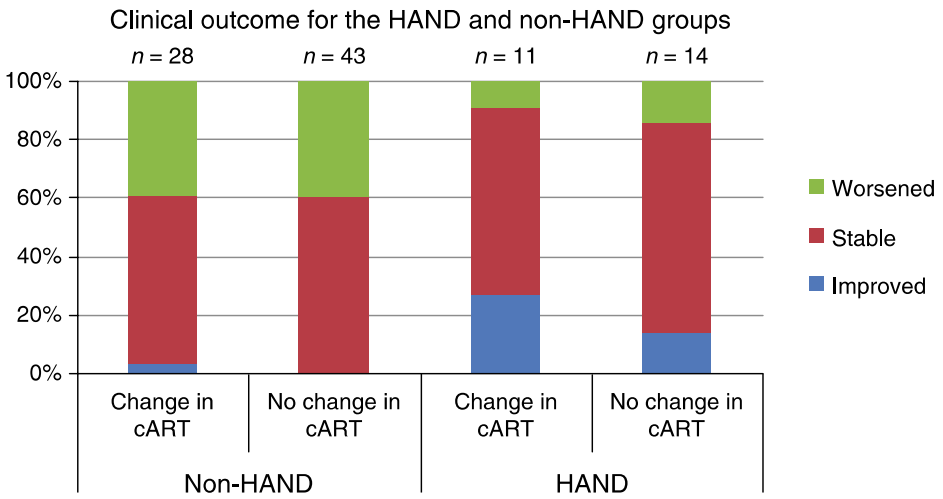
Objective: The link between CNS penetration of antiretrovirals and AIDS-defining neurologic disorders remains largely unknown.

Methods: HIV-infected, antiretroviral therapy–naive individuals in the HIV-CAUSAL Collaboration who started an antiretroviral regimen were classified according to the CNS Penetration Effectiveness (CPE) score of their initial regimen into low (<8), medium (8–9), or high (>9) CPE score. We estimated "intention-to-treat" hazard ratios of 4 neuroAIDS conditions for baseline regimens with high and medium CPE scores compared with regimens with a low score. We used inverse probability weighting to adjust for potential bias due to infrequent follow-up.

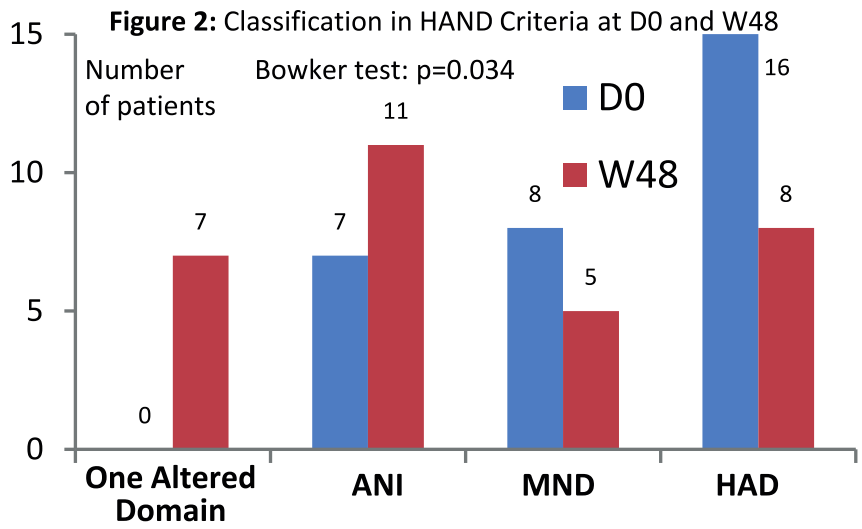
Results: A total of 61,938 individuals were followed for a median (interquartile range) of 37 (18, 70) months. During follow-up, there were 235 cases of HIV dementia, 169 cases of toxoplasmosis, 128 cases of cryptococcal meningitis, and 141 cases of progressive multifocal leukoencephalopathy. The hazard ratio (95% confidence interval) for initiating a combined antiretroviral therapy regimen with a high vs low CPE score was 1.74 (1.15, 2.65) for HIV dementia, 0.90 (0.50, 1.62) for toxoplasmosis, 1.13 (0.61, 2.11) for cryptococcal meningitis, and 1.32 (0.71, 2.47) for progressive multifocal leukoencephalopathy. The respective hazard ratios (95% confidence intervals) for a medium vs low CPE score were 1.01 (0.73, 1.39), 0.80 (0.56, 1.15), 1.08 (0.73, 1.62), and 1.08 (0.73, 1.58).

Conclusions: We estimated that initiation of a combined antiretroviral therapy regimen with a high CPE score increases the risk of HIV dementia, but not of other neuroAIDS conditions. ***Neurology*®** **2014;83:134–141**

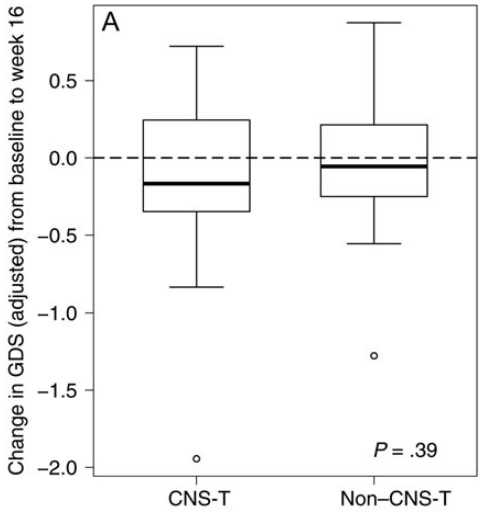
Prospective studies



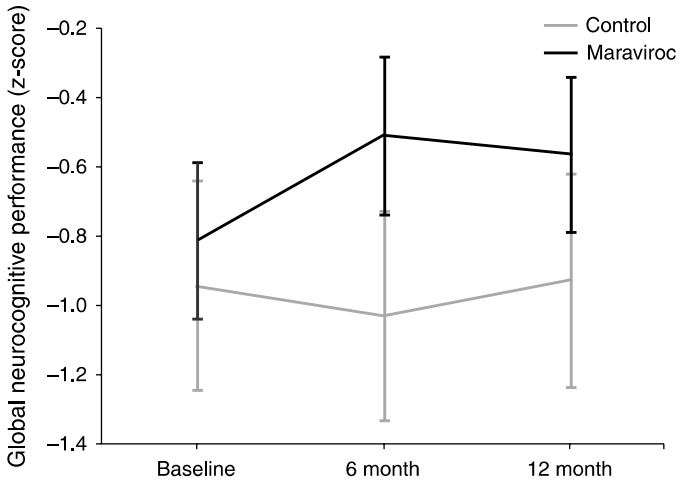
Vassallo M, et al. AIDS 2014



Force G, et al. CROI and Glasgow 2016

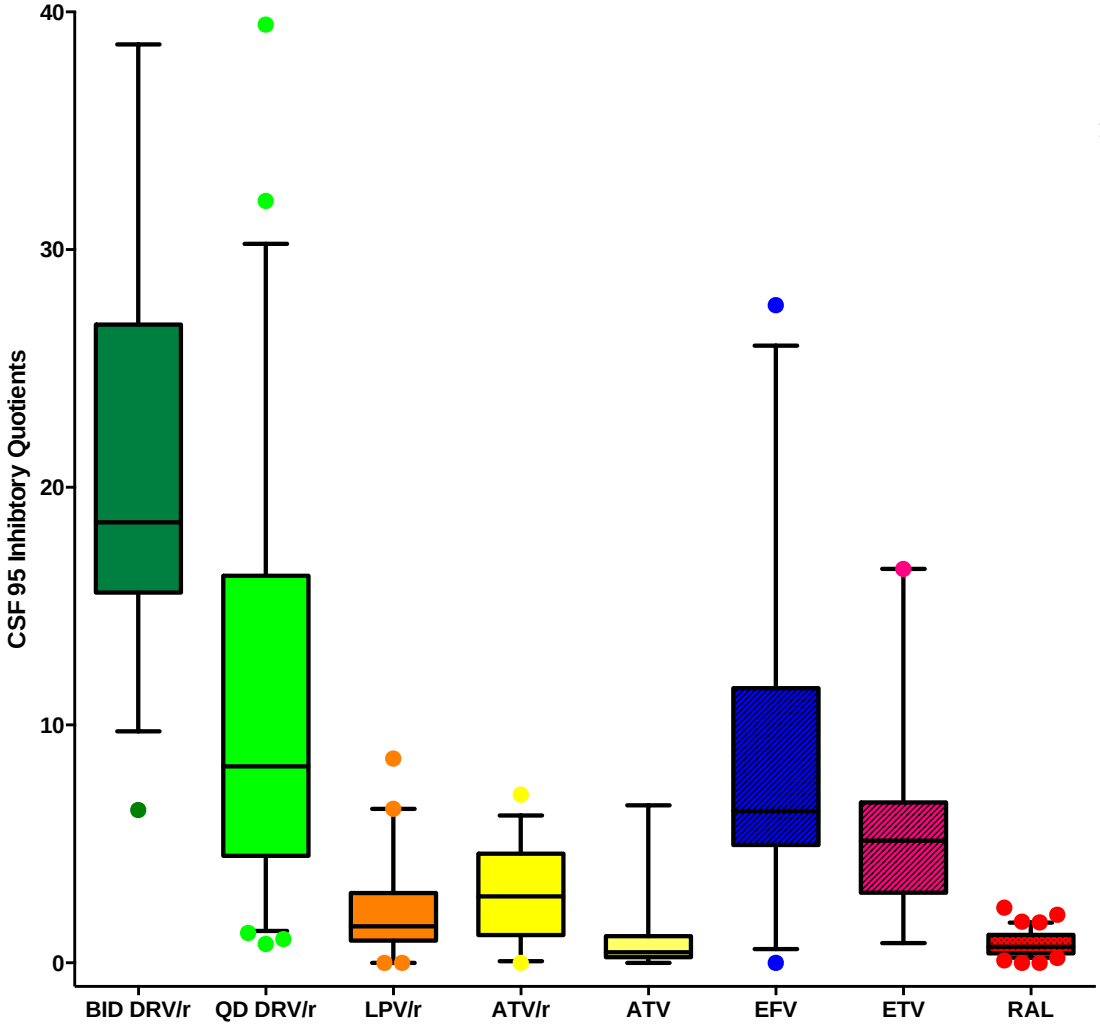


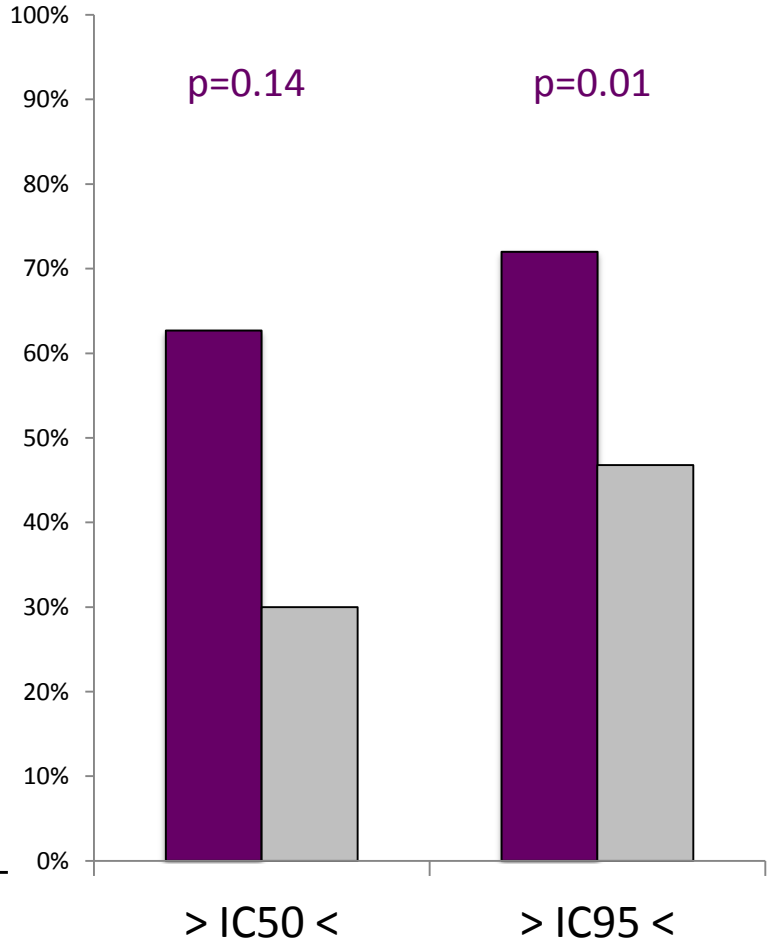
Ellis R, et al. CID 2014



Gates TM, et al. AIDS 2016

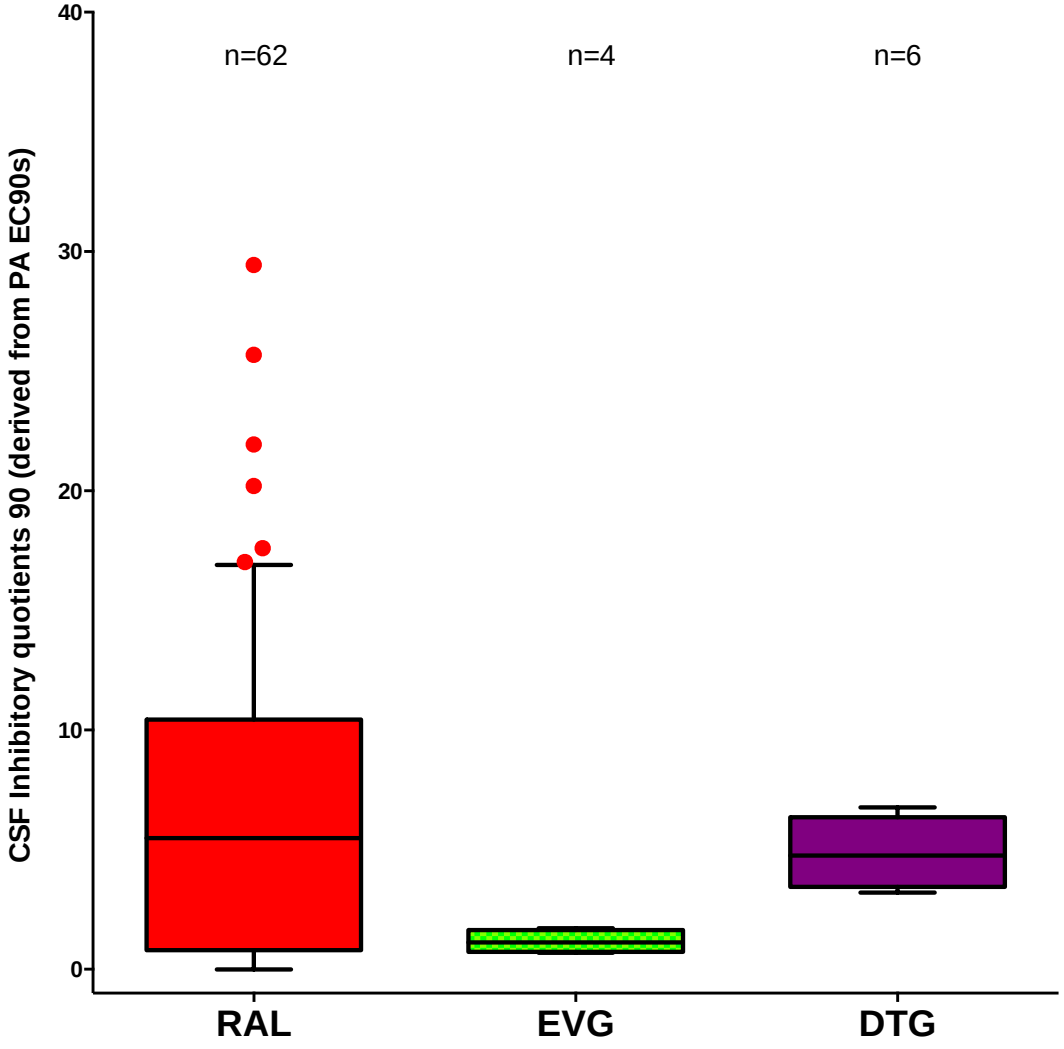
CSF IQ_{95}



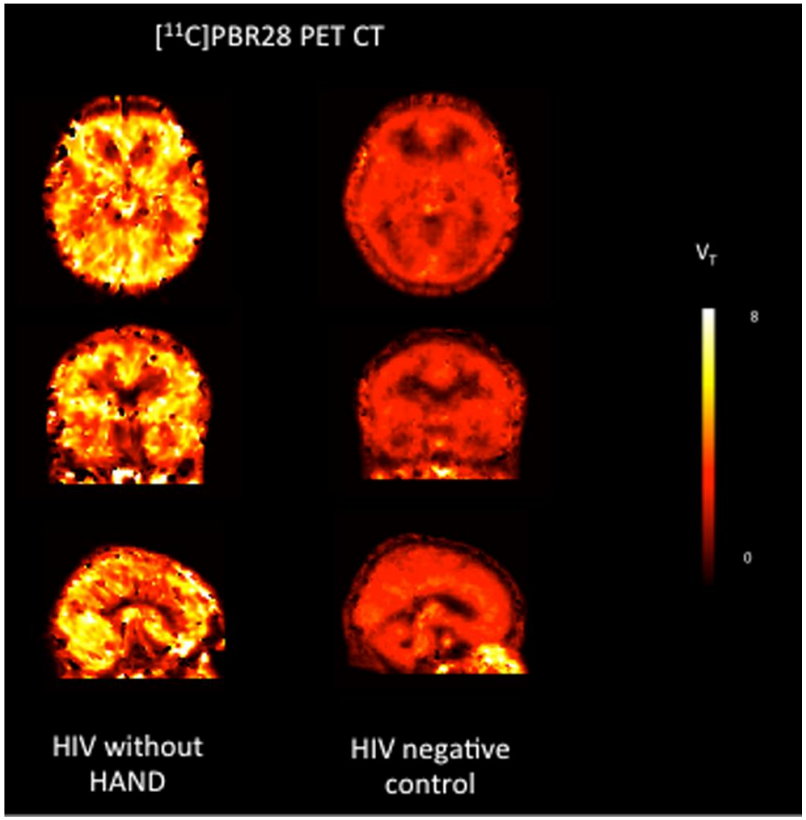


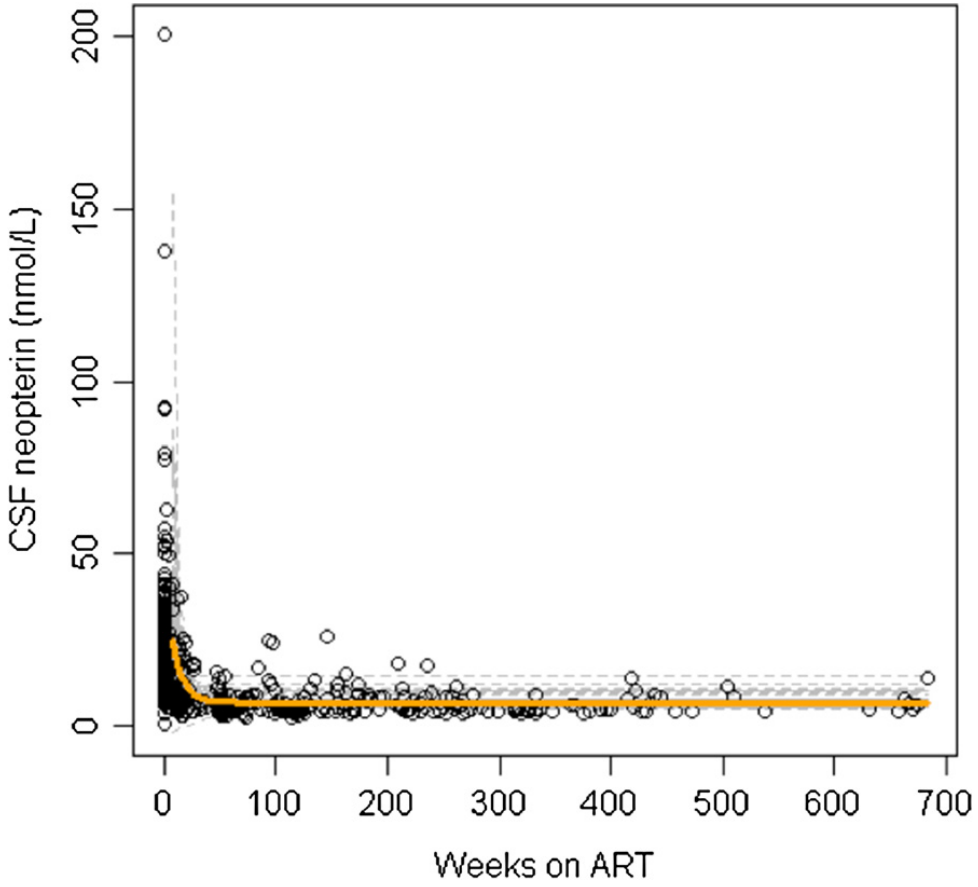
Calcagno A, et al. CID 2014 e unpublished

CSF IQ_{90} INSTIs



Microglial Activation



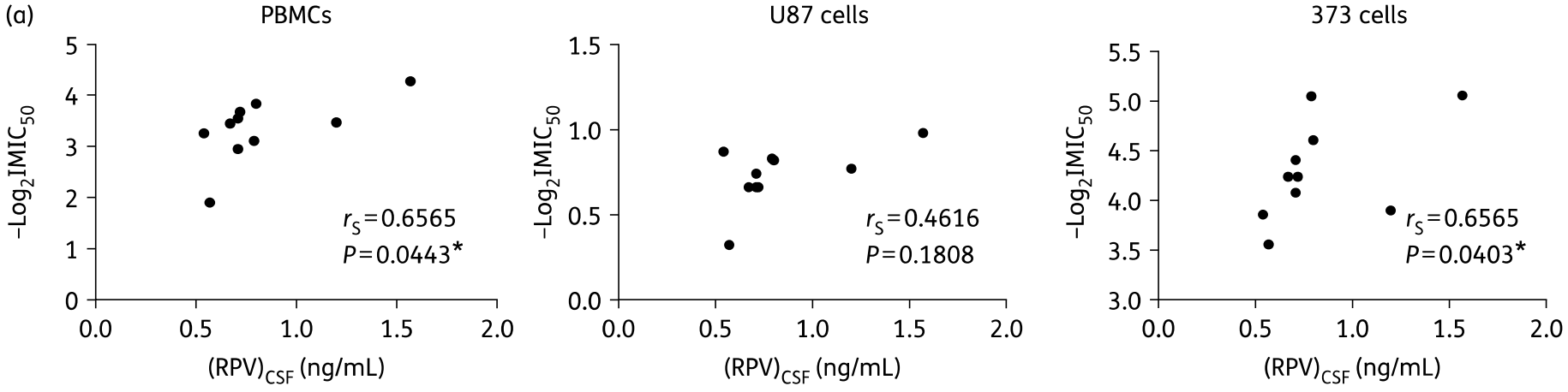


Vera JH, et al. Eur J Nucl Med Mol Imaging 2017; Yilmaz A, et al. J Neuroinflammation 2013

Ex vivo efficacy

Patients' CSF on PBMCs, glioblastoma/astrocytoma and astrocytoma cells

- **TDF/FTC+LPV/r+MVC > TDF/FTC+RPV**
- **CSF LPV and RPV concentrations associated with antiviral effect and MRS changes**

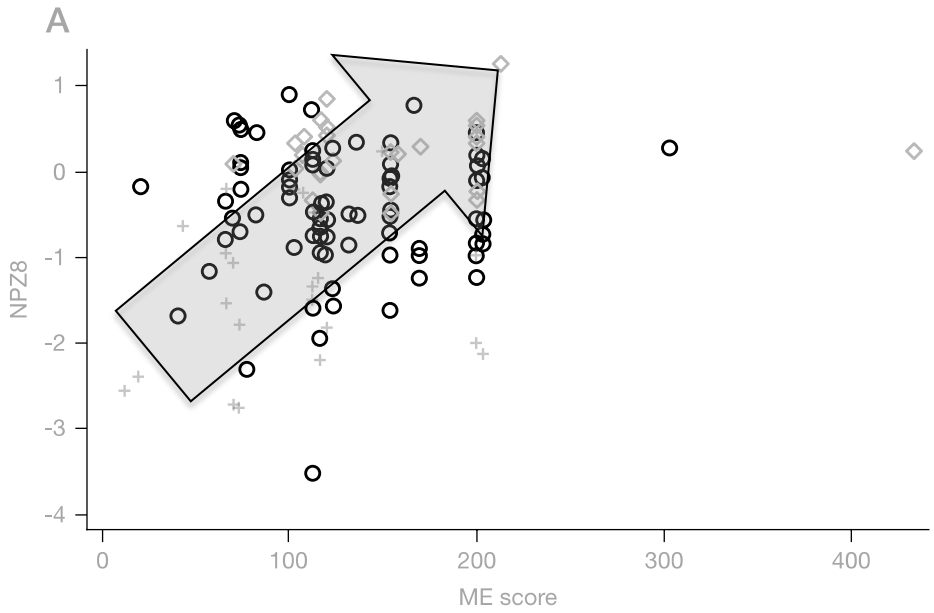


Mora-Perris B, et al. JAC 2015

Microglia-targeted treatment?

Table 1. Published *in vitro* EC_{50} acute infection values for various ARV drugs in primary macrophage cell cultures and the calculated ME scores

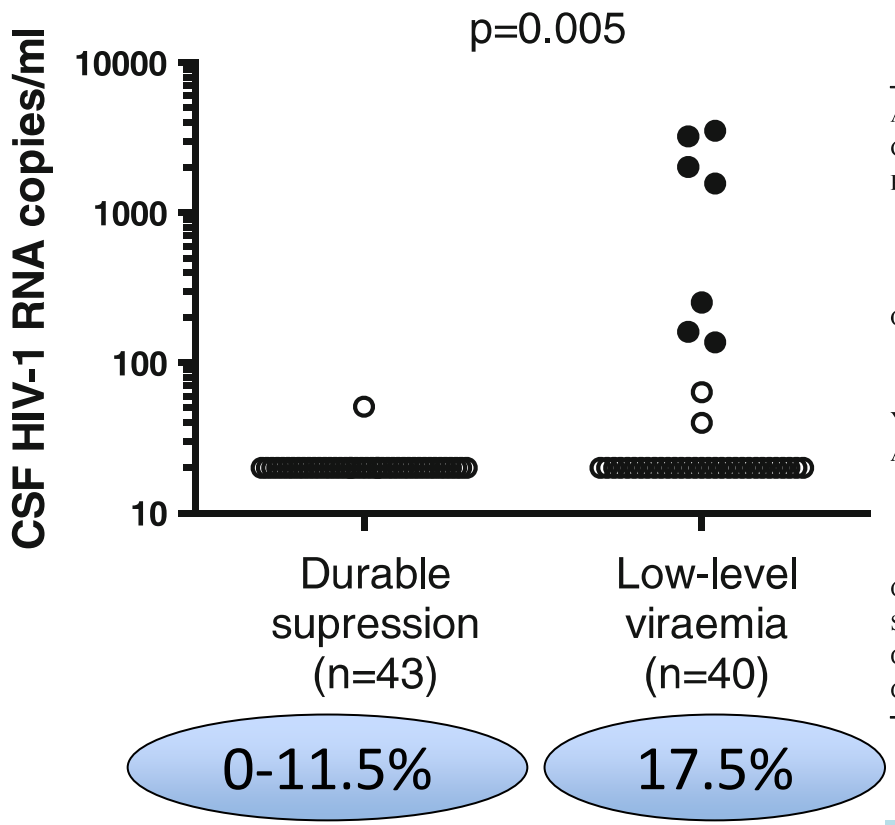
ARV drug	Acute infection in macrophages EC_{50}, nM	ME score[a]
NRTI		
Abacavir sulfate	300	3
Didanosine	50	20
Emtricitabine[b]	80	12.5
Lamivudine	20	50
Stavudine	240	4
Tenofovir disoproxil fumarate	20	50
Zalcitabine	3	333
Zidovudine	20	50
NNRTI		
Delavirdine	10	100
Efavirenz	10	100
Nevirapine	50	20
Protease inhibitor		
Amprenavir[c]	10	100
Indinavir	60	17
Nelfinavir	80	12.5
Ritonavir	120	8.3
Saquinavir	50	20
Fusion inhibitor		
Enfuvirtide	20	50



Shikuma C, et al. Antiviral Therapy 2012

PK and Antiretroviral strategies

CSF escape e LLV



	CSF/plasma discordance		*p* value
	Yes (*n* = 20)	No (*n* = 133)	
Age, median years (IQR)	46 (43, 50)	46 (41, 54)	0.913
Gender male, *n* (%)	15 (75)	117 (88)	0.156
Risk group/ethnicity, *n* (%)			0.007
White MSM	7 (35)	80 (60)	
Black heterosexual	8 (40)	17 (13)	
Other	5 (25)	36 (27)	
CD4, median cells/mm^3 (IQR)			
Nadir	32 (21, 256)	159 (49, 281)	0.030
Current	374 (190, 613)	464 (310, 707)	0.163
Years since HIV diagnosis, median (IQR)	10 (7, 16)	9 (5, 16)	0.833
ART at sampling, *n* (%)			0.178
PI/r based	14 (70)	74 (55)	
NNRTI based	3 (15)	47 (35)	
Other	3 (15)	12 (9)	
CPE, median (IQR)	7 (7, 10)	7 (6, 8)	0.250
Self reported adherence <95 %, *n* (%)	2 (10)	12 (9)	1.000
CSF WCC median cells/mm^3 (IQR)	11 (<1, 21)	<1 (<1, 3)	0.018
CNS infection, *n* (%)	3 (15)	18 (14)	0.740

CSF RAMs in 5 pts in the LLV group and 6 in the clinical cohort

Nightingale S, et al. JNV 2016

Antiretroviral neuropenetration scores better correlate with cognitive performance of HIV-infected patients after accounting for drug susceptibility

	Global cognitive impairment (HAND)		Memory impairment		Attention impairment		Speed of mental processing impairment		Fine motor functioning impairment		Language impairment	
	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
CPE	0.83 (0.63, 1.10)	0.192	0.82 (0.63, 1.07)	0.149	1.20 (0.88, 1.65)	0.253	0.89 (0.65, 1.20)	0.436	1.10 (0.86, 1.42)	0.453	0.90 (0.67, 1.19)	0.456
GSS_{ANRS}	0.55 (0.26, 1.15)	0.116	0.64 (0.32, 1.26)	0.196	1.68 (0.69, 4.12)	0.254	1.28 (0.58, 2.85)	0.547	1.92 (0.92, 4.00)	0.084	0.58 (0.27, 1.22)	0.149
GSS_{HIVDB}	0.60 (0.31, 1.17)	0.135	0.83 (0.45, 1.51)	0.542	1.14 (0.52, 2.50)	0.753	1.13 (0.56, 2.27)	0.734	1.66 (0.88, 3.15)	0.120	0.74 (0.38, 1.44)	0.376
GSS_{REGA}	0.64 (0.32, 1.26)	0.194	0.74 (0.40, 1.38)	0.347	1.33 (0.59, 2.98)	0.487	1.47 (0.69, 3.13)	0.321	1.97 (0.97, 3.88)	0.060	0.56 (0.28, 1.12)	0.101
CPE-GSS_{ANRS}	0.75 (0.58, 0.96)	**0.022**	0.83 (0.66, 1.03)	0.091	1.13 (0.84, 1.53)	0.431	0.94 (0.72, 1.21)	0.607	1.22 (0.96, 1.55)	0.106	0.89 (0.70, 1.13)	0.348
CPE-GSS_{HIVDB}	0.77 (0.61, 0.99)	**0.038**	0.89 (0.72, 1.10)	0.274	1.06 (0.79, 1.42)	0.713	0.94 (0.73, 1.22)	0.654	1.17 (0.93, 1.48)	0.178	0.93 (0.74, 1.18)	0.562
CPE-GSS_{REGA}	0.78 (0.61, 0.99)	**0.038**	0.86 (0.69, 1.06)	0.158	1.05 (0.78, 1.40)	0.772	0.97 (0.76, 1.25)	0.819	1.24 (0.98, 1.56)	0.078	0.88 (0.69, 1.11)	0.269

Fabbiani M, et al. Antiv Ther 2015

Patient A.G.

- Beclomethasone/formeterol 2 puff x 2
- Tiotropium (bromide) 2 puff
- Pregabalin 150 mg x 2
- Oxcarbamazepine 300 mg x 2
- Pantoprazole 20 mg
- Delorazepam 0.5 mg x 2
- Flumazepam 15 mg
- Methadon 125 mg (!)
- Calcium/colecalciferol 1g/d – XXVIII/w

- Ceftazidim 1g x3
- Amikacin 600 mg
- methylprednisolone 20 mgx2

- Atazanavir 200 mg x 2
- Raltegravir 400 mg x 2

Symptomatic CSF escape

CSF HIV RNA 579 copies/mL (plasma >20)

	plasma PK	CSF PK	
ATV	54	0.9	1.7%
RAL	296	19	6.4%

Pantoprazole lowers ATV (70-90%)

RAL functional monotherapy in the CSF/CNS

N155H and K95Q on CSF

Maraviroc effect

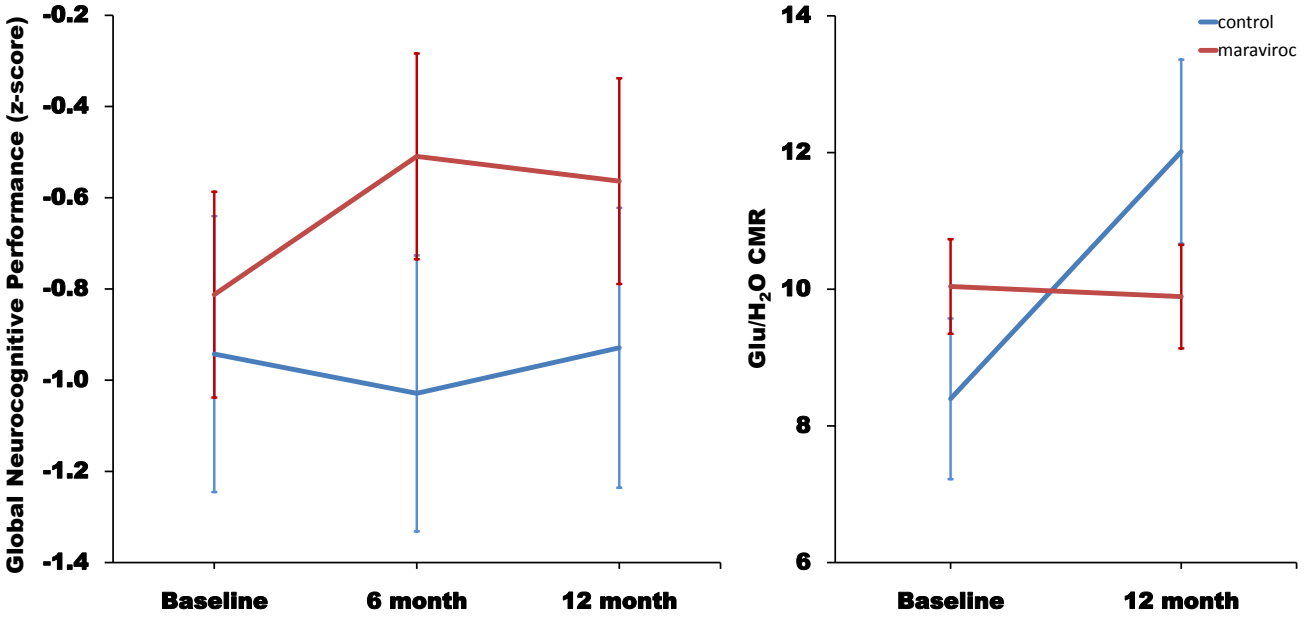
- Antiviral? CSF viruses often R5 tropic
  - Astrocyte infected via CXCR4
- Protective for SIV infection in macaques
- **Maraviroc intensification**
  - increase in MRS Naa/Cr (neuronal integrity)
  - reduction in CSF CXCL10 (IP-10)
  - better with higher MVC plasma conc
  - Reduction in CD16+ monocytes, monocyte-associated HIV DNA and NC function

Souliè C, et al. JAIDS 2009; Li G-H, et al. AIDS 2015; Garvey L, et al. JAC 2012; Vera JH, et al. HIV Clin Trials 2012; Ndhlovu LC, et al. JNV 2014

Maraviroc effect (2)

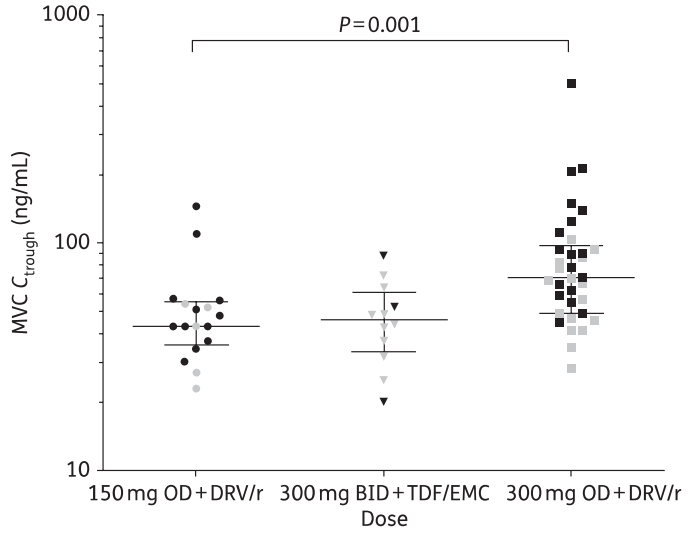
14 virally-suppressed (blood and CSF) HIV+ males on stable cART with recent progression to HAND

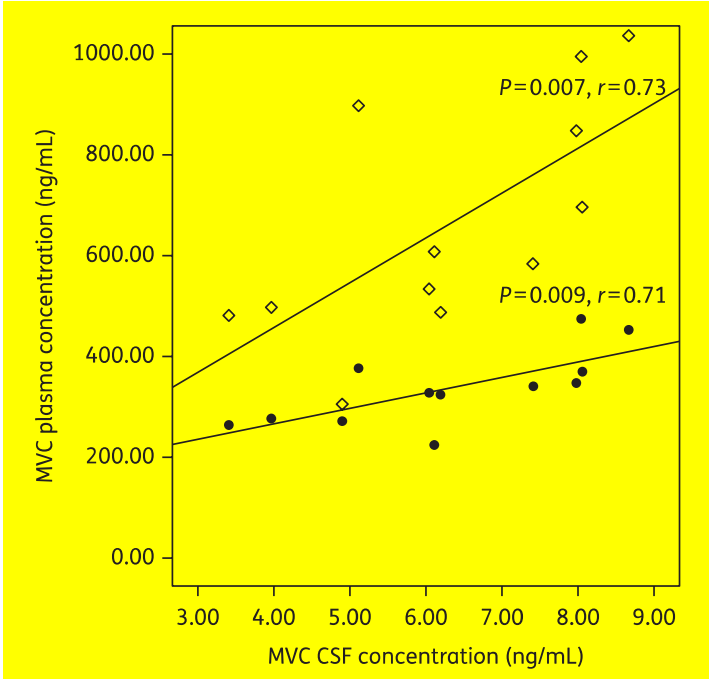
Open-label RCT of MVC-intensification



MVC DOSE!

trial	Study drugs	Virological Efficacy	Immunological efficacy
MODERN	DRV/R + MVC 150 QD	Inferior (stopped)	equal
A4401078	ATV/R + MVC 150 QD	Inferior (slightly)	equal
VEMAN	LPV/rR+ MVC 150 QD	equal	superior



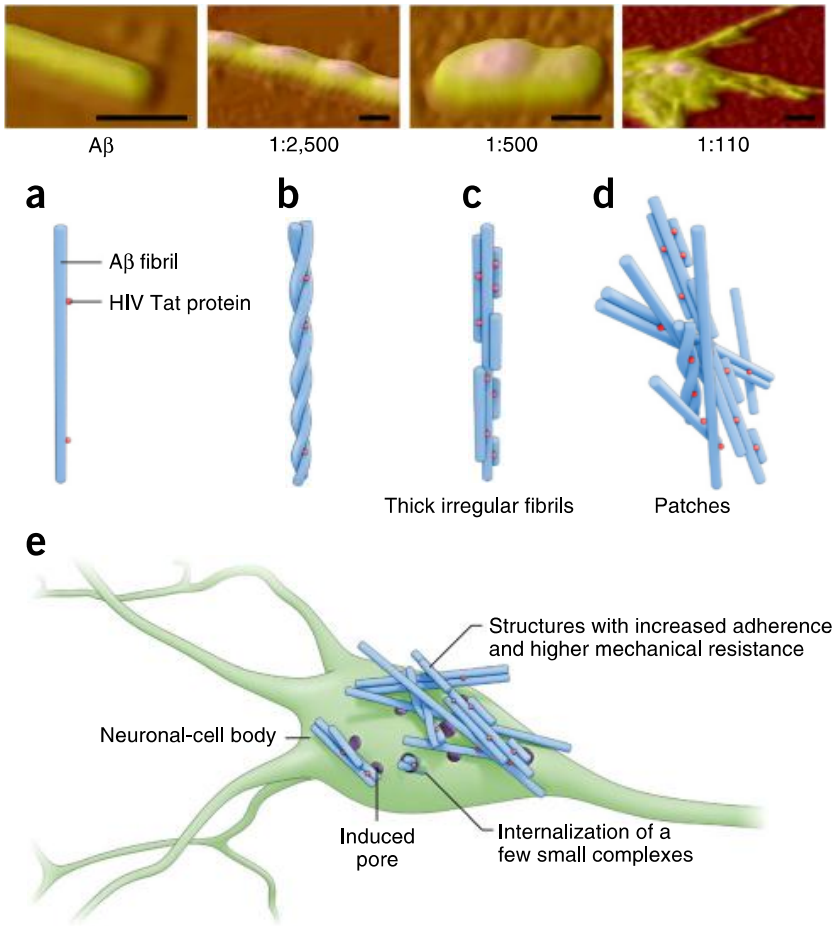


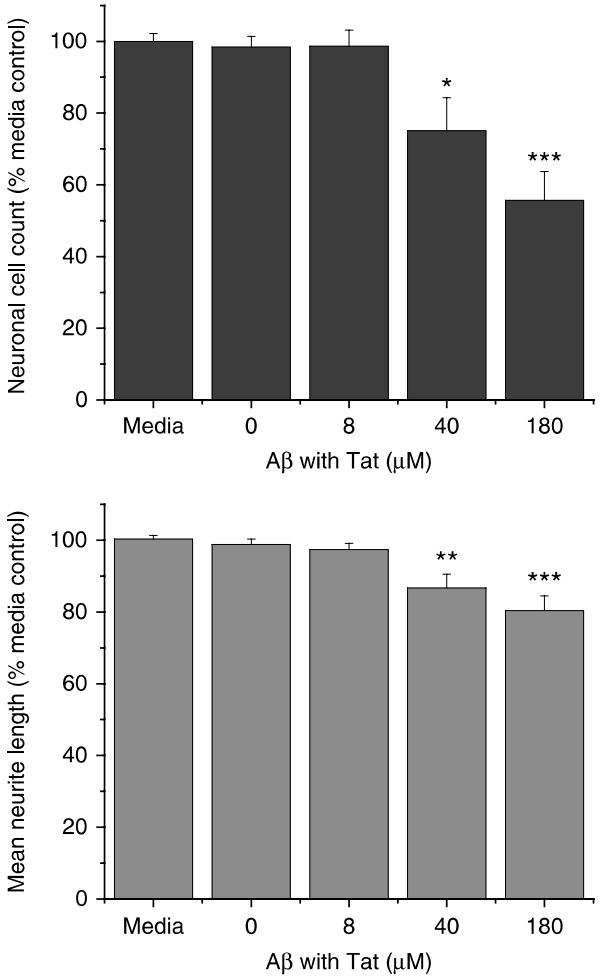
Stellbrink HJ, et al. AIDS 2016; Mills A, et al. JAIDS 2013; Nozza S, et al. Clin Micr Infe 2015; Okoli C, et al. JAC 2012; Garvey L, et al. JAC 2012

PK and Neurotoxicity

HIV Tat protein and amyloid-β peptide form multifibrillar structures that cause neurotoxicity

Alina Hategan[1], Mario A Bianchet[2,3], Joseph Steiner[1], Elena Karnaukhova[4], Eliezer Masliah[5], Adam Fields[5], Myoung-Hwa Lee[1], Alex M Dickens[2], Norman Haughey[2], Emilios K Dimitriadis[6] & Avindra Nath[1]





Hategan A, et al. Nature Structural and Molecular Biology 2017

Neurotoxicity

① *In vitro* and in macaques neuronal toxicity

② Improvement in neurocognitive functioning at **ARVs interruption** (better in **EFV** recipients);

③ **Beta amyloid** metabolism interference (**EFV** and PIs)

④ **EFV** and neurocognitive disorders

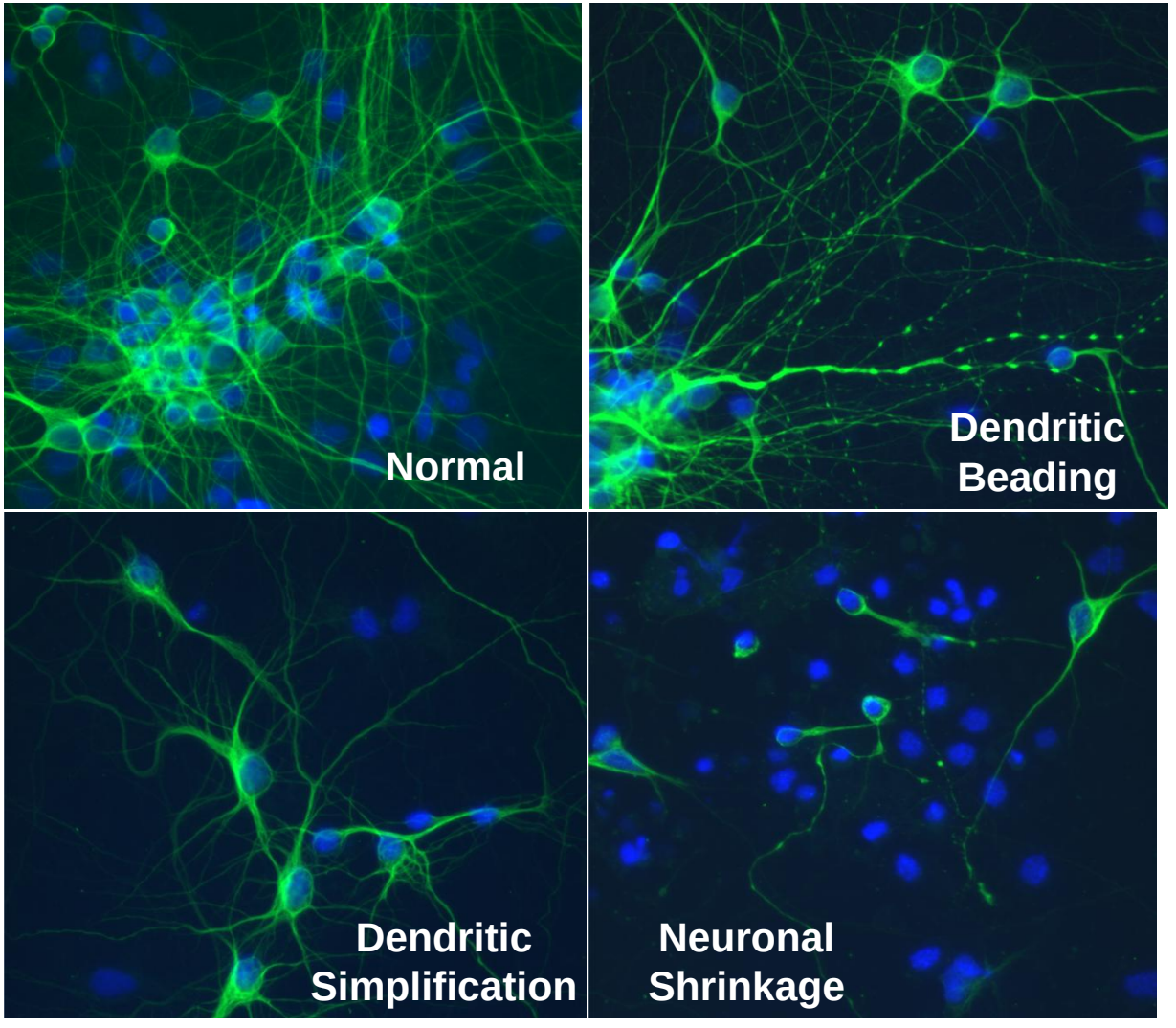
⑤ PIs disrupt astrocytic glutamate transporter function and neurobehavioral performance

⑥ Might be dose-dependant (**EFV**)

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

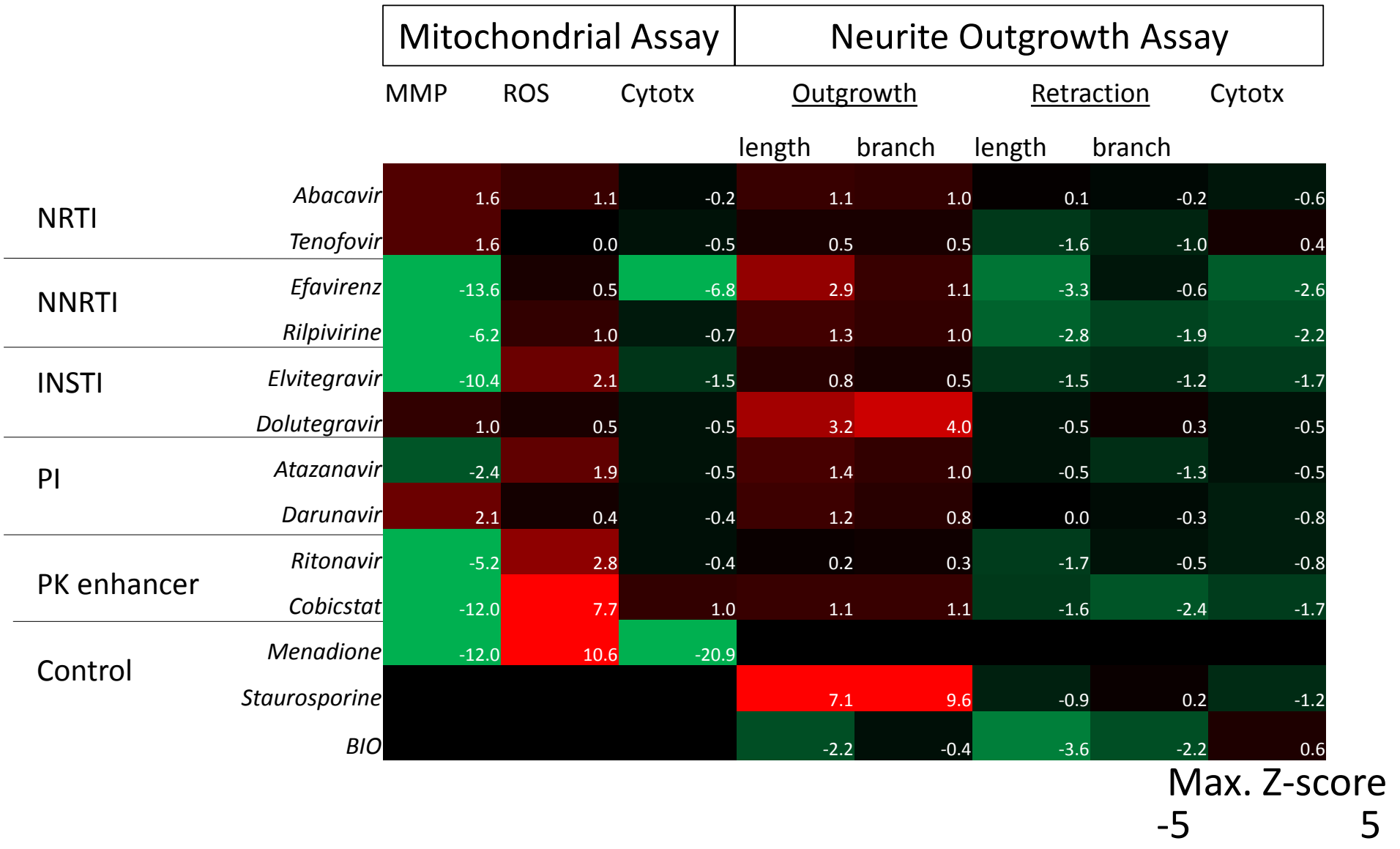
In vitro neurotoxicity

- Fetal rat cortical neuron cultures
- Some degree of **functional** injury seen with all drugs
- **EFV>others> FTC,DRV,MVC**
- no additive effect



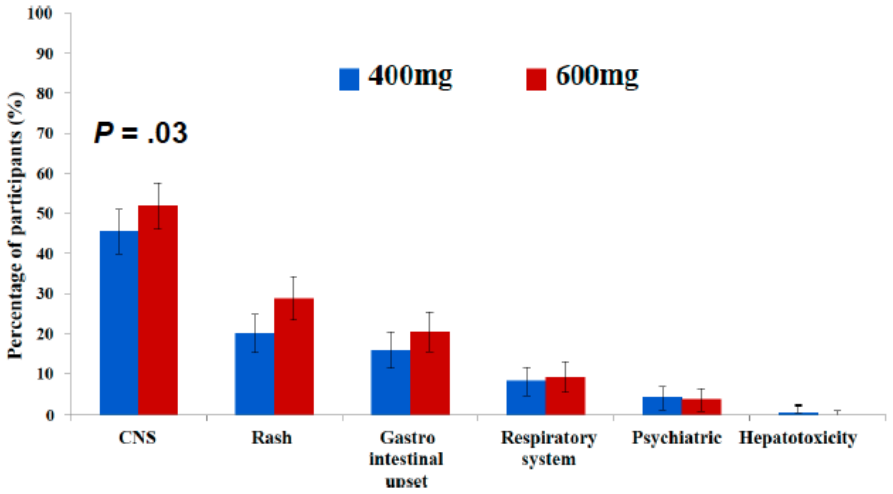
Robertson K, et al. JNV 2012

Neurotoxicity @ CROI2016



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



- **Debated association between EFV use and HAND**

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

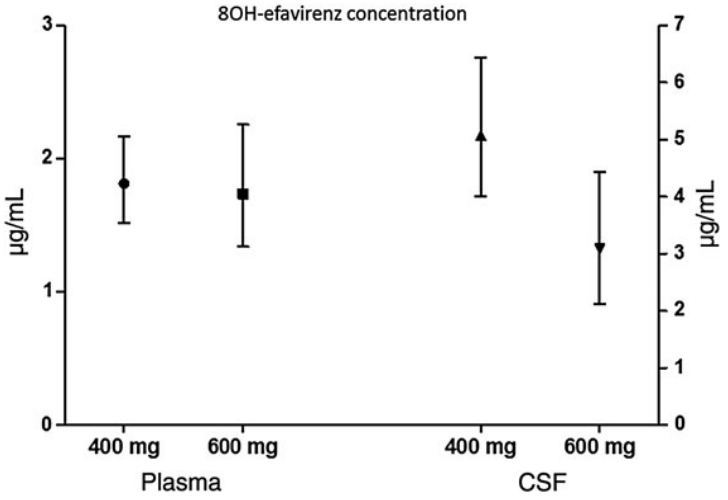
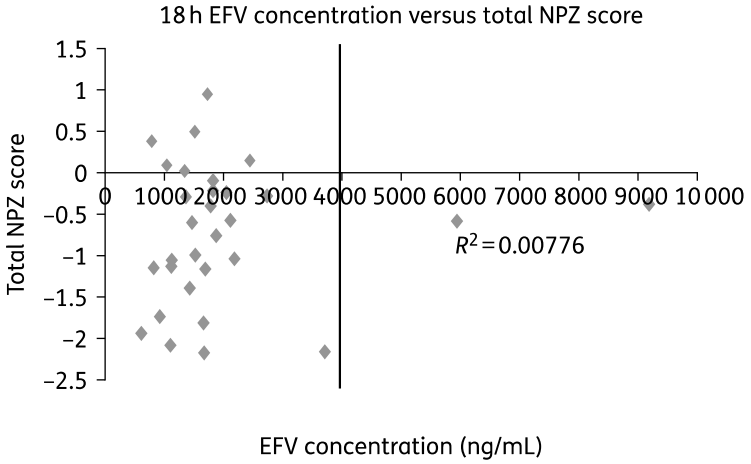
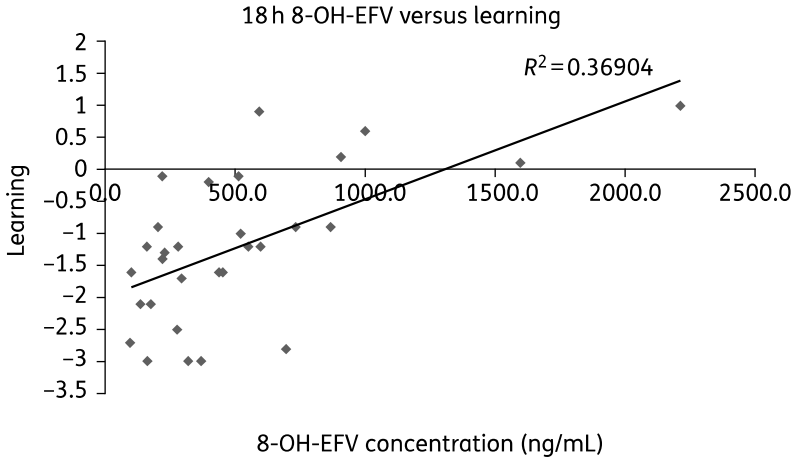


Table 4. Correlation Between Cerebrospinal Fluid 8-Hydroxy Efavirenz Exposure and Patient-Completed Questionnaires

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.





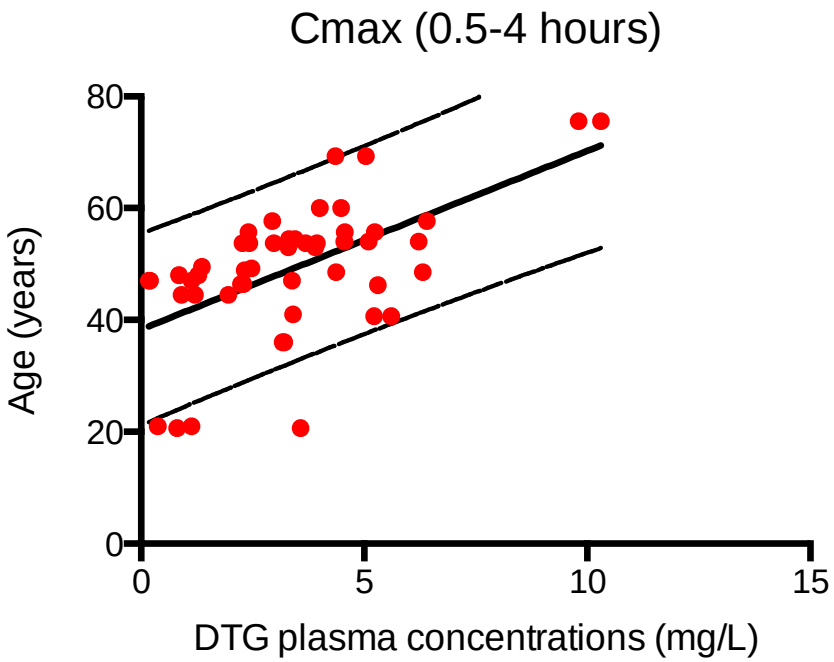
Tovar-y-Romo LB, et al. J Pharmacol Exp Ther 2012 ; Winston A, et al. CID 2015; Sandkovski U, et al. JAC 2017

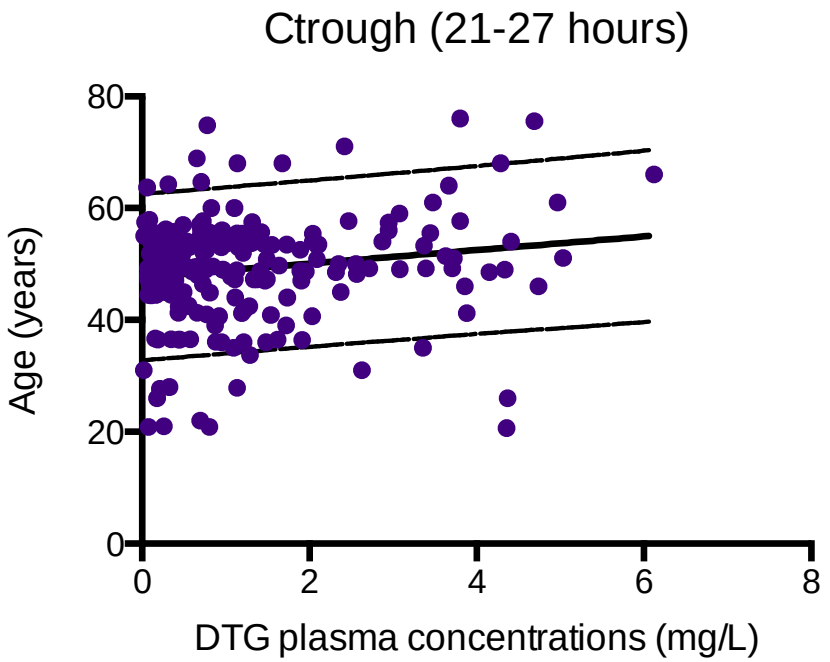
Dolutegravir

- 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
- Neurotoxicity?
- PK matters?
  - higher incidence in patients on concomitant abacavir, female and older subjects

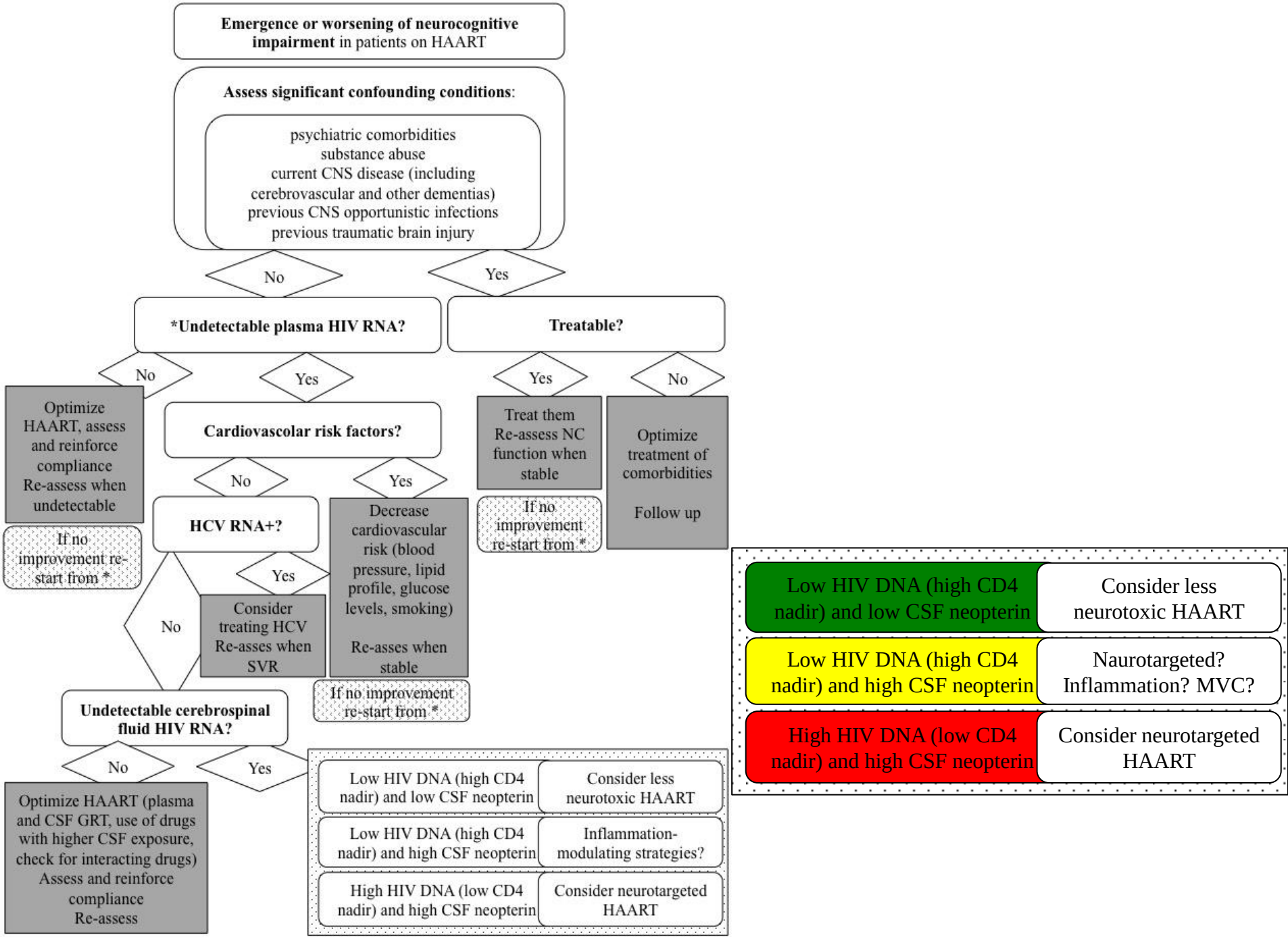
De Boer MG, AIDS 2016; Hoffman C, et al. HIV Medicine 2017; Fettiplace A, et al. JAIDS 2016; Bonfanti P, et al. AIDS 2017

Dolutegravir and PK?





	Drug	CPE score	95% Inhibitory Quotients	Macrophage efficacy score	in vitro neurotox
NRTIs	Abacavir	3	NA	3	+
	Emtricitabine	3	NA	12.5	0
	Lamivudine	2	NA	50	+
	Tenofovir disoproxil fumarate	1	NA	50	0
	Zidovudine	4	NA	50	+
NNRTIs	Nevirapine	4	NA	20	+
	Efavirenz	3	6.4	100	++
	Etravirine	2	5.1	NA	+
	Rilpivirine	3?	NA	NA	+
PIs	Atazanavir	2	0.4	NA	+
	Atazanavir/r	2	2.8	NA	+
	Darunavir/r	3	8.2-18.5	NA	0
	Lopinavir/r	3	1.5	NA	NA
INIs	Raltegravir	3	0.7	NA	+
	Elvitegravir/r	3?	NA	NA	+
	Dolutegravir	4?	NA	NA	+?
EIs	Maraviroc	3	NA	NA	0
	Enfuvirtide	1	NA	50	NA


Emergence or worsening of neurocognitive impairment in patients on HAART
Assess significant confounding conditions:
psychiatric comorbidities
substance abuse
current CNS disease (including cerebrovascular and other dementias)
previous CNS opportunistic infections
previous traumatic brain injury
No
Yes
*Undetectable plasma HIV RNA?
Treatable?
No
Yes
Yes
No
Optimize HAART, assess and reinforce compliance Re-assess when undetectable
If no improvement re-start from *
Cardiovascolar risk factors?
Treat them Re-assess NC function when stable
If no improvement re-start from *
Optimize treatment of comorbidities
Follow up
No
Yes
HCV RNA+?
Decrease cardiovascular risk (blood pressure, lipid profile, glucose levels, smoking)
Re-asses when stable
If no improvement re-start from *
Yes
No
Consider treating HCV Re-asses when SVR
Undetectable cerebrospinal fluid HIV RNA?
No
Yes
Optimize HAART (plasma and CSF GRT, use of drugs with higher CSF exposure, check for interacting drugs) Assess and reinforce compliance Re-assess
Low HIV DNA (high CD4 nadir) and low CSF neopterin
Consider less neurotoxic HAART
Low HIV DNA (high CD4 nadir) and high CSF neopterin
Inflammation-modulating strategies?
High HIV DNA (low CD4 nadir) and high CSF neopterin
Consider neurotargeted HAART
Low HIV DNA (high CD4 nadir) and low CSF neopterin
Consider less neurotoxic HAART
Low HIV DNA (high CD4 nadir) and high CSF neopterin
Naurotargeted? Inflammation? MVC?
High HIV DNA (low CD4 nadir) and high CSF neopterin
Consider neurotargeted HAART

HIV DNA/CD4 nadir

1: Circulating HIV DNA Correlates With Neurocognitive Impairment in Older HIV-infected Adults on Suppressive ART. Oliveira MF et al. Sci Rep. 2015

2: Peripheral blood mononuclear cells HIV DNA levels impact intermittently on neurocognition. Cysique LA, et al. PLoS One. 2015

3: HIV DNA in CD14+ reservoirs is associated with regional brain atrophy in patients naive to combination antiretroviral therapy. Kallianpur KJ et al. AIDS. 2014

4: Peripheral blood HIV DNA is associated with atrophy of cerebellar and subcortical gray matter. Kallianpur KJ, et al. Neurology. 2013

5: Regional cortical thinning associated with detectable levels of HIV DNA. Kallianpur KJ et al. Cereb Cortex. 2012

6: Amount of HIV DNA in peripheral blood mononuclear cells is proportional to the severity of HIV-1-associated neurocognitive disorders. et al. J Neuropsychiatry Clin Neurosci. 2009

J. Neurovirol. (2017) 23:216–225
DOI 10.1007/s13365-016-0490-z

A decreasing CD4/CD8 ratio over time and lower CSF-penetrating antiretroviral regimens are associated with a higher risk of neurocognitive deterioration, independently of viral replication

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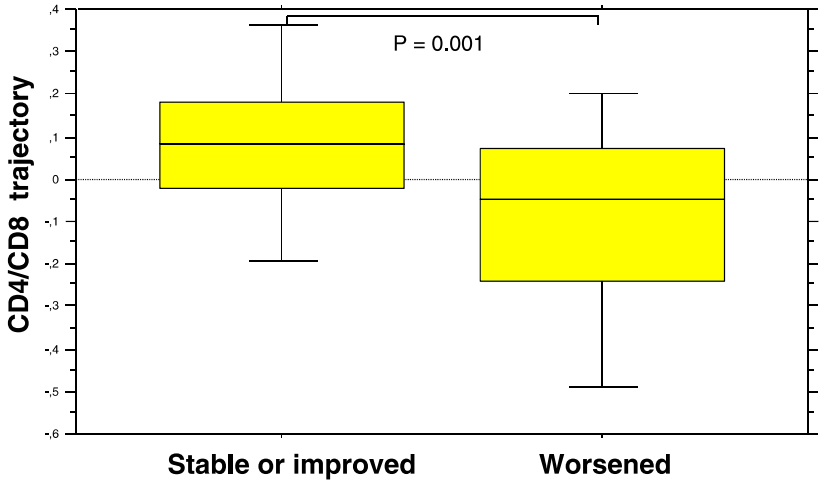

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