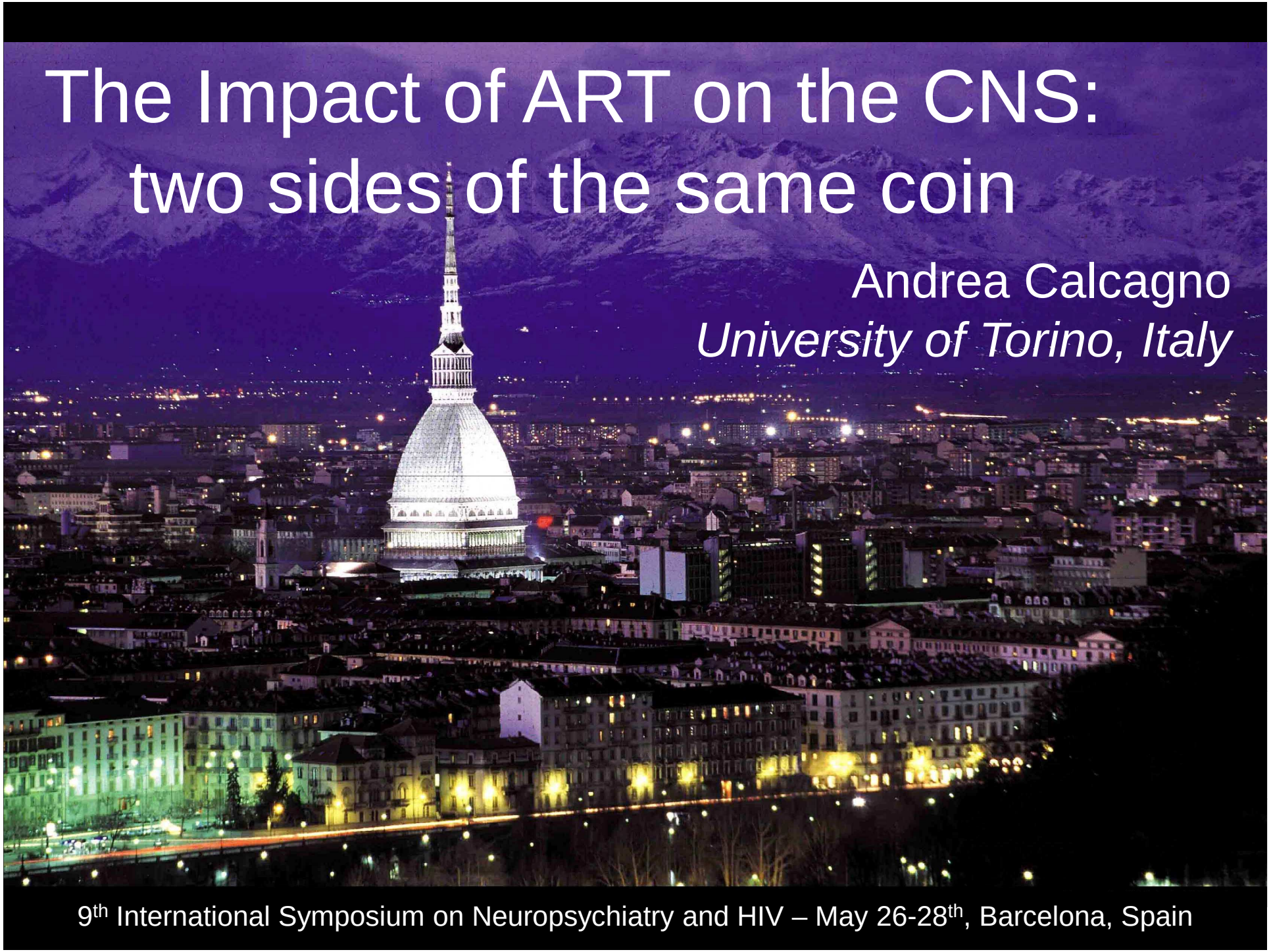
The Impact of ART on the CNS: two sides of the same coin

Andrea Calcagno
University of Torino, Italy



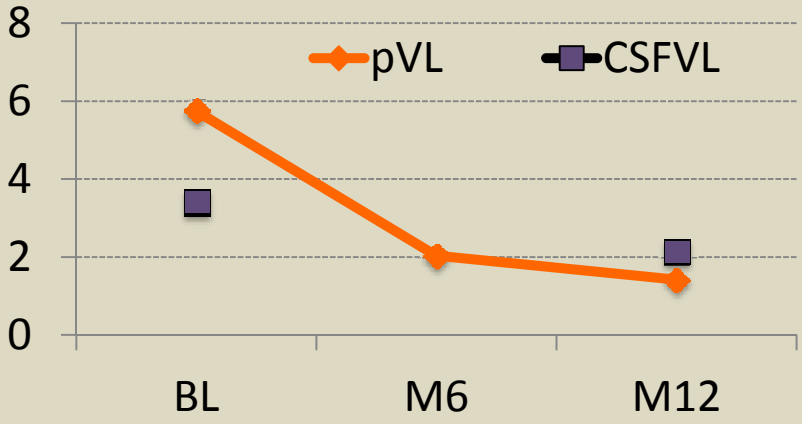
9th International Symposium on Neuropsychiatry and HIV – May 26-28th, Barcelona, Spain

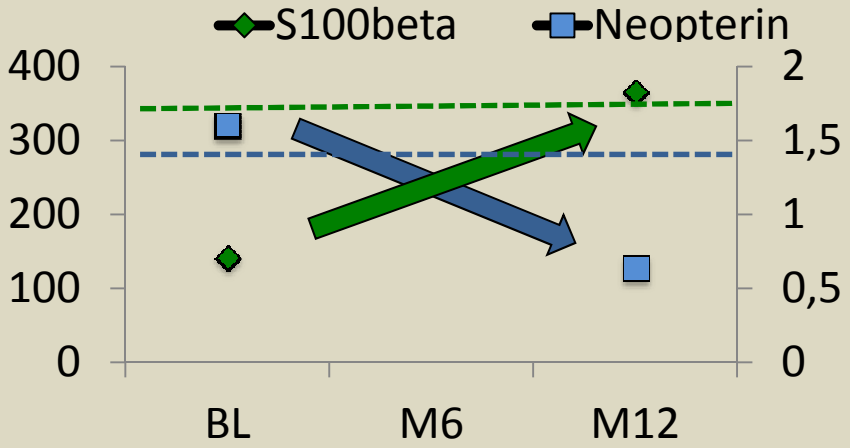
G-L

- Female, Caucasian
- 47 yy
- HIV+ since 1999 (heterosexual, ex partner HIV+)
  - on HAART 1999-2004 then self-interrupted
  - 2012 admitted for PJ pneumonia and wasting syndrome
  - HIV RNA 557351 copies/mL
  - NRTIs RAMs K70R, M184V
  - R5
  - TDF + DRV/r (800/100) + MVC (300)

A-G – Neurological

- Normal brain MRI





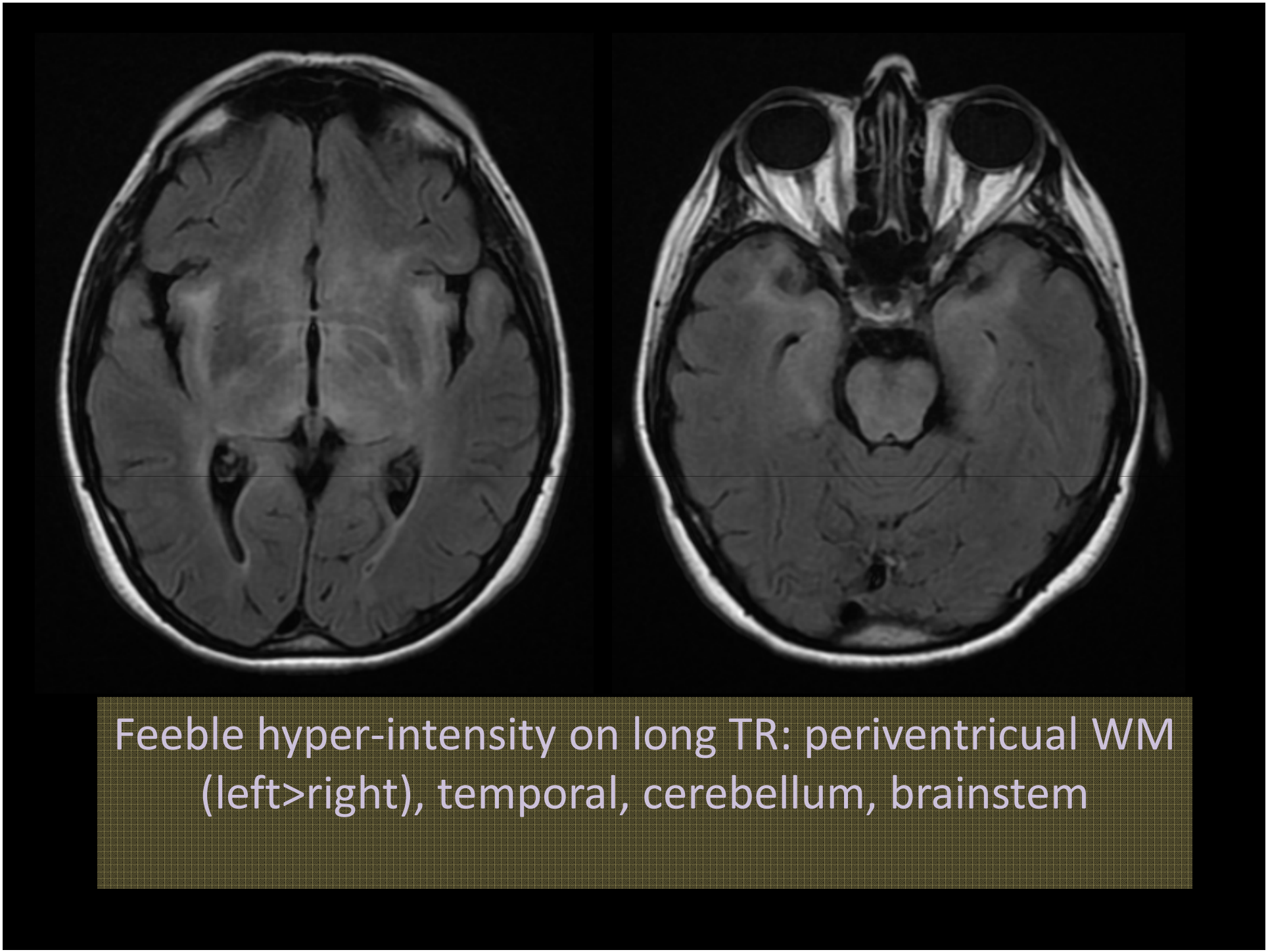
- Normal NP tests at baseline
- Mild depressive symptoms

Follow up

- Discharged in good health
- Reported optimal adherence in the first 12 months
  - pVL slowly undetactable (26-<20-30 copies/mL)
- Uncertain adherence afterwards
  - Low level viremia and blips
  - <20 – 56 – 84 - <20 - <20 – 105 – 62
- Unwilling to change treatment

Clinical Presentation - @3.5 years

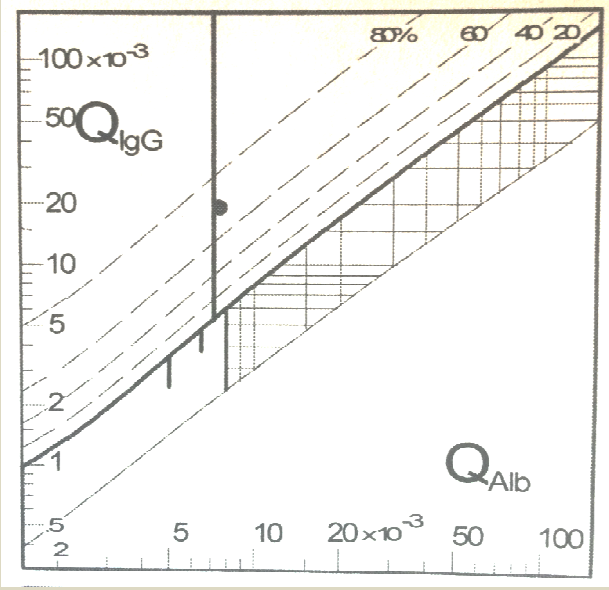
- Complains of forgetfulness and troubles in concentrating lasting approximately 4 months
  - NP testing: moderate abnormalities in attention and short-term memory (Rey's Figure, Corsi test, etc.)
- CD4 714/uL (32%, ratio 0.9)
- 3 months later: slow onset of dizziness, gait abnormalities and unintentional tremors



Feeble hyper-intensity on long TR: periventricual WM (left>right), temporal, cerebellum, brainstem

CSF

- clear, colourless
- 44 cells (atypical T lymph)
  - $CD3^{dim}CD5^{neg}$
- protein 99 mg/dL (rv <45)
- **HIV RNA 7566 copies/mL**
  - **no RAMs and R5**
- CMV & JCV neg, EBV DNA 82 copies/mL
- Minimal BBB impairment: CSAR 7.6 (rv <6.5)
- High IgG production (70% of IgG from CSF)



Symptomatic CSF escape wo RAMs

- **PK?**

	plasma PK ng/mL	**CSF PK** ng/mL	
DRV	1999	14.6	0.7%
TFV	51	60	120% (?)
MVC	118	4.6	3.9%

RAL (400x2) + **DRV/r** (600/100x2) + **ETV** (200x2)

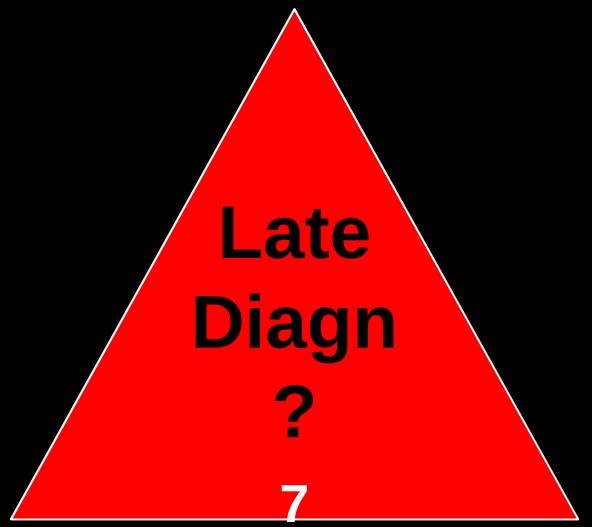
Follow up (2)

- Fast improvement in gait and tremors
- @ 1 month
  - HIV RNA TND
  - CD4 784 (33%, ratio 1)

- MRI/LP done yesterday!

Open questions

- Limited cellular activity?
- Incomplete penetration?
- Compartimentalization?
- Predictable since 2012?



- Incomplete adherence?
- Untreated depression?

Outline

50’

1. Epidemiology
   - HAND vs. CSF escape
2. CNS Pharmacology
3. Pathogenesis
4. HAND despite HAART vs. because of ARVs
5. Clinical management of HAND (???)

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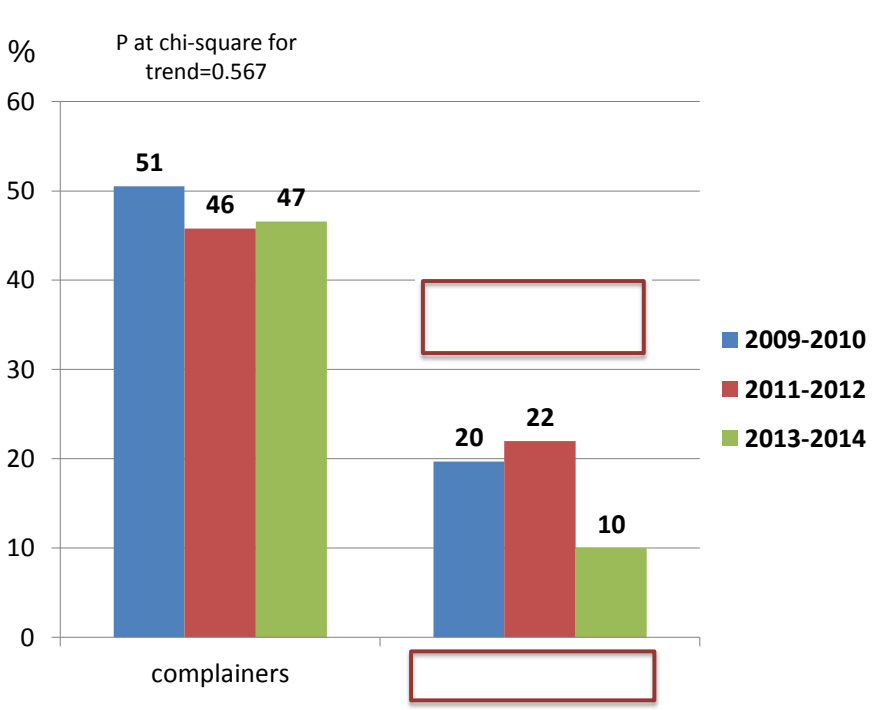
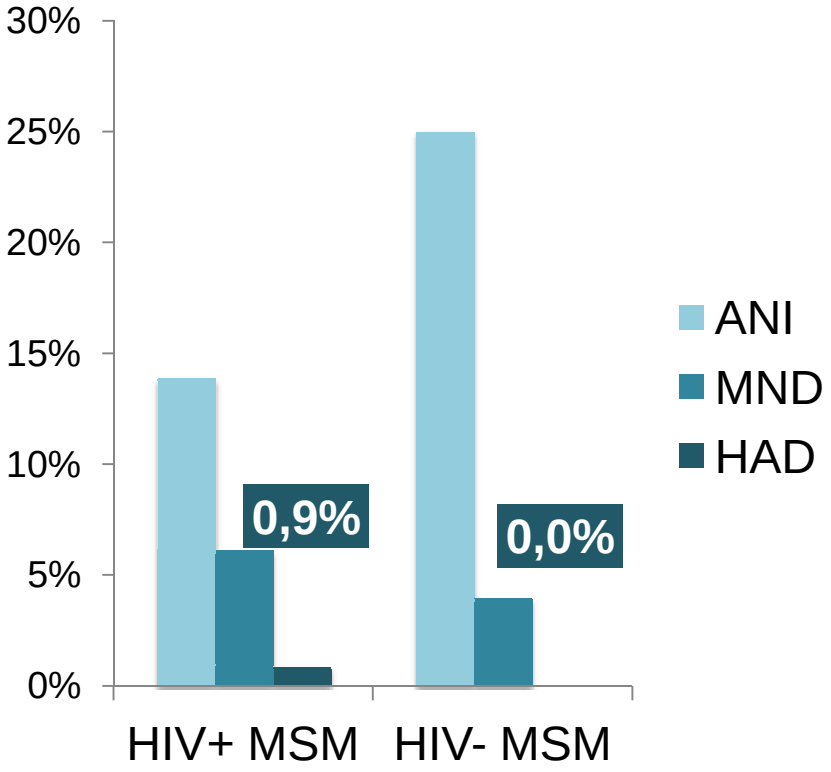
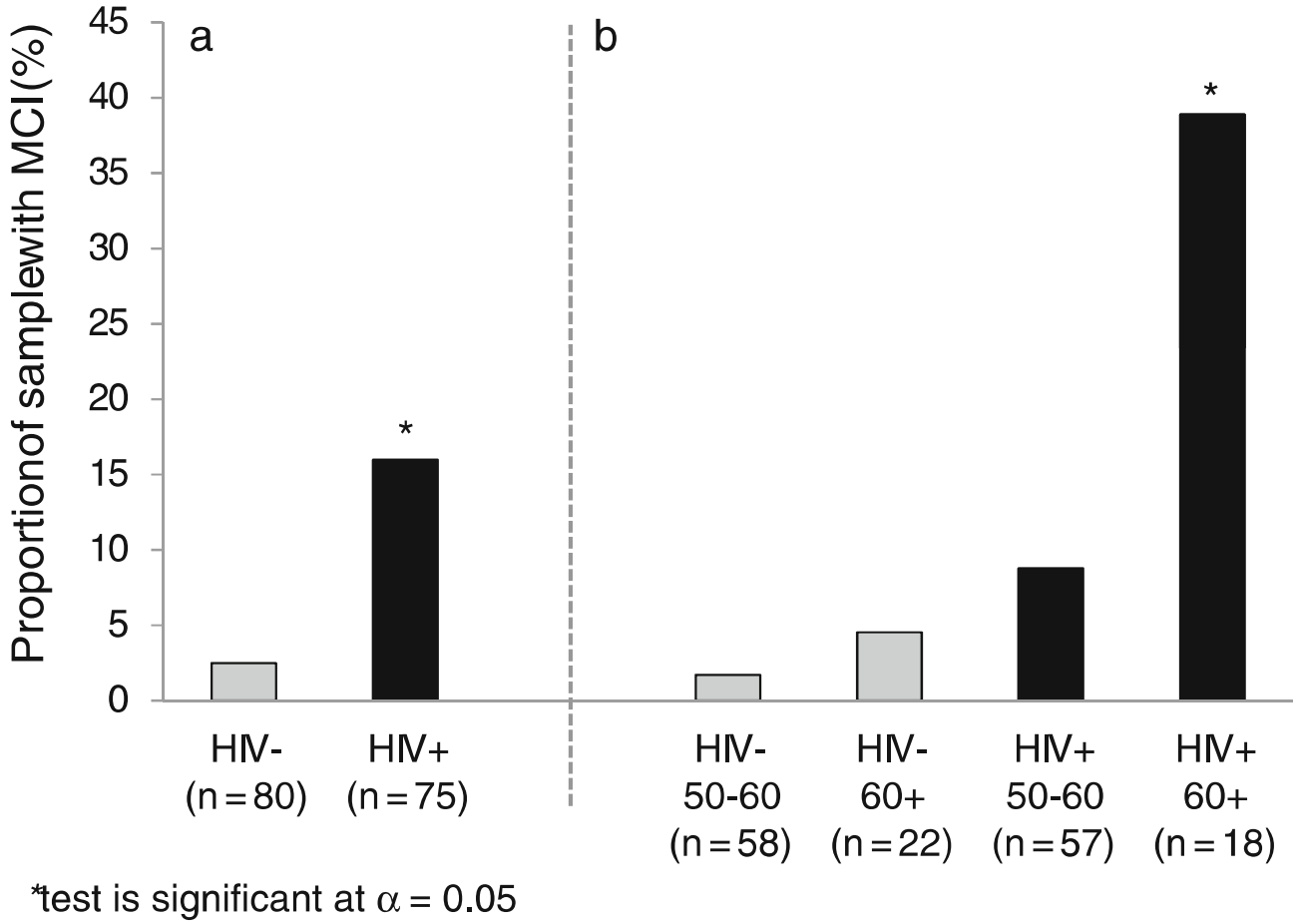
Prevalence of HAND over time





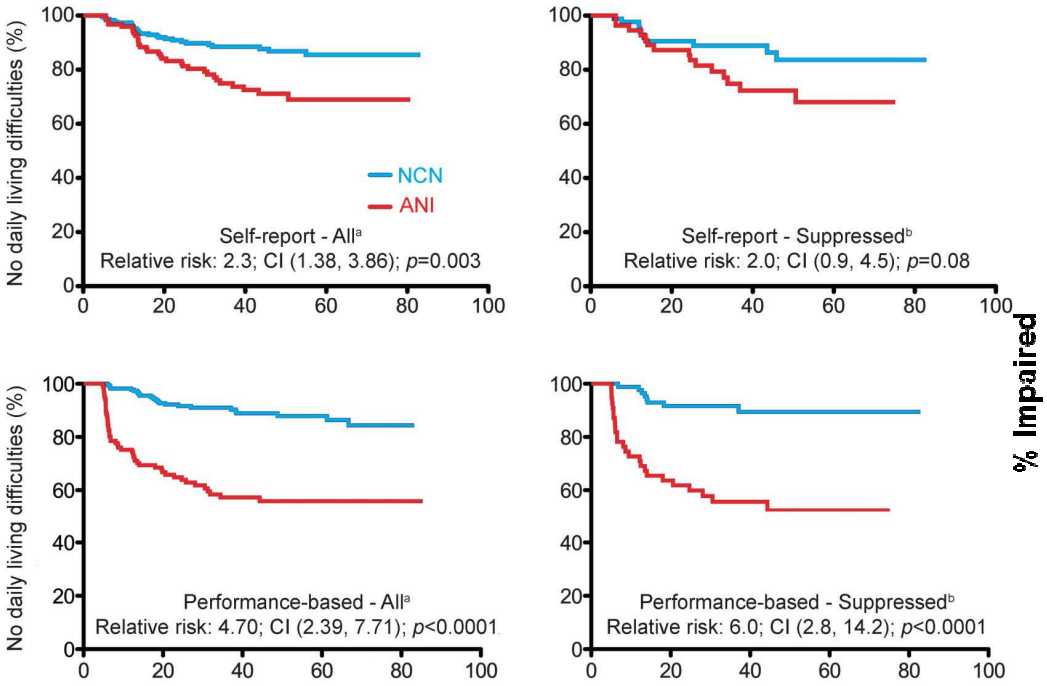
Pinnetti C, et al. CROI 2015; McDonnel J, et al. JAIDS 2014

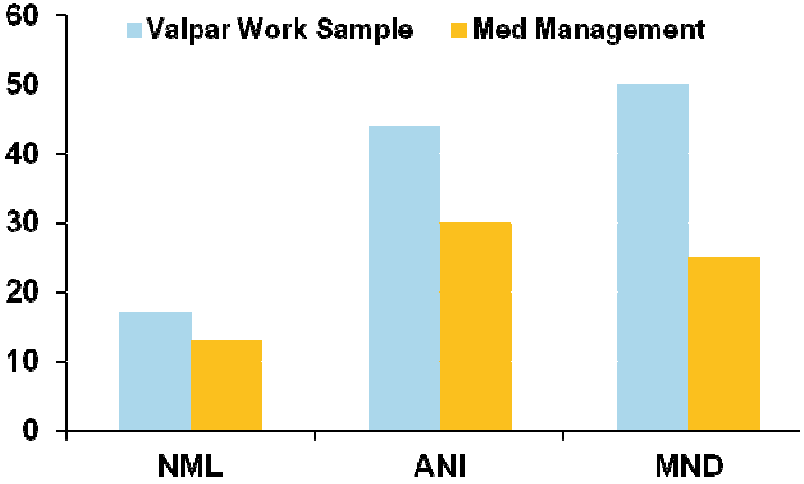
Age and MND/MCI



*test is significant at $\alpha = 0.05$

Asymptomatic NC impairment?



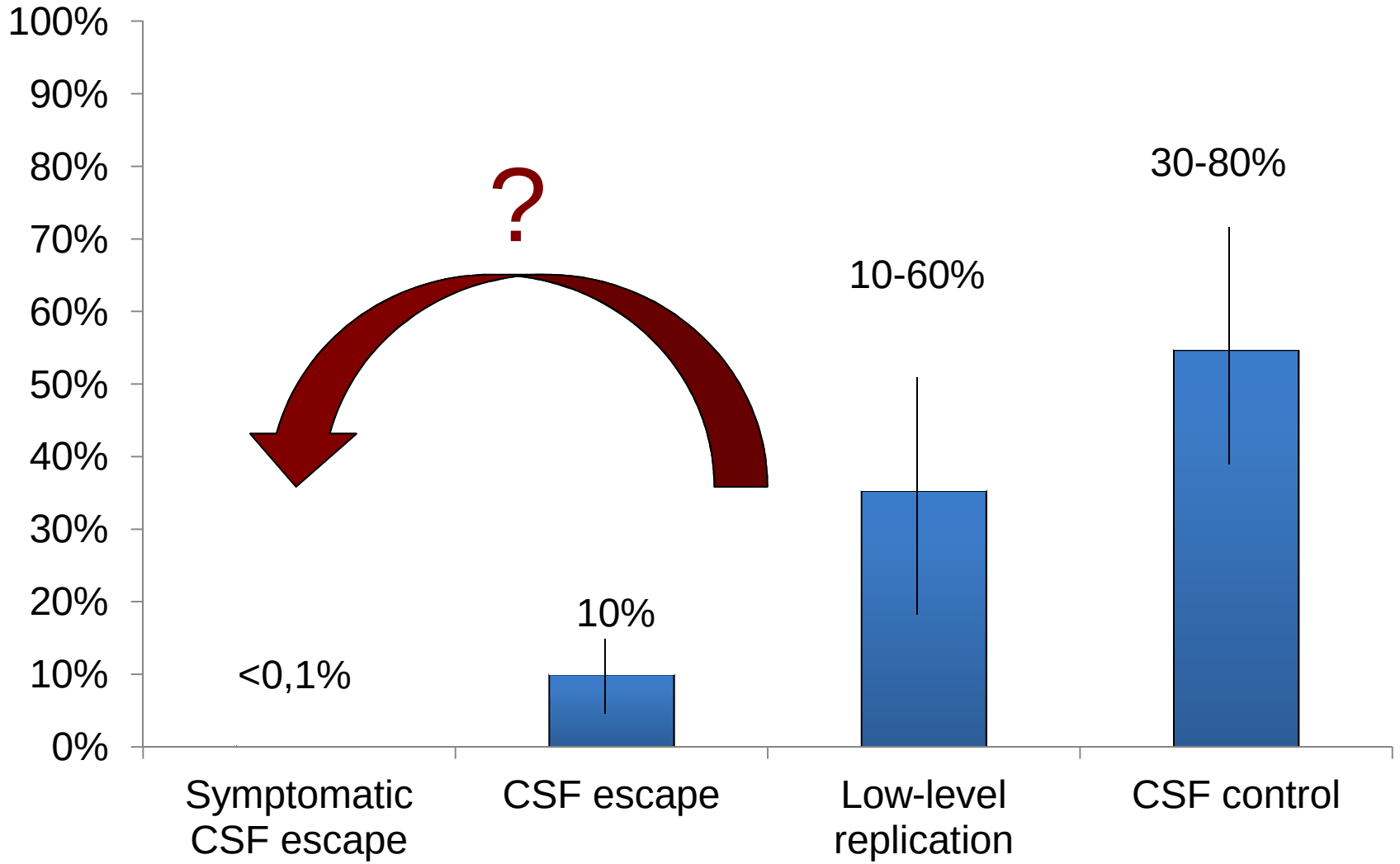


Grant I, et al. Neurology 2014; Blackstone K et al. JINS 2012

Cerebrospinal fluid HIV RNA

- Usually lower than plasma HIV RNA (1 Log_{10});
- Parallels plasma HIV RNA reduction under HAART;
- **CSF escape**
  - Detectable CSF HIV RNA with undetectable plasma HIV RNA
  - CSF HIV RNA 1 Log10 > plasma HIV RNA

CSF HIV RNA strata under HAART

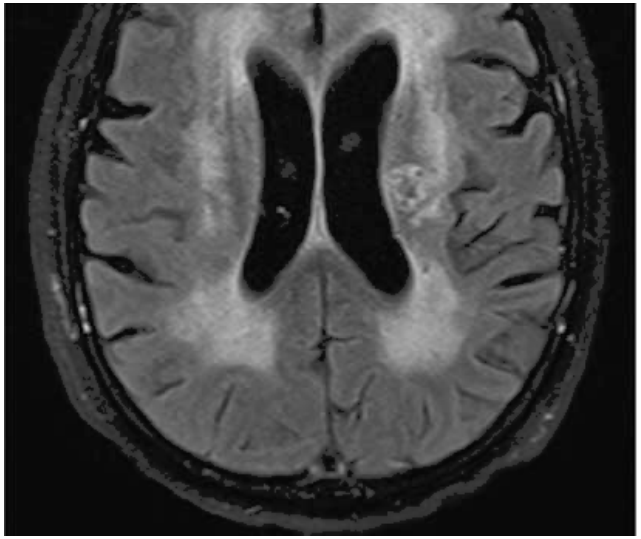


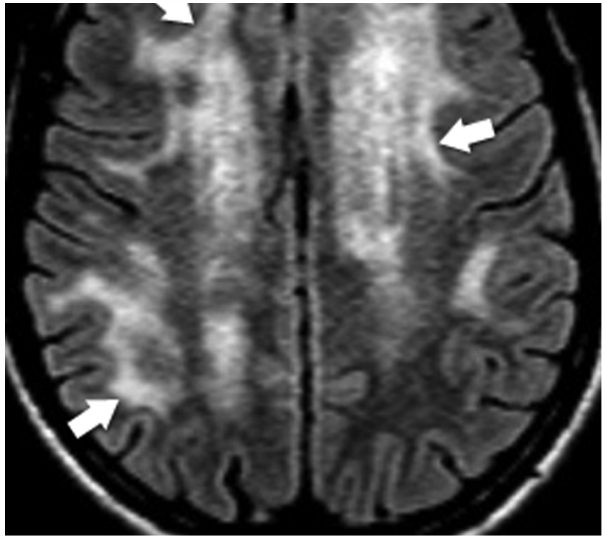
Yilmaz A, et al. JAIDS 2008; Dahl V, et al. AIDS 2014; Calcagno A, et al. ICAR 2015

CURRENT OPINION

Immune activation in the central nervous system throughout the course of HIV infection

Serena S. Spudich



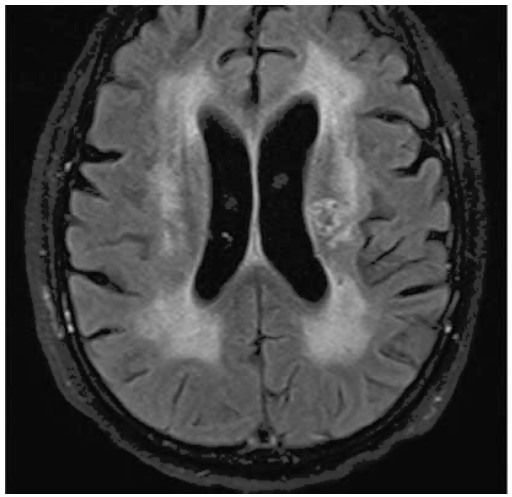


Symptomatic CSF escape

Two case series and few case reports

n=27

- 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

- Retrospective study on 1256 HIV+ patients in India
- 6 months of ART and HIV RNA <1000 copies/mL
- 105 with neurological disease at baseline (39% CNS TB, 19% cryptoM, 19% neurotoxo)
- Median ART duration 36 months (15-52)
- 79.4% on NNRTIs and 19.8% on PIs

32 cases of incident neurological disorders with
13 patients with HIV-encephalitis

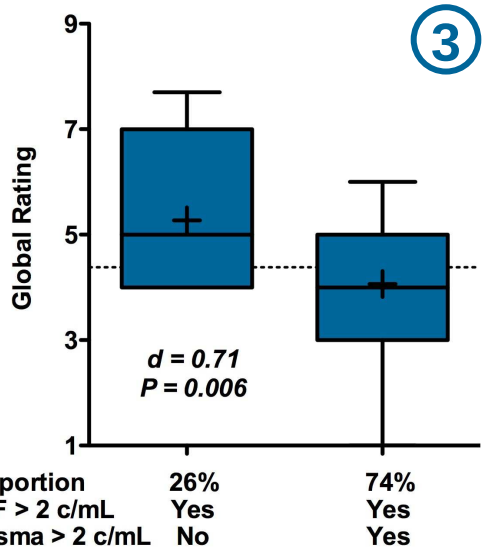
Symptomatic CSF escape – India (2)

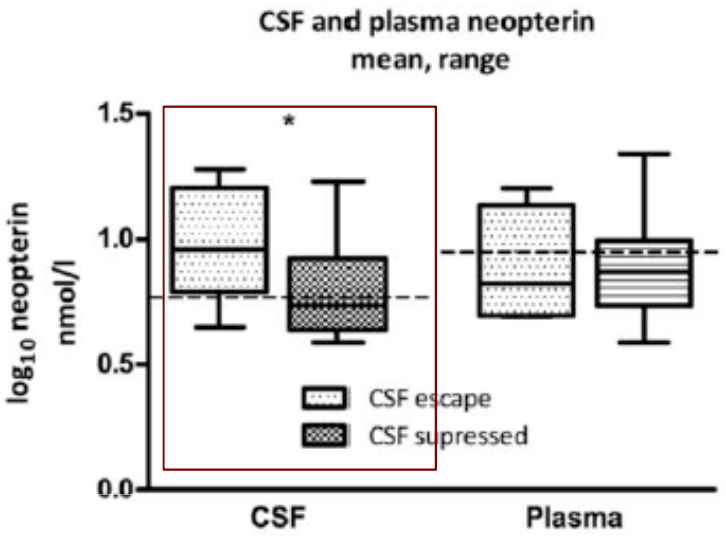
Pt	ART regimen	CSF RAMs			
		NRTI	NNRTI	PI	INI
4	AZT/3TC + LPV/r	D67N, K70R, L74I, M184V, T215V, K219Q	K101E, V108I, Y181C	V82A	NO
6	TDF/3TC + ATV/r	M41L, D67N, T69N, K70R, M184V, T215V, K219E	K101E, Y181C, H221Y	I50L	NO
9	AZT/3TC/TDF + ATV/r	D67N, T69N, K70R, Q151M, M184V, T215V, K219E	K101E, V108I, Y181C, H221Y	I50L	NO
10	TDF/FTC + ATV/r	D67N, T69N, K70R, M184V, T215V, K219E	K103S, G190A	M46I	NO
11	TDF/FTC + ATV/r	M184I	K103N	NO	NO
13	RAL + LPV/r	M41L, M184V, T215Y,	K103N, P225H, K238T	V82A	N155H

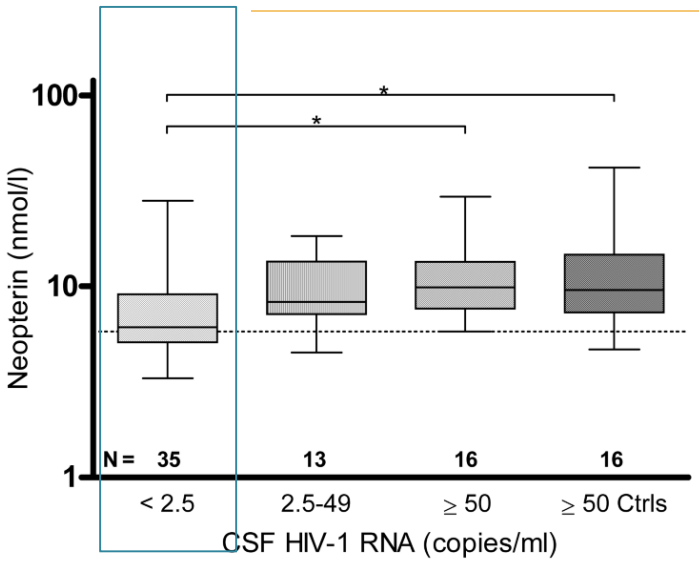
First line EFV, HIV RNA once a year, HAART change to PI/r (mostly ATV/r) with recycled NRTIs, low CD4 nadir

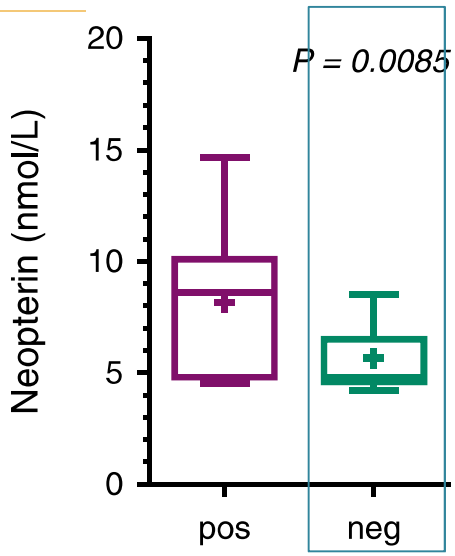
Dravid A, EACS 2015 PE15/76

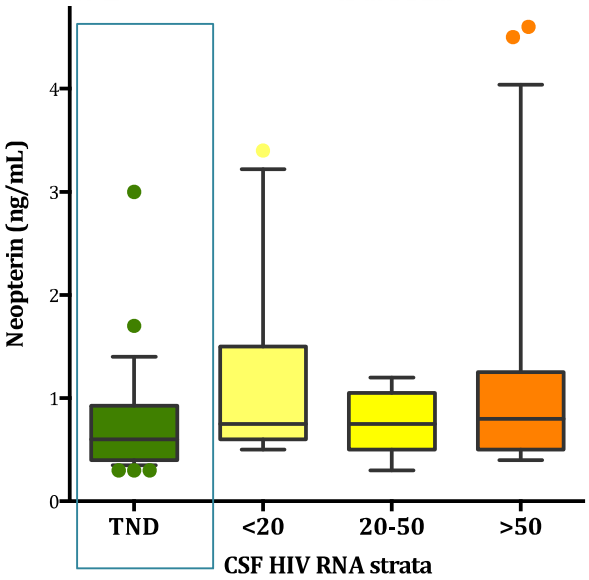
CSF low level replication – NC function?











Letendre S, et al. Croi 2009; Eden A, et al. JID 2010; Yilmaz A, et al. JAIDS 2008; Dahl V, et al. AIDS 2014; Calcagno A, et al. ICAR 2015

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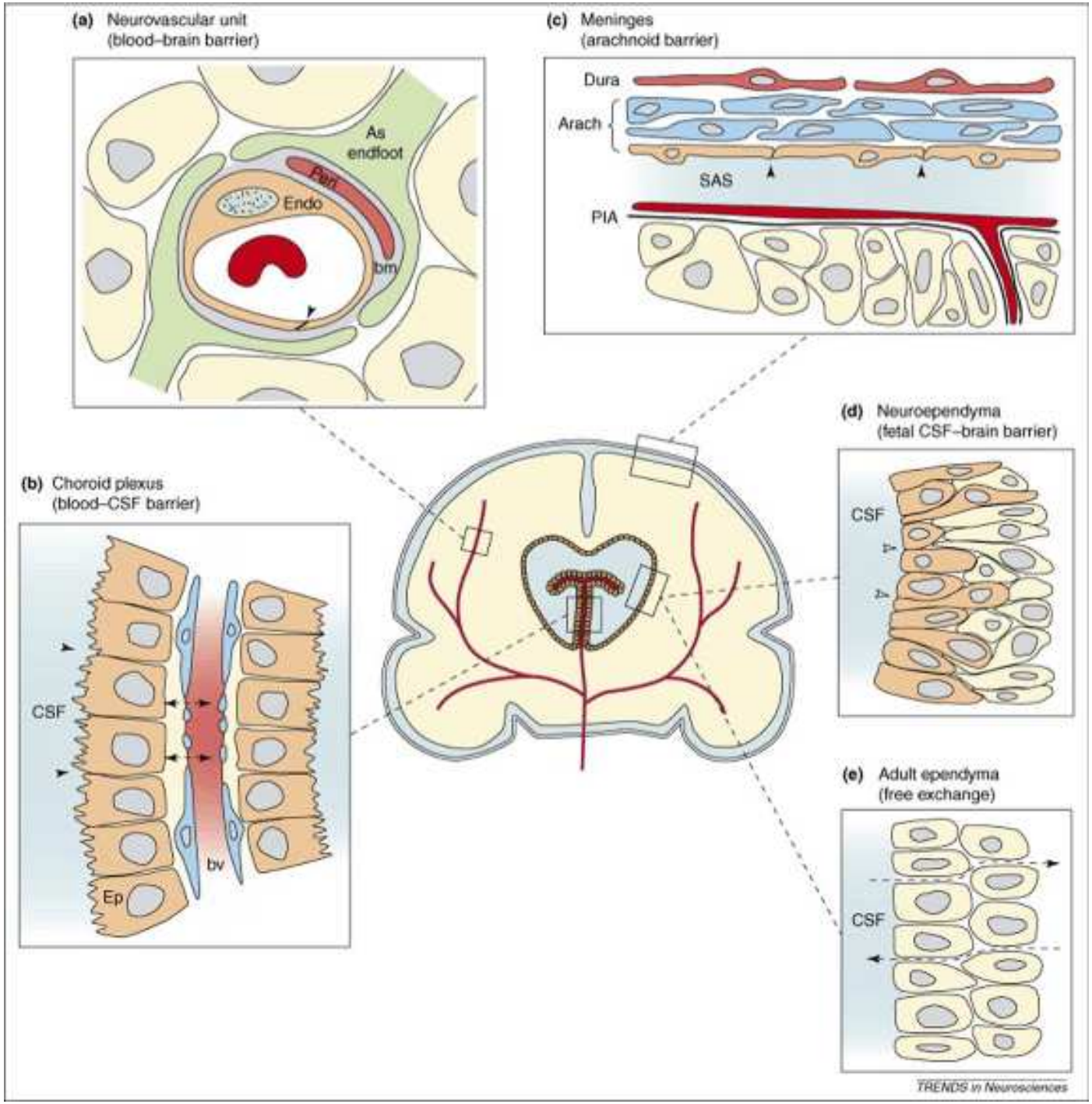
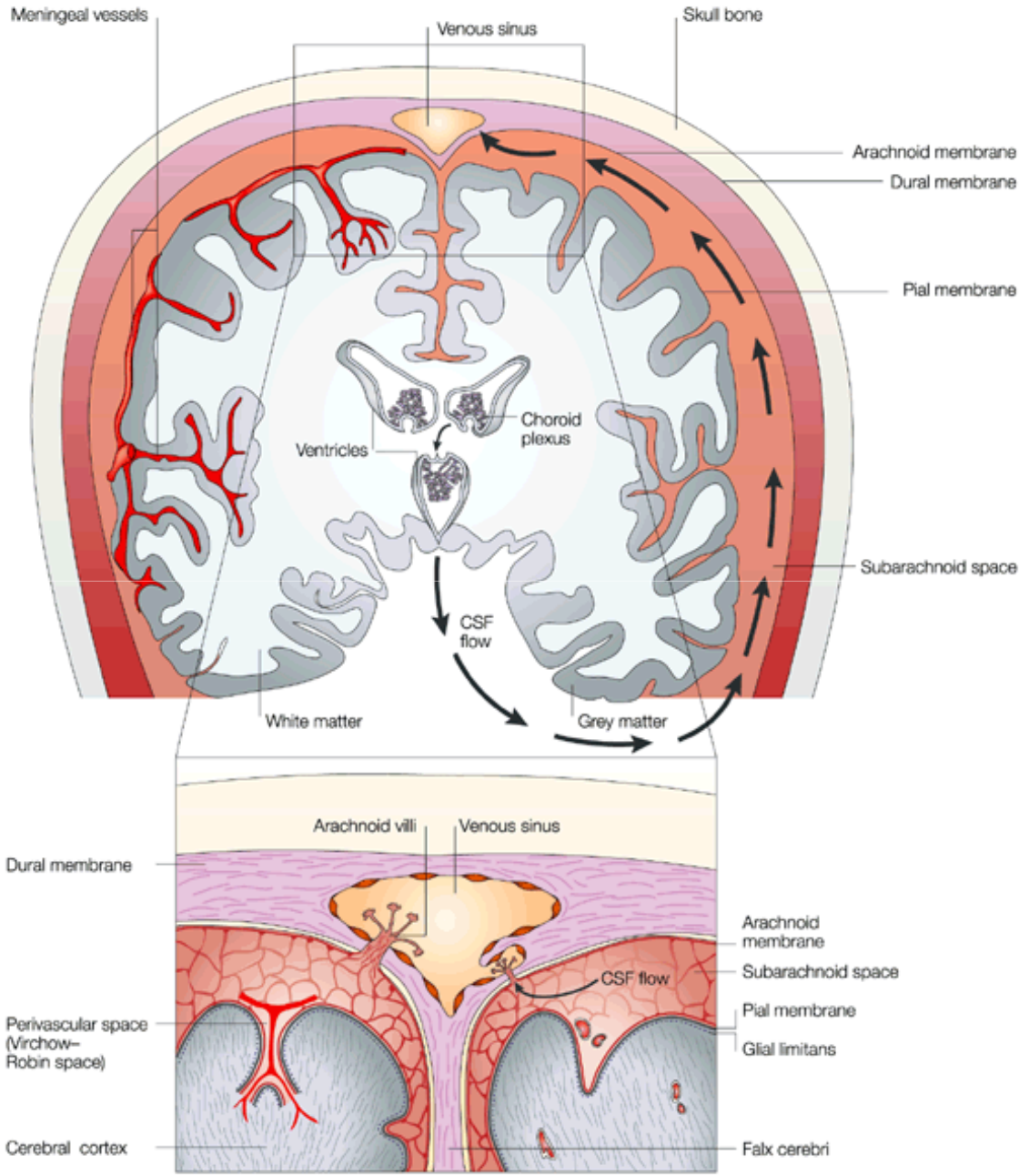

(a) Neurovascular unit
(blood–brain barrier)
As endfoot
Peri
Endo
bm
(c) Meninges
(arachnoid barrier)
Dura
Arach
SAS
PIA
(b) Choroid plexus
(blood–CSF barrier)
CSF
bv
Ep
(d) Neuroependyma
(fetal CSF–brain barrier)
CSF
(e) Adult ependyma
(free exchange)
CSF
TRENDS in Neurosciences



Targeting the CNS not the CSF

- CSF is not the target (as in bacterial meningitis)
- 2/3 from brain extracellular fluid

RRansohoff RM, et al. Nat Rev Immunol. 2003

CSF → CNS exposure?

- CSF is a surrogate marker for cerebral tissue concentrations for most of the drugs (22/33); **CSF exposure may predict CNS efficacy in rodents[5]**
- **unbound plasma [ ] < CSF[ ] < microdyalisis [ ]**
- **CSF>ISF**
  - efficient efflux transport at the BBB or an active process of intracellular uptake or sequestration
  - AZT BBB efflux > BCSFC (CSF/ISF >1.5)
- **CSF<ISF**
  - CSF “sink” action and slow kinetic equilibration of drug in the CSF
  - active influx at the BBB or redistribution of drug from the intracellular pool

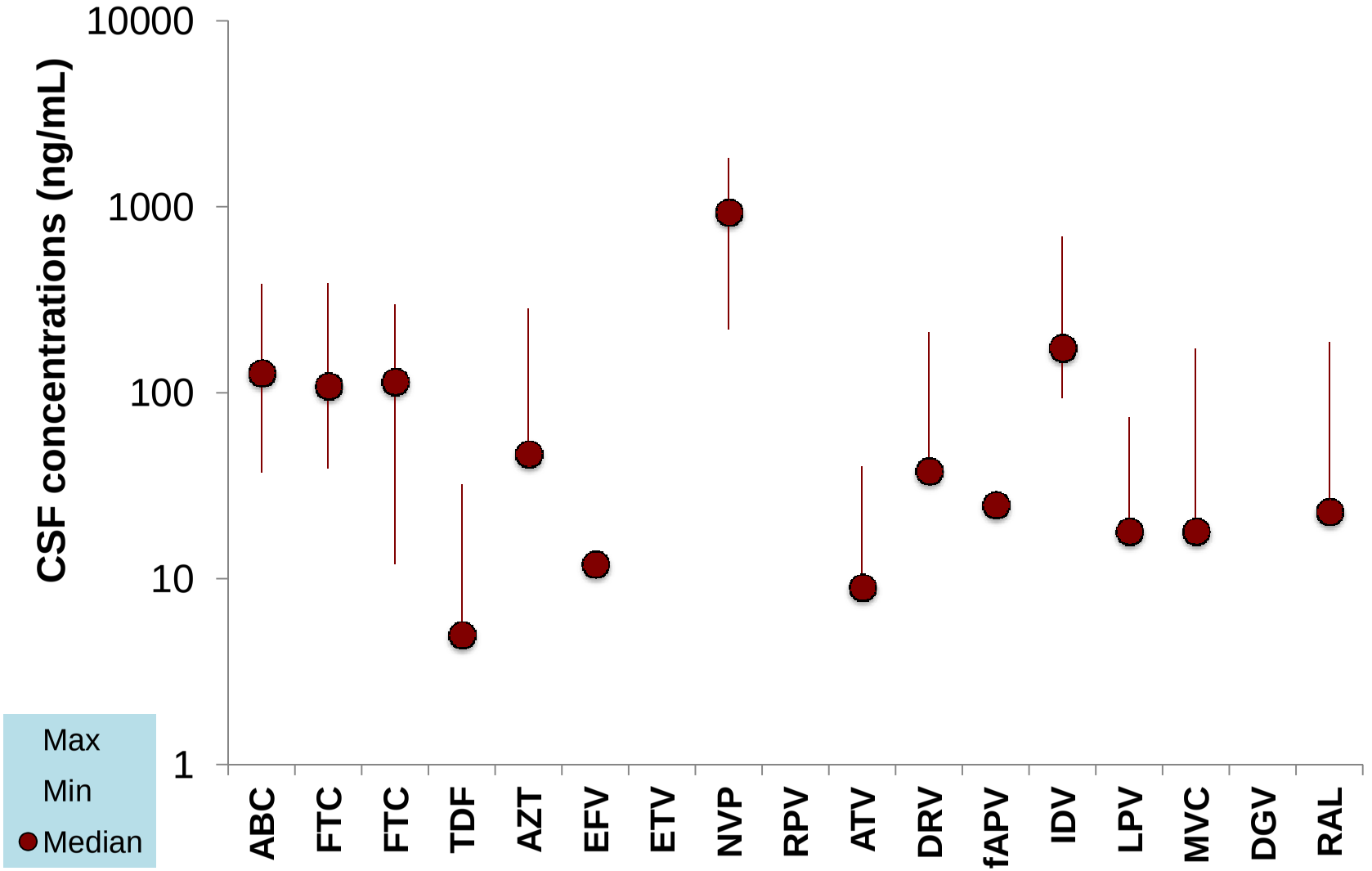
1. Hammarlund-Udenaes M, 2009; 2. Friden M, 2009; 3. Maurer TS, 2005; 4. Shen DD, 2004; Liu X, 2009; 5. Caruso A, et al. Biochemical Pharmacology 2013.

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.

High variability in CSF exposure



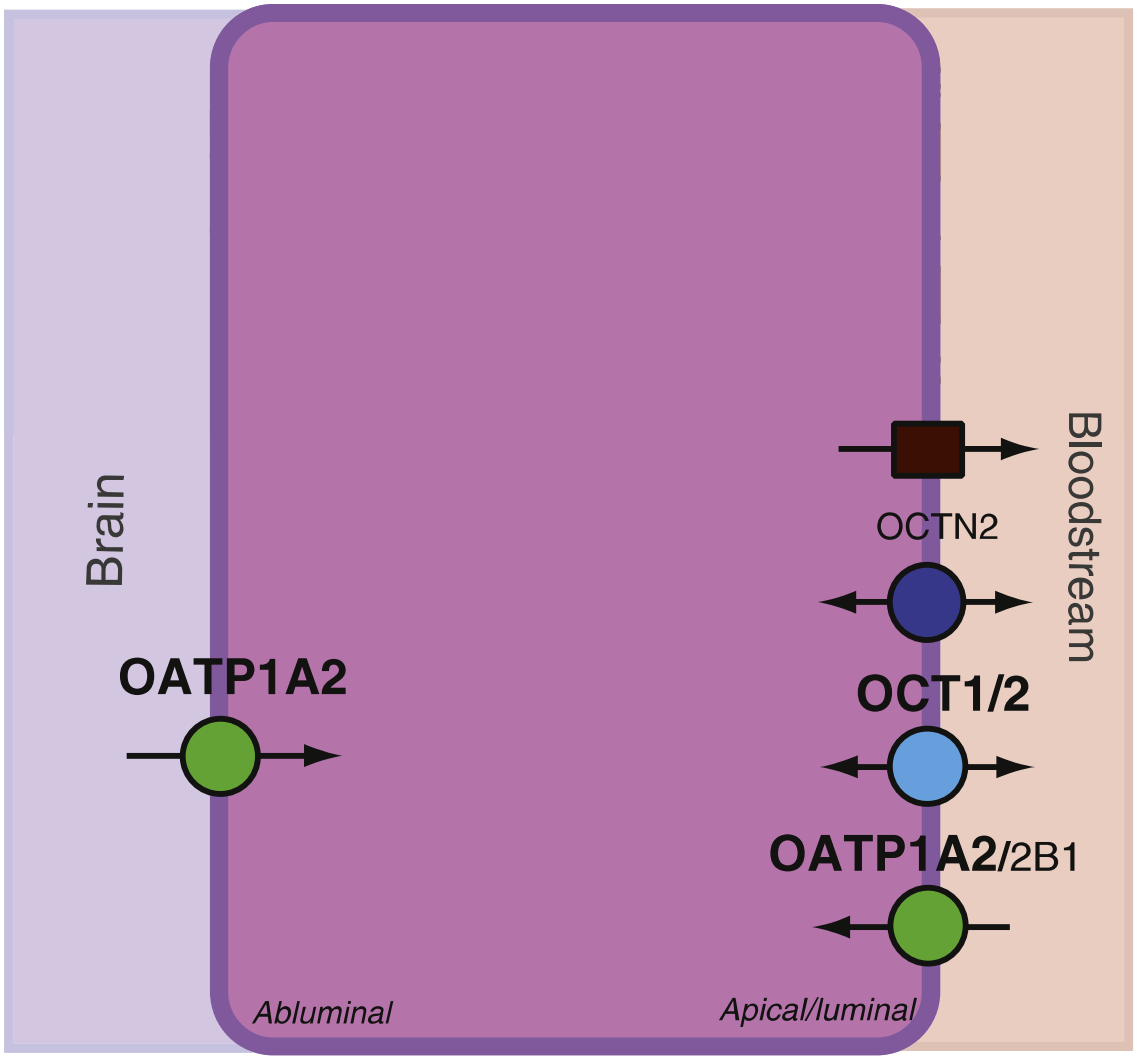
Calcagno A, et al. Clin Pharmac 2014

Factors affecting CSF concentrations

- **Patients' related:**
  - Age (⇧infants and elderly)
  - Meningeal inflammation (⇧)
  - CSF flow alterations (⇩)
  - BBB permeability (⇧RAL, TDF, FTC)
- **Drug related:**
  - Molecular Size (⇩)
  - Lipophilicity (⇧)
  - Plasma Protein Binding (⇩)
  - Ionization (⇩)
  - Active Transport/PG (⇧⇩)
- **Patient and drug related:**
  - Plasma concentrations (⇧)
  - Concomitant drugs (⇩⇧)

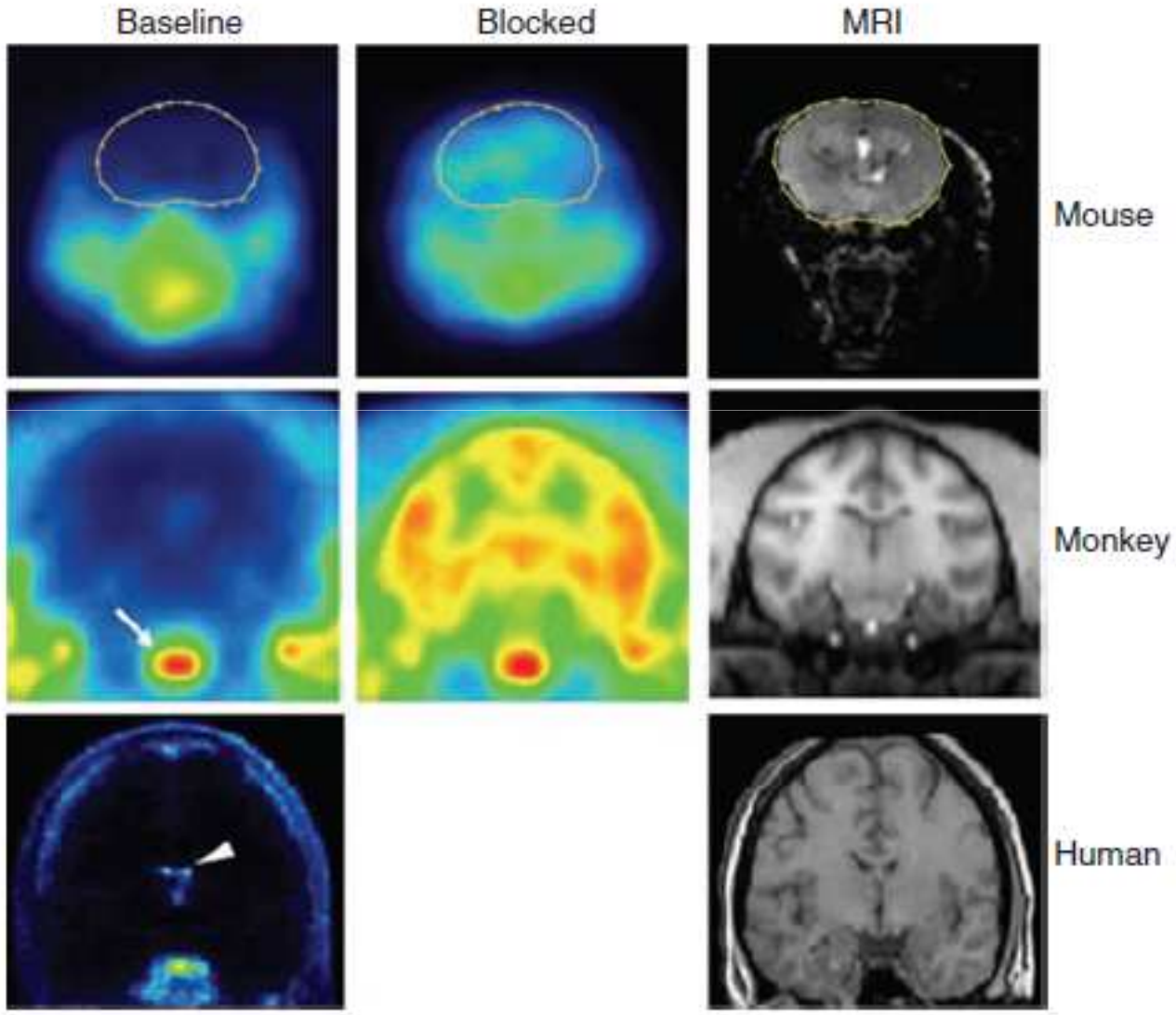
Yilmaz A. JAC 2012; Calcagno A, et al. Clin Pharmac 2014

BBB Transporters



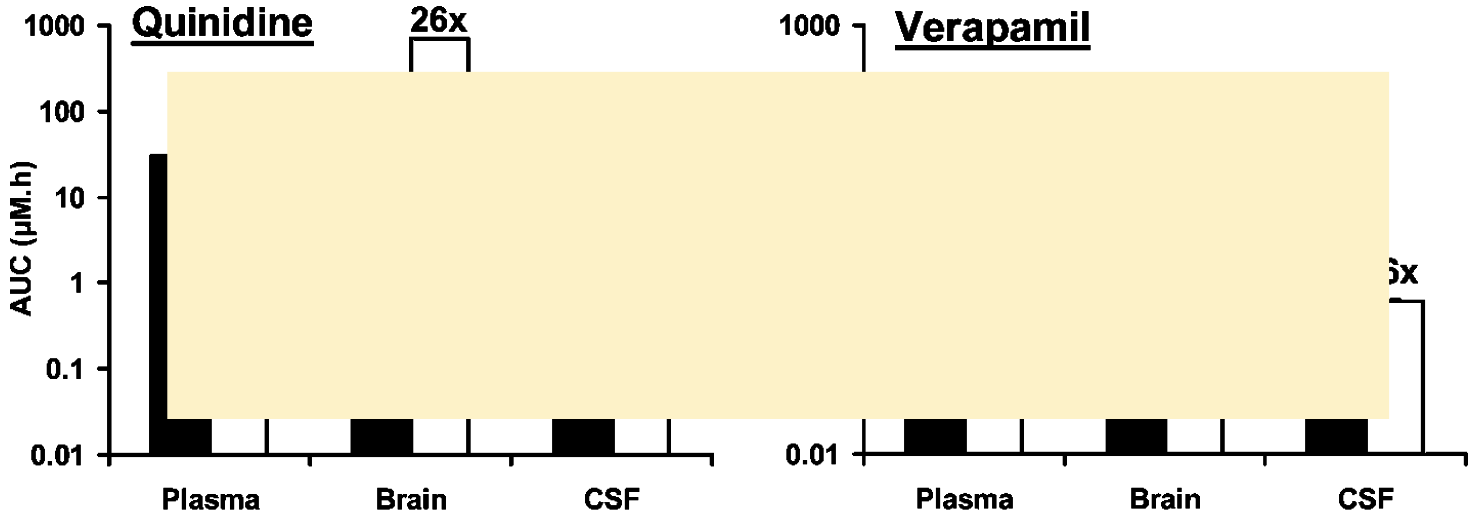
G. Minuesa et al. / Pharmacology & Therapeutics 132 (2011) 268–279

P-glycoprotein inibition

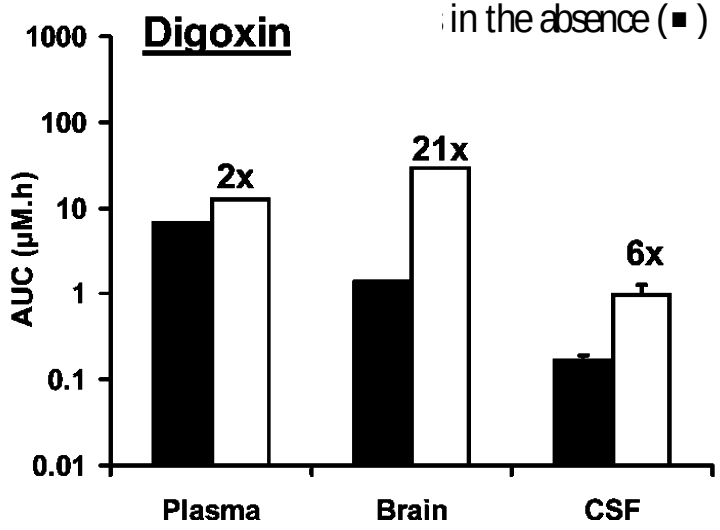


Kannan P, et al. Clinical Pharm and Ther 2009

Pg-p inhibition and exposure



in the absence (■) and presence (□) of elacridar.

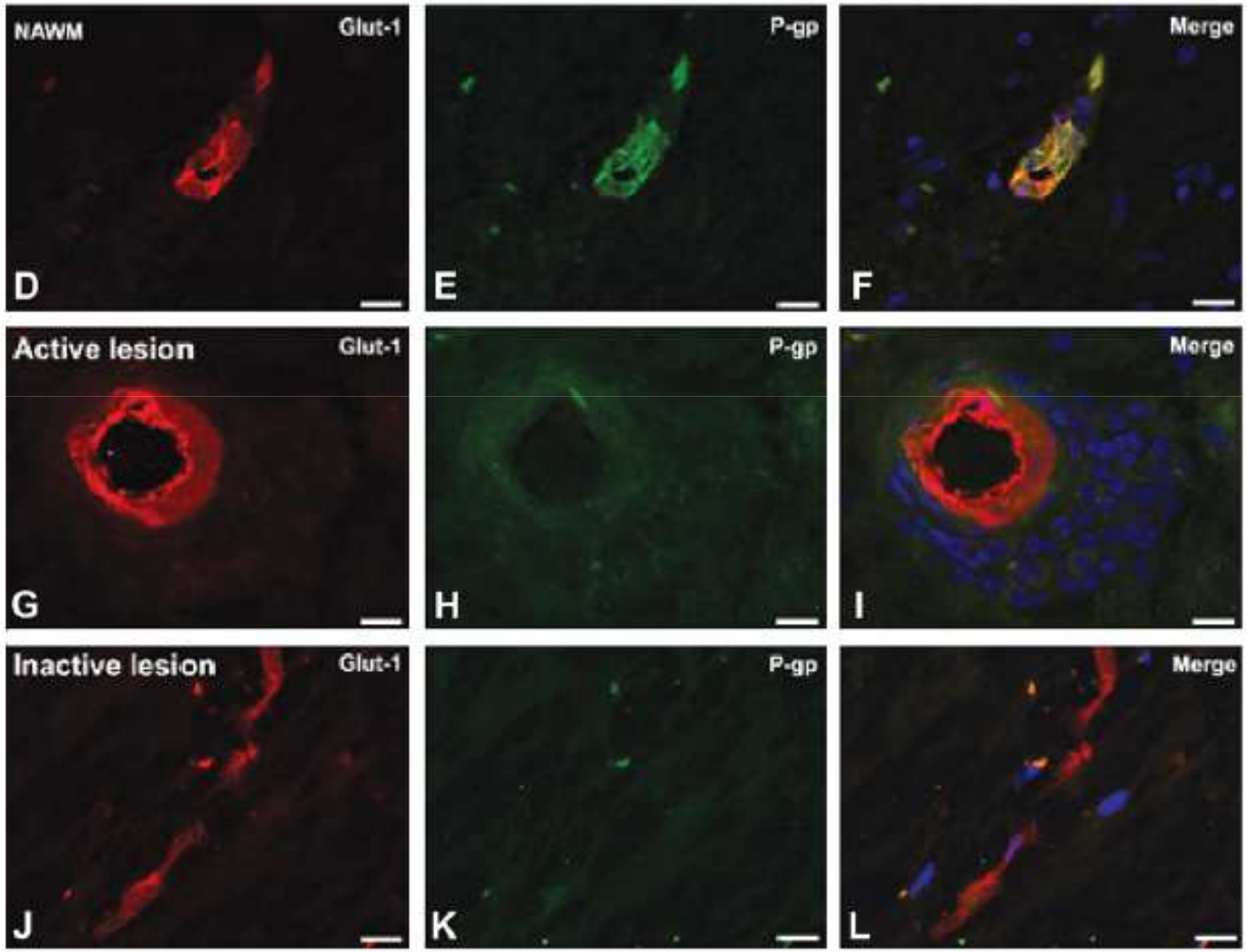


Mariappan TT, et al. Molecular Pharmaceutics 2013

Modulation of PgP in MS

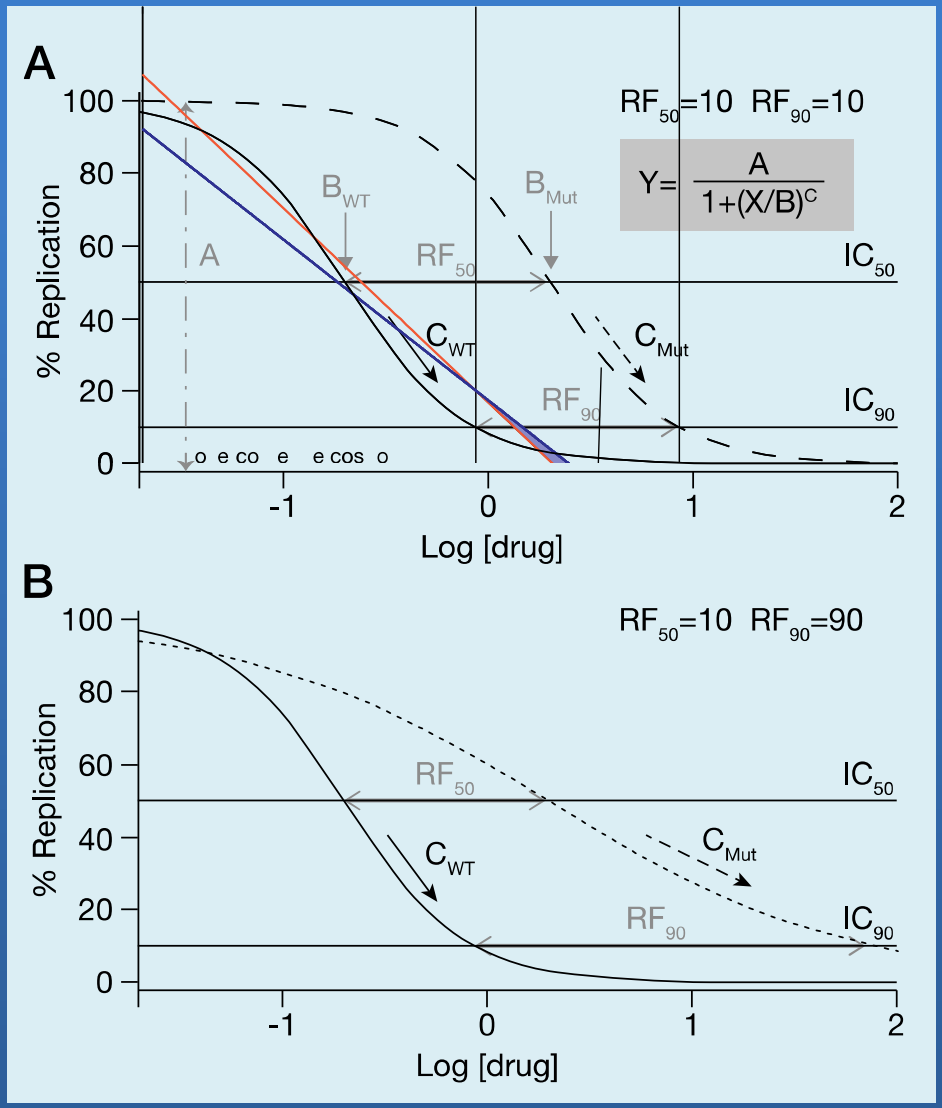
Loss of vascular P-gp expression in MS lesions

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



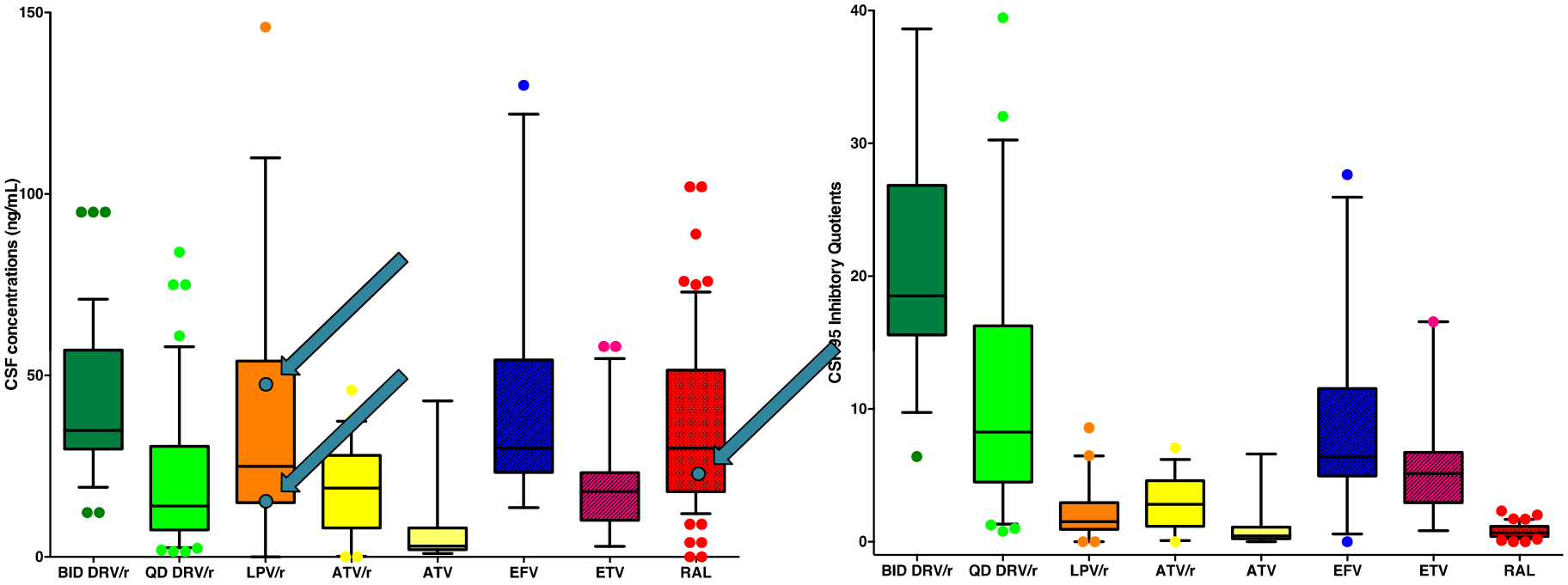
Kooij G, et al Journal of Autoimmunity 2010; 34: 416-425

IC_{50} vs $IC_{90/95}$



Lorenzo-Redondo R, et al. Nature 2016; Geipel A, et al. Antiv Ther 2015

Interpatient variability and ICs



- DRV>EFV>ETV> Others
- Drugs>IC_{95} and detectable NRTIs associated with undetectable CSF HIV RNA

Calcagno A, et al. CID 2014

Patients' characteristics

Gender: male	91	71.7%
Age: year	46	40.5-54.5
BMI: Kg/m²	22.2	20-25.2
HCV+	33	26%
CD4+ T Lymph current (/uL)	321	145-575
CD4+ T lymph nadir (/uL)	108	29-210
LPs for: Asymptomatic	63	49.6%
HAND	30	23.6%
Neurological	22	17.3%
WMA	12	9.4%
HAART: Triple	80	63%
NRTI-sparing (M-D)	22	17.3%
Multiple	25	19.7%

Calcagno A, et al. CID 2014

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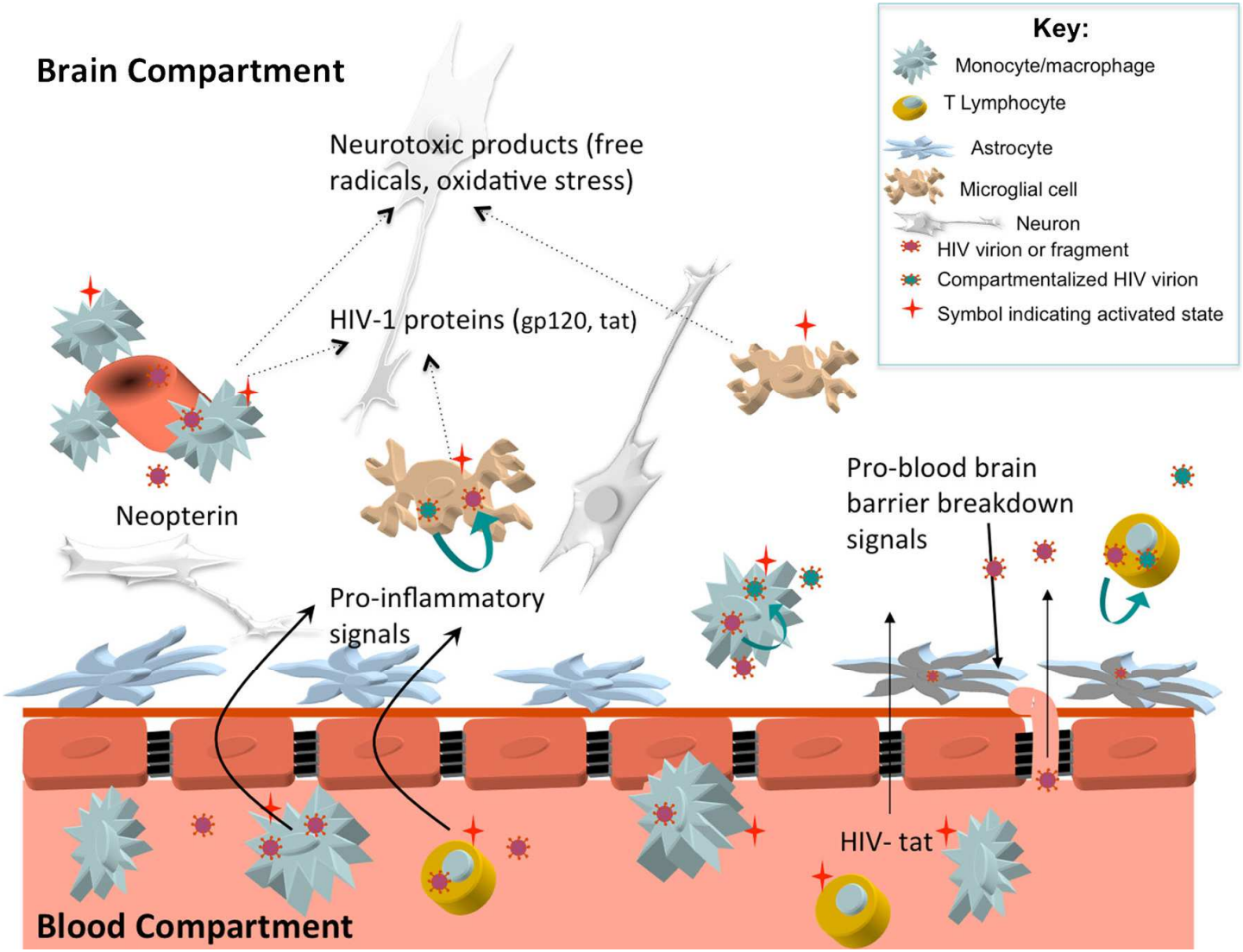
Neuroinvasion



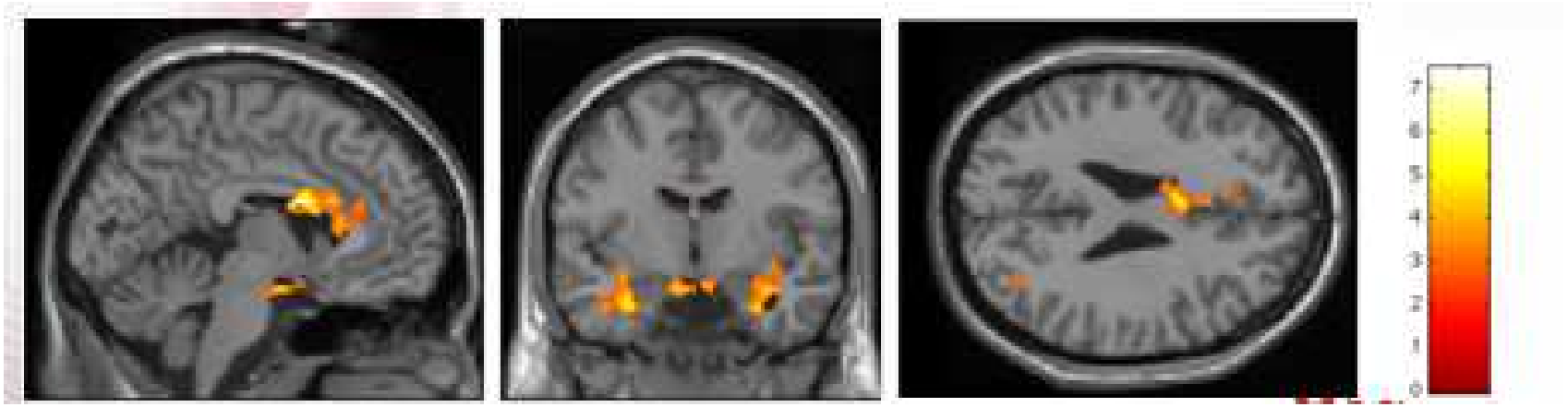
Zayyad Z. and Spudich S. Curr HIV/AIDS Rep 2015

Microglial activation

- 7 neurologically and cognitively asymptomatic HIV+
- [11C]-PK11195 PET, a marker of translocator protein (TSPO) expressed by activated microglia

focal cortical areas of activated microglia

- greater [11C]-PK11195 binding and poorer executive function performance (anterior cingulate, corpus callosum and posterior cingulate)



Monocyte/macrophages activity

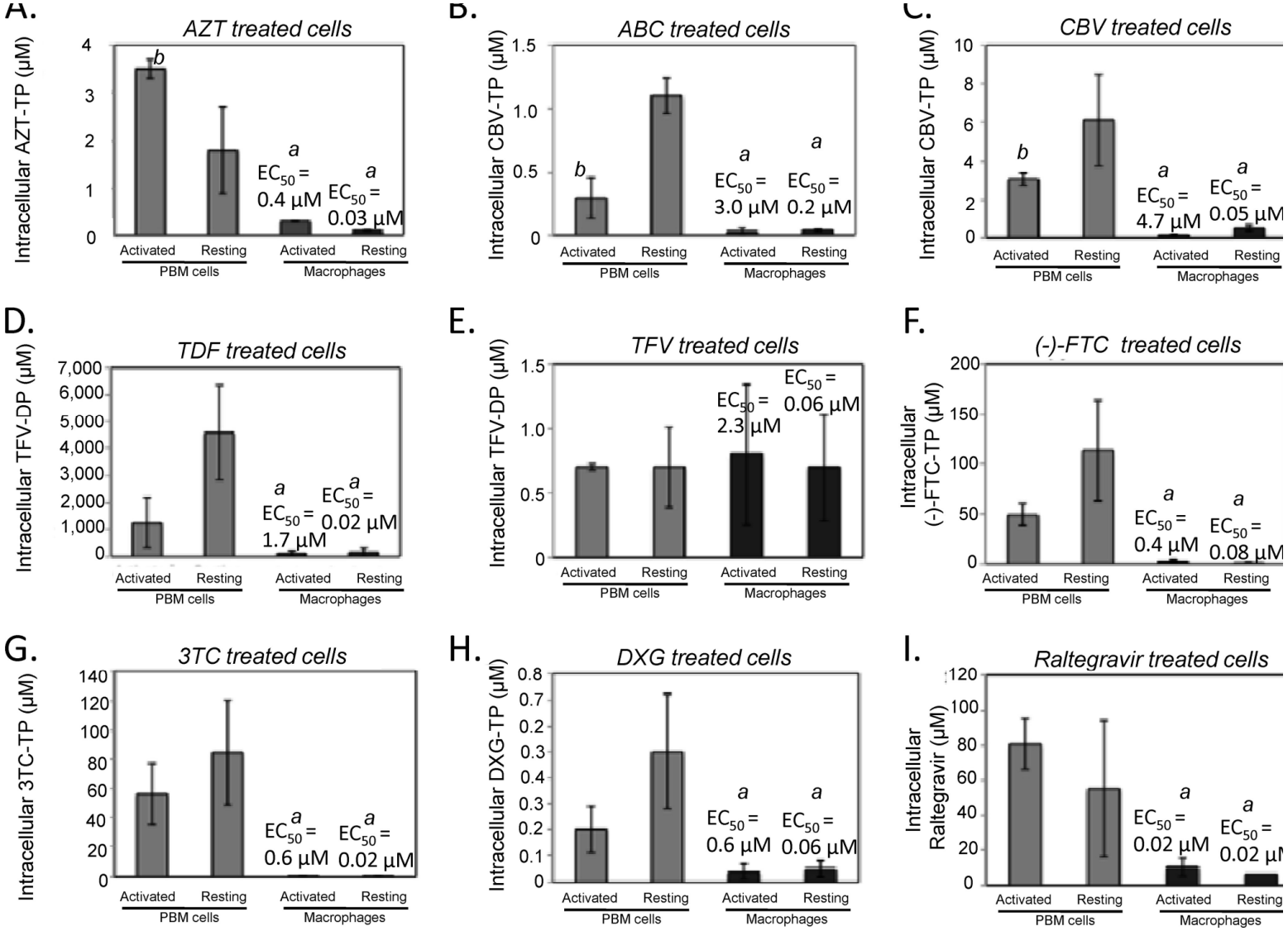
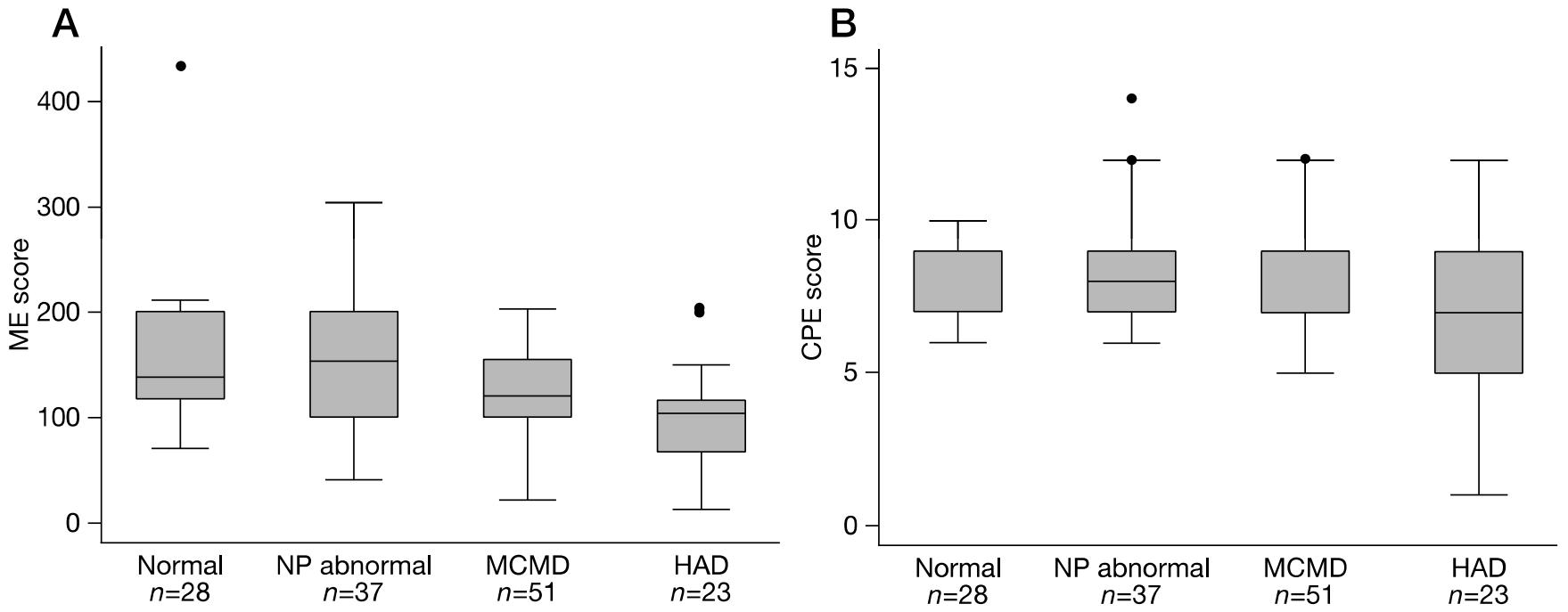


FIG 1 Intracellular concentrations of ART drugs are significantly lower in Mϕ than in PBM cells independent of the activation state (A to D and F to I) with

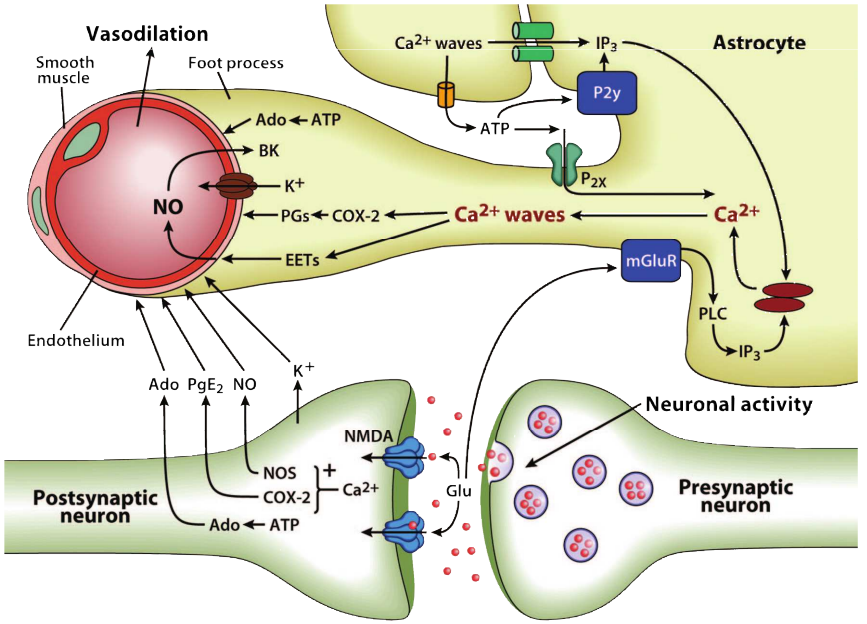
Gavegnano C, et al. AAC 2013

Monocyte activity score



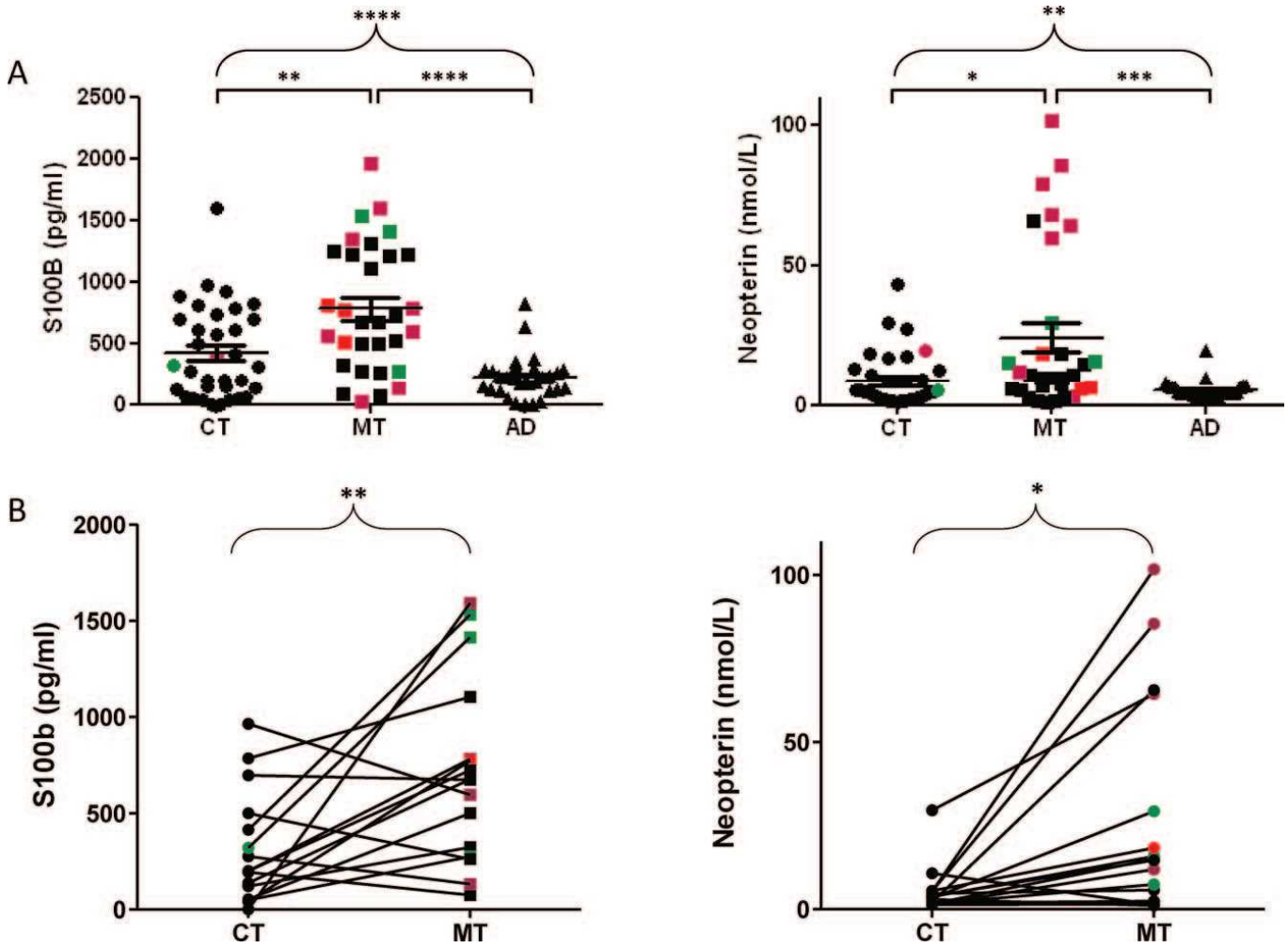
Astrocytosis

- Approximately 5% astrocytes are infected
- Restricted infection: viral proteins production
- Associated with deficit in verbal fluency
- Alteration of the **neurovascular unit** and of the **blood-brain barrier** impact on drug exposure (TDF, FTC, RAL)



Brack-Werner R. AIDS 1999; Eugenin EA, et al. J Neuroscience 2011; Woods SP, et al. J Clin and Exp Neuropsychology 2007; Calcagno A, et al. JNV 2015.

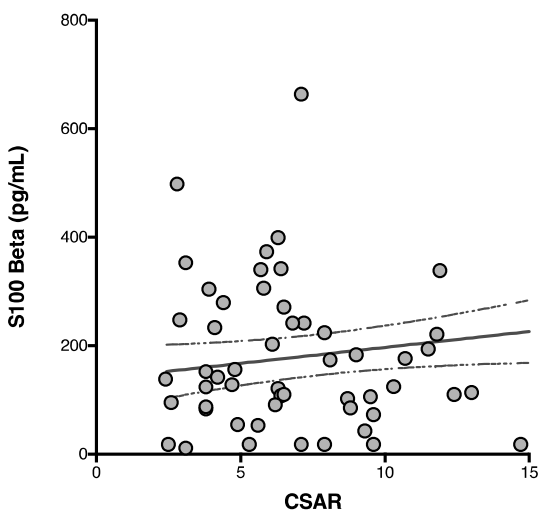
Astrocytosis and LPV/r monoT

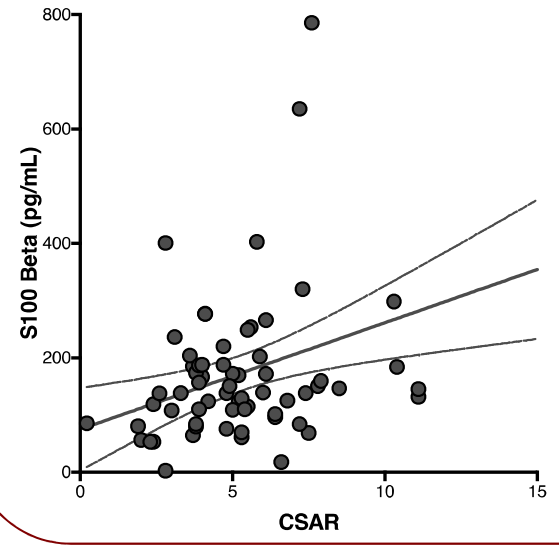


Two models of BBB damage

LATE PRESENTERS (<100 CD4/uL)

CSF HIV replication and inflammation





CSF HIV RNA <50 cps/mL

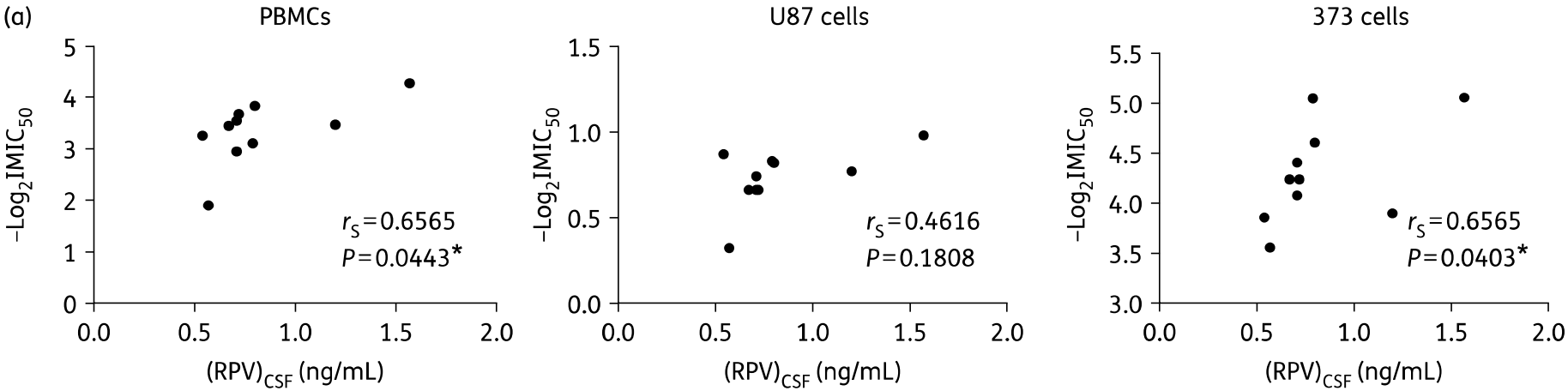
Astrocytosis and neuronal damage

Calcagno A, et al. *under review*

Ex vivo efficacy

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

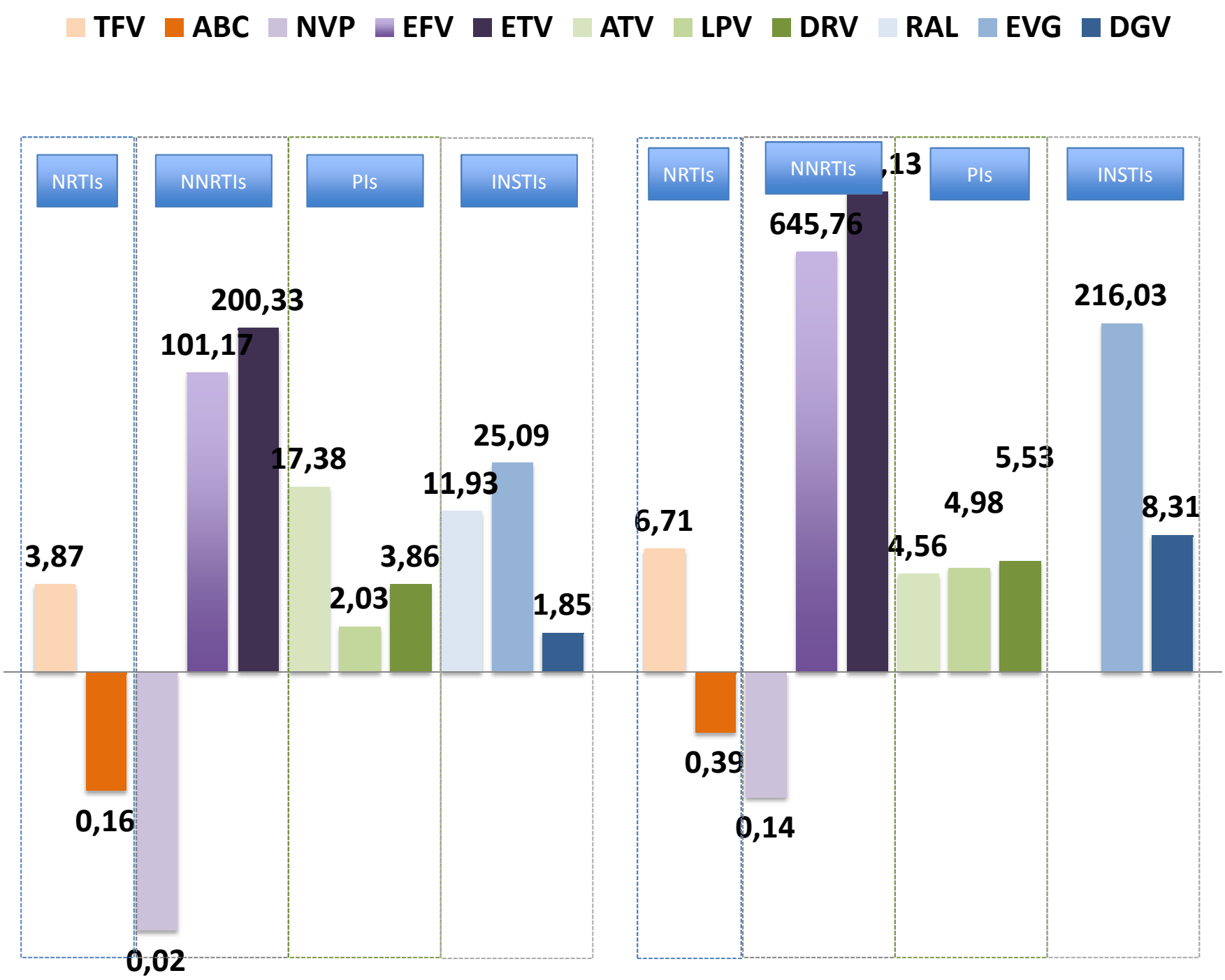
- **TDF/FTC+LPV/r+MVC > TDF/FTC+RPV**
- **CSF LPV and RPV concentrations associated with antiviral effect and MRS changes**



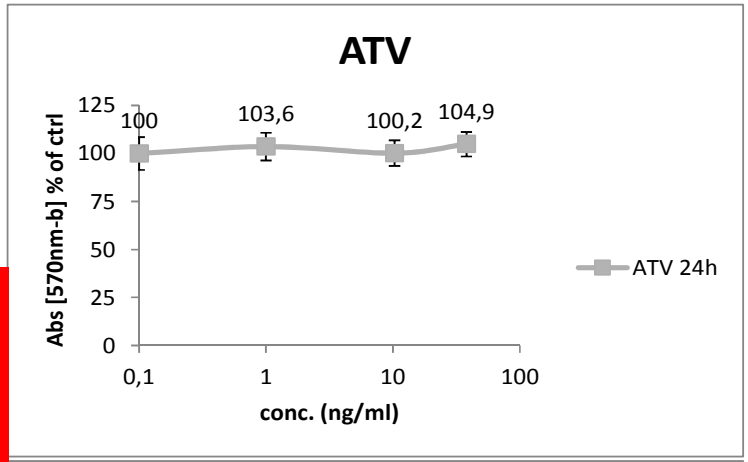
Mora-Perris B, et al. JAC 2015

Astrocyte IC concentrations

- Astrocyte-rich primary cultures (Sprague Dawley rats)
- Incubated with three different concentrations (the minimum or IC_{50}, median and maximum cerebrospinal fluid concentrations reported in humans)
- Medium was changed every day for 14 days.
- Surnatant and intracellular accumulation were evaluated through HPLC/MS-MS.
- 24-hour and 14 days toxicity was evaluated in 24-well plates through the MTT method and expressed as percentage of viable cells (related to controls with no drug exposure).
- Surnatant damage and activation markers (*ongoing*)


TFV
ABC
NVP
EFV
ETV
ATV
LPV
DRV
RAL
EVG
DGV
NRTIs
NNRTIs
PIs
INSTIs
3,87
0,16
0,02
101,17
200,33
17,38
2,03
3,86
11,93
25,09
1,85
NRTIs
NNRTIs
PIs
INSTIs
6,71
0,39
0,14
645,76
,13
4,56
4,98
5,53
216,03
8,31

DAY 1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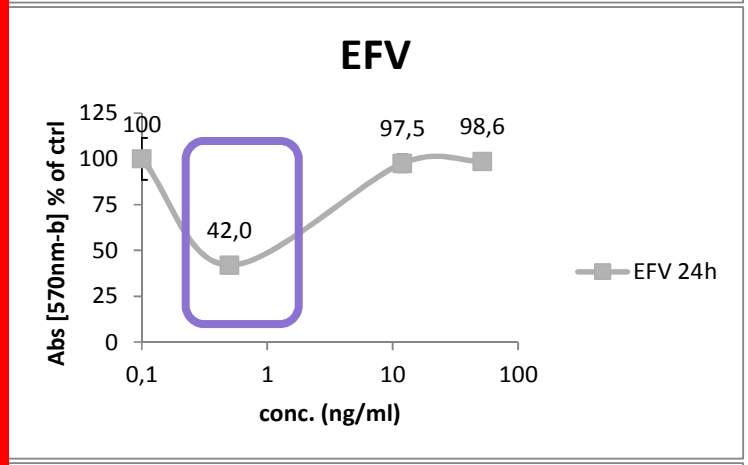
100
75
50
25
0
100
103,6
100,2
104,9
0,1
1
10
100
conc. (ng/ml)
ATV 24h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100
42,0
97,5
98,6
0,1
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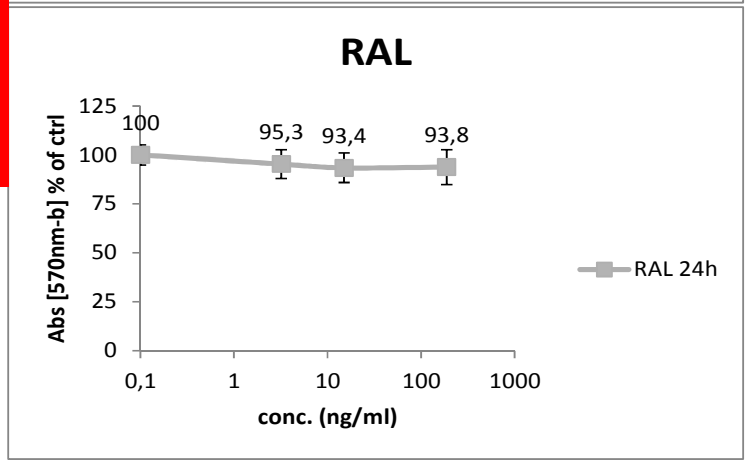
10
100
conc. (ng/ml)
EFV 24h


RAL
Abs [570nm-b] % of ctrl
125
100
75
50
25
0
100
95,3
93,4
93,8
0,1
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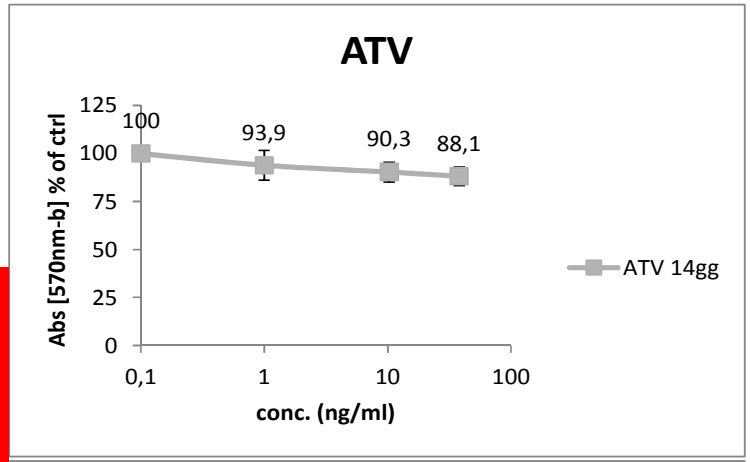
10
100
1000
conc. (ng/ml)
RAL 24h

DAY 14


ATV
Abs [570nm-b] % of ctrl
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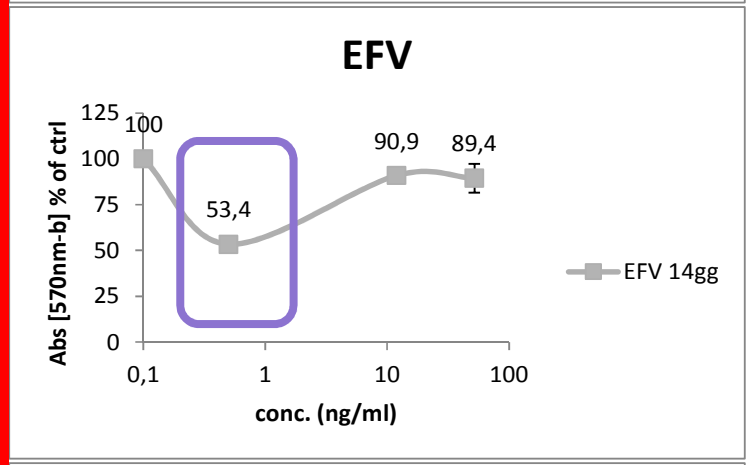
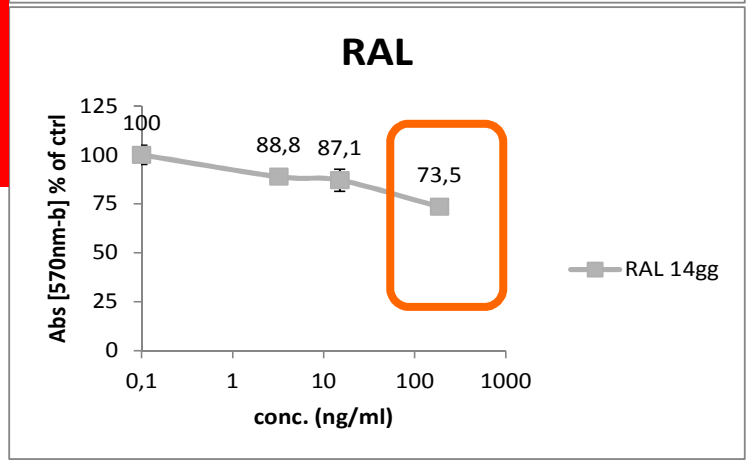
100
75
50
25
0
100
93,9
90,3
88,1
0,1
1
10
100
conc. (ng/ml)
ATV 14gg


EFV
Abs [570nm-b] % of ctrl
125
100
75
50
25
0
100
53,4
90,9
89,4
0,1
1
10
100
conc. (ng/ml)
EFV 14gg


RAL
Abs [570nm-b] % of ctrl
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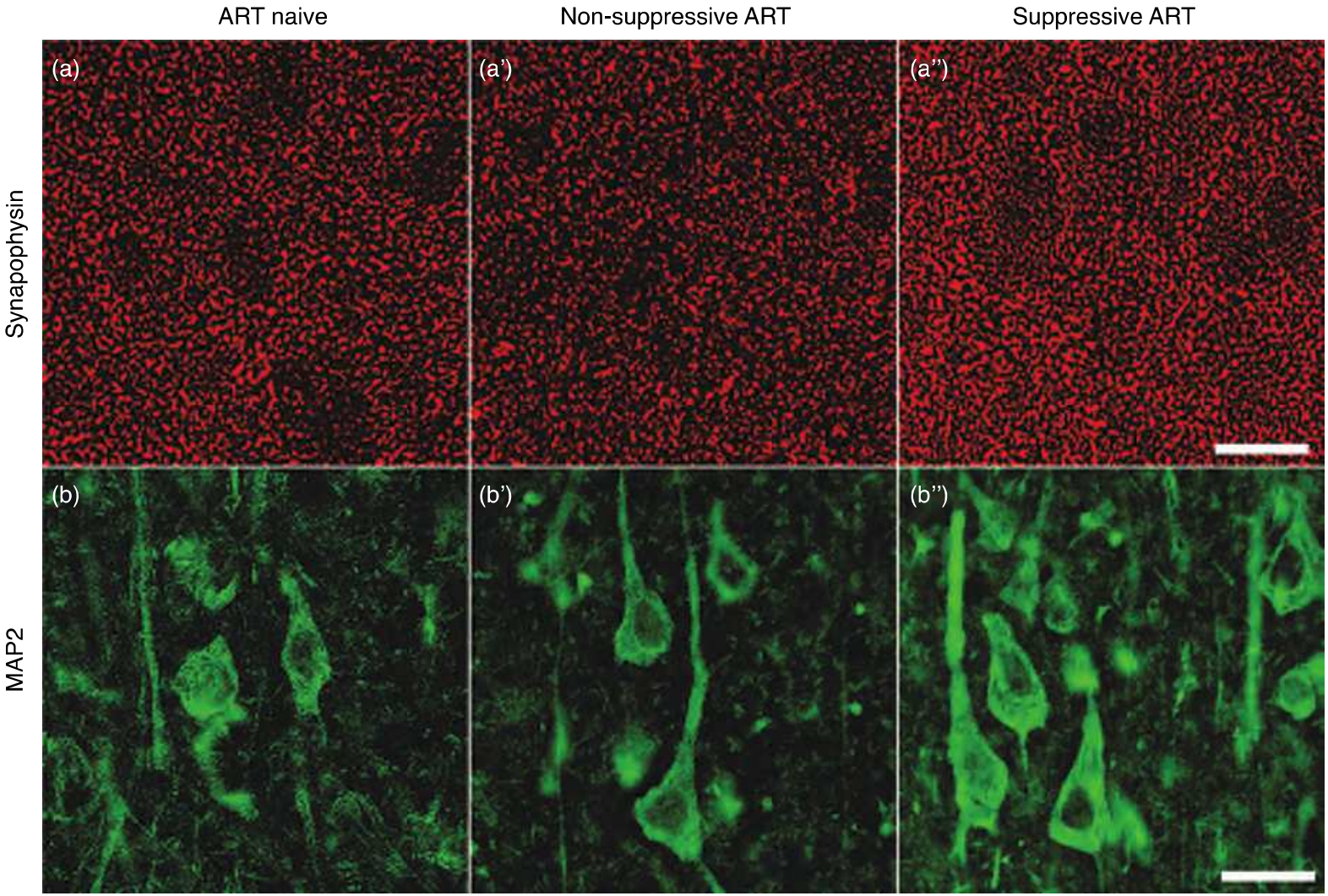
100
75
50
25
0
100
88,8
87,1
73,5
0,1
1
10
100
1000
conc. (ng/ml)
RAL 14gg

Outline

1. Epidemiology
   - HAND vs. CSF escape
2. CNS Pharmacology
3. Pathogenesis
4. HAND despite HAART vs. because of ARVs
5. Clinical management of HAND (???)

HAART and Neurodegeneration



Bryant AK, et al. AIDS 2015

Are some drugs more neuroeffective?

1. Concentrations of some antiretrovirals in CSF **do not exceed** the inhibitory concentration for wild-type HIV replication;
2. Drugs with **poor estimated CNS effectiveness are associated with high levels of HIV RNA** in CSF;
3. Some studies have shown that drugs with high estimated CNS effectiveness are associated with **improved cognitive function**;
4. Studies have shown that some antiretrovirals are **neurotoxic**;
5. Some observational studies have reported **a decline** in the levels of HIV RNA in CSF and **improvement**s in cognitive function after **changes to ART regimines on the basis of estimated CNS effectiveness**

1. **CSF viral escape is uncommon** with any antiretroviral combination when using routing HIV RNA assays
2. Some observational studies **have not shown an association between ART with drugs that have high estimated CNS effectiveness and neurocognitive function**
3. Estimates of CNS effectiveness are largely based on the **pharmacokinetics of ART in CSF,** which might not accurately reflect the pharmacokinetics of antiretroviral drugs in HIV-infected glial cells or brain macrophages

Nightingale S, et al. Lancet Neurology 2014

Not enough coffee…

The CPE score

Appendix Table 1. Central Nervous System Penetration Effectiveness Rankings of Frequently Used Antiretroviral Regimen (10)

Antiretroviral Class	Central Nervous System Penetration Effectiveness Ranking[a]			
	4	3	2	1
Nucleoside analogue reverse transcriptase inhibitors	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
Nonnucleoside analogue reverse transcriptase inhibitors	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
Protease inhibitors	Indinavir/ritonavir	Darunavir/ritonavir	Atazanavir	Nelfinavir
		Fosamprenavir/ritonavir	Atazanavir/ritonavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir/ritonavir		Saquinavir/ritonavir
				Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

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**	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

Ellen C. Caniglia
Lauren E. Cain, PhD
Amy Justice, PhD
Janet Tate, PhD
Roger Logan, PhD
Caroline Sabin, PhD
Alan Winston, MD
Ard van Sighem, PhD
Jose M. Miro, PhD
Daniel Podzamczer, PhD
Ashley Olson, PhD
José Ramón Arribas, MD
Santiago Moreno, PhD
Laurence Meyer, PhD
Jorge del Romero, MD
François Dabis, PhD
Heiner C. Bucher, MD
Gilles Wandeler, MD
Georgia Vourli, MSc
Athanasios Skoutelis, MD
Emilie Lanoy, PhD
Jacques Gasnault, MD
Dominique Costagliola,

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**

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
$CPE\text{-}GSS_{ANRS}$	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
$CPE\text{-}GSS_{HIVDB}$	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
$CPE\text{-}GSS_{REGA}$	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

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

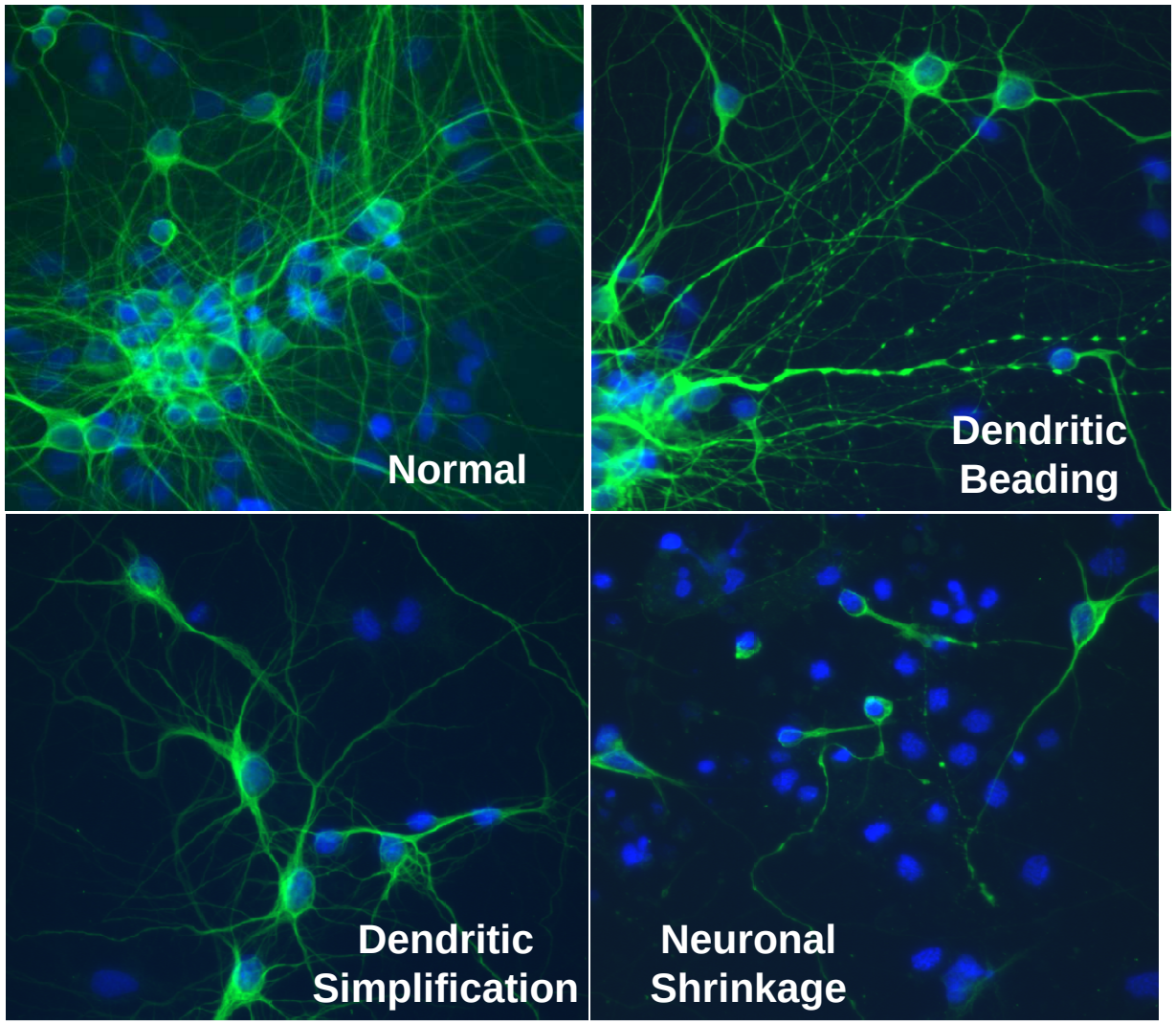
⑤ PIs disrupt astrocytic glutamate transporter function and neurobehavioral performance

⑥ Might be dose-dependant (**EFV**)

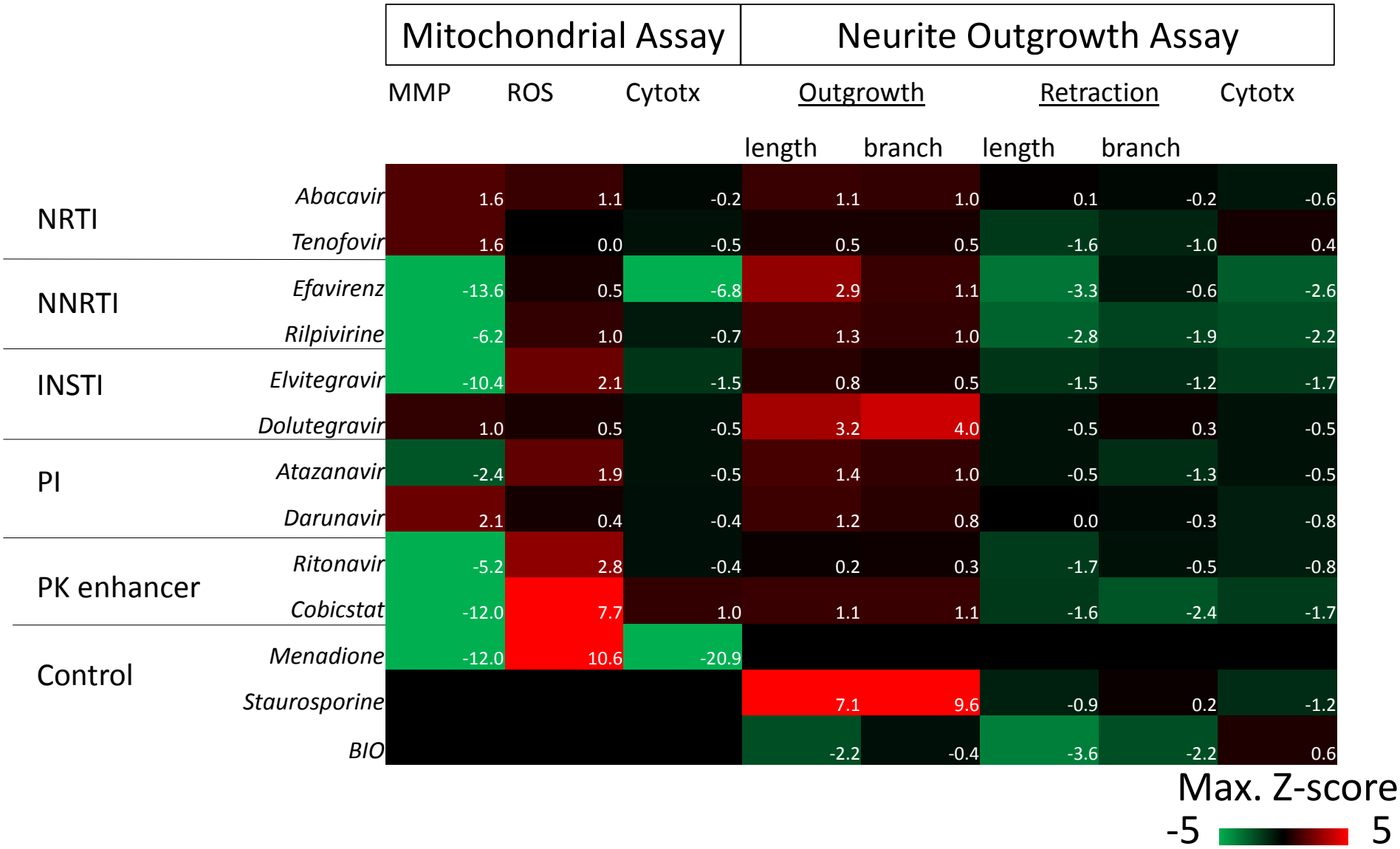
Tovar-y-Romo LB, et al. J Pharmacol Exp Ther, 2012; Robertson K, et al. JNV 2012; Akay C, et al. JNV 2014; Giunta B, et al. Mol Brain 2011; Robertson K, et al. Neurology 2010; Achim CL, et al. J Neuroimmune Pharmacol 2009; Ortega M and Ances BM, J Neuroimmune Pharmacol 2014; Ciccarelli N, et al. Neurology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

In vitro neurotoxicity

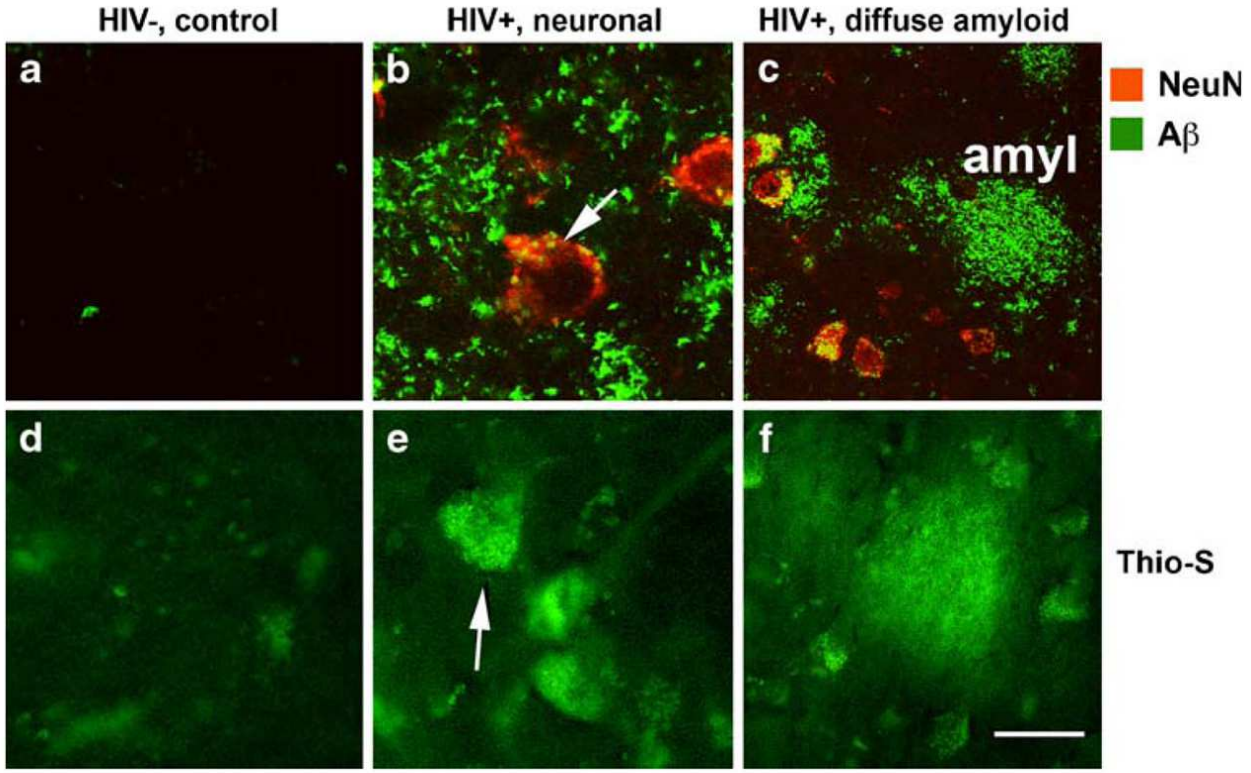
- Fetal rat cortical neuron cultures
- Some degree of **functional** injury seen with all drugs
- **EFV>others> FTC,DRV,MVC**
- no additive effect



Neurotoxicity @ CROI2016



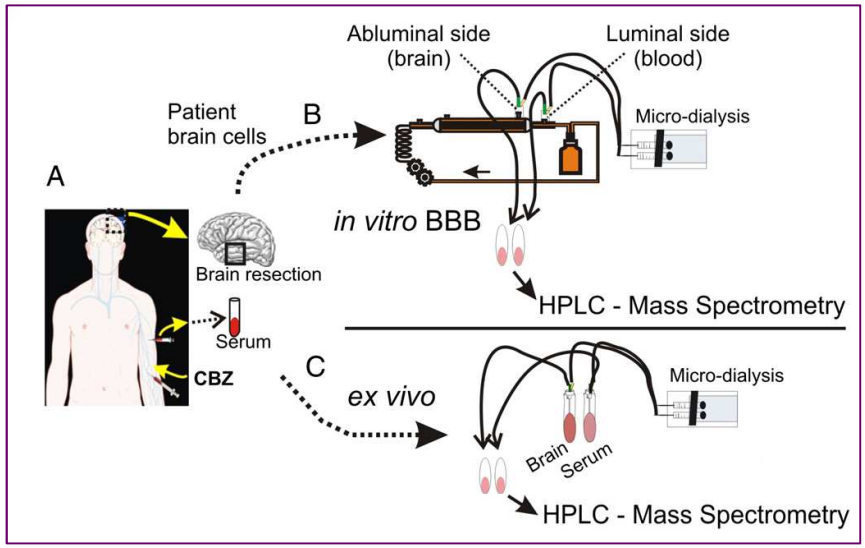
β Amyloid Deposition

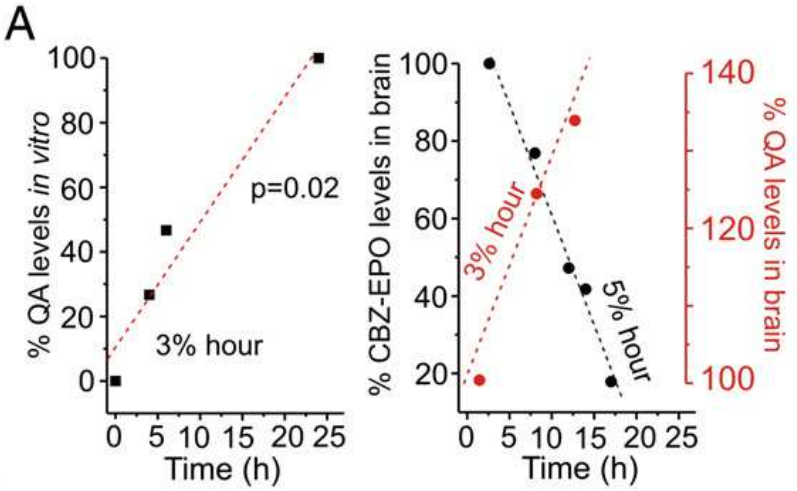


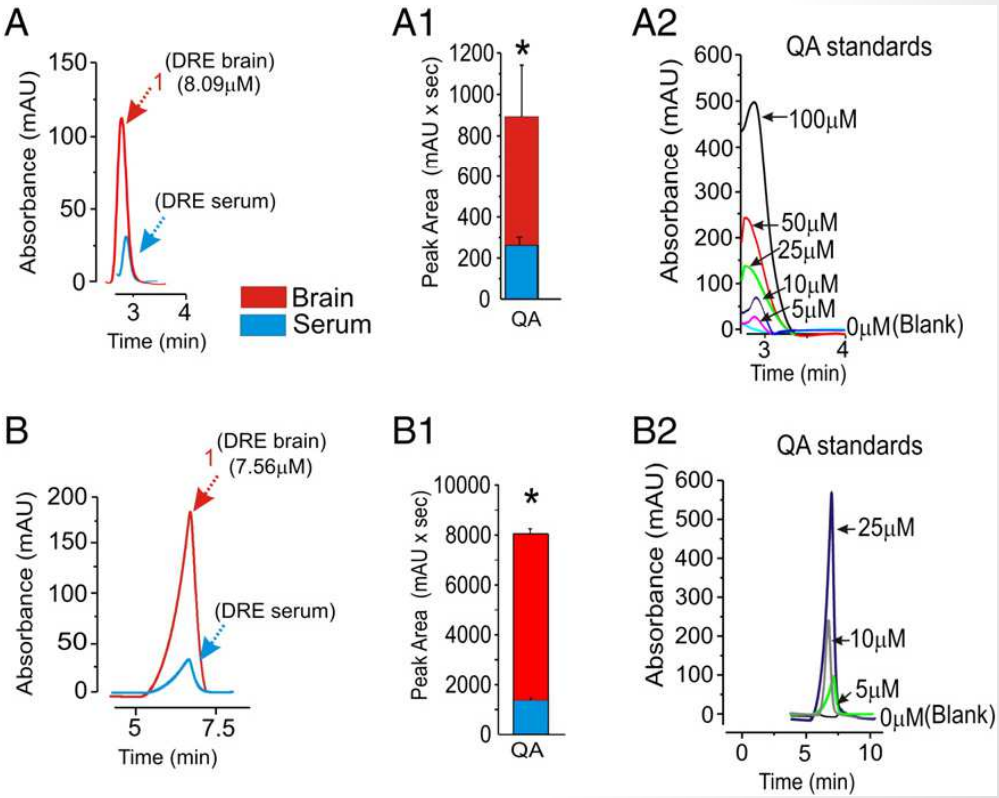
- Impairment of beta amyloid metabolism:
  - *in vitro* additive effect of ARVs;
  - EFV (trough reduced microglial phagocytosis).

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

Metabolism of brain endothelial cells







Ghosh C, et al. Neurobiology of disease 2012

Outline

1. Epidemiology
   - HAND vs. CSF escape
2. CNS Pharmacology
3. Pathogenesis
4. HAND despite HAART vs. because of ARVs
5. Clinical management of HAND (???)

1. **Plasma viral load control is paramount in controlling CNS replication in the majority of patients**
   - Durable suppression

2. Low nadir CD4/high PBMCs HIV DNA is associated with a higher incidence of HAND
   - neurotargeted HAART?

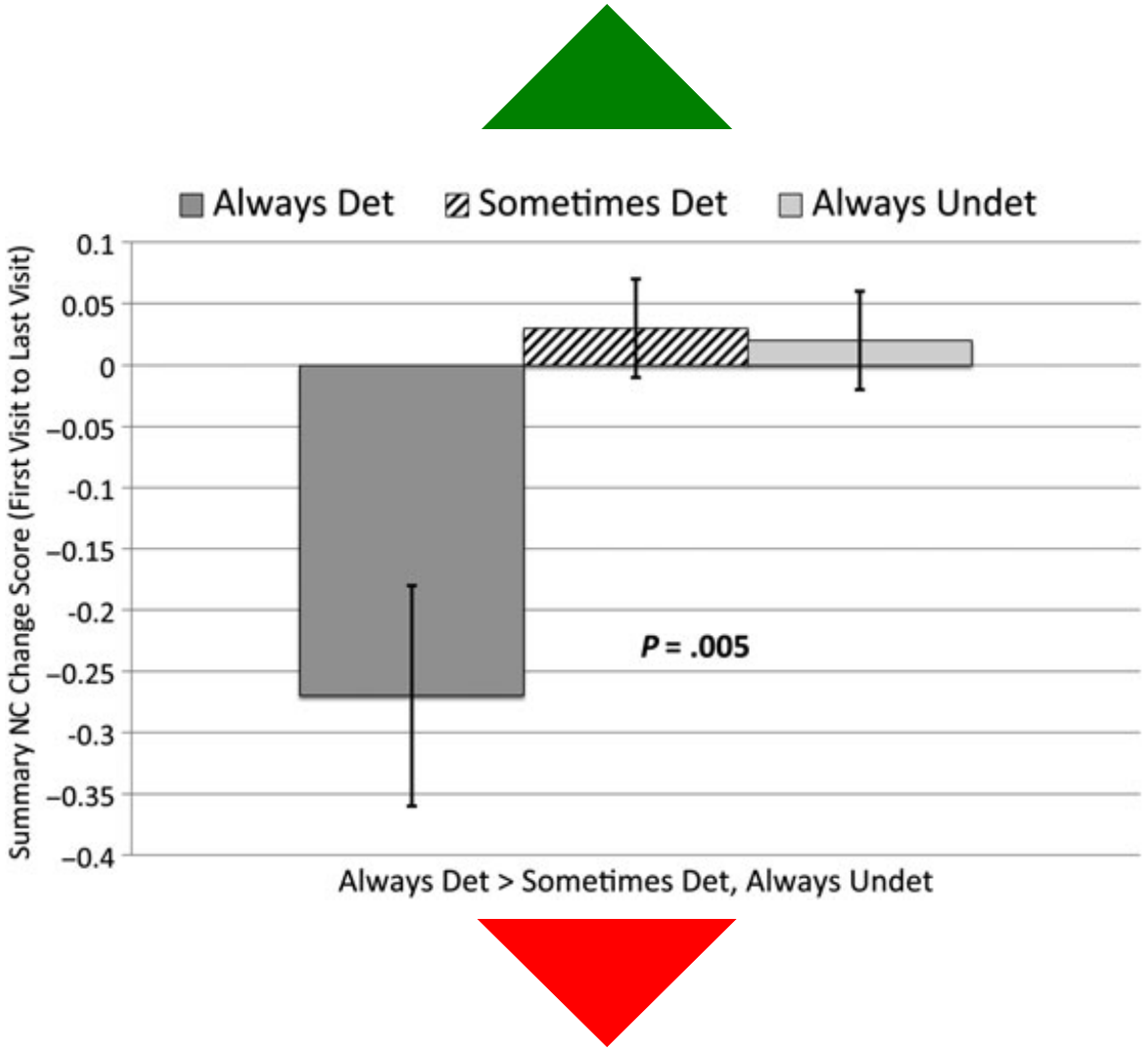
3. Vascular abnormalities are predominant in CNS HIV infection
   - Management!

CPE modifiers

CPE score: ≥10	**0**
5–9	**6**
<5	**9**
plasma HIV RNA: <50	**0**
50-200	**2**
200-10.000	**10**
>10.000	**18**
Race: Black vs. Hispanic/Other vs. White	**3/4**
Current depression: Yes vs. No	**4**
HIV medication adherence: <85% vs. 85-94% vs. >95%	**3**
Current cART (months): ≥36 vs. 25–35 vs. 13–24 vs. 7–12 vs. ≤6	**2/4**

Hammond ER, et al. Am J Epidemiology 2014

3-year progression in NC



Heaton RK, et al. CID 2014

1. Plasma viral load control is paramount in controlling CNS replication in the majority of patients
   - Durable suppression

2. **Low nadir CD4/high PBMCs HIV DNA is associated with a higher incidence of HAND**
   - neurotargeted HAART?

3. Vascular abnormalities are predominant in CNS HIV infection
   - Management!

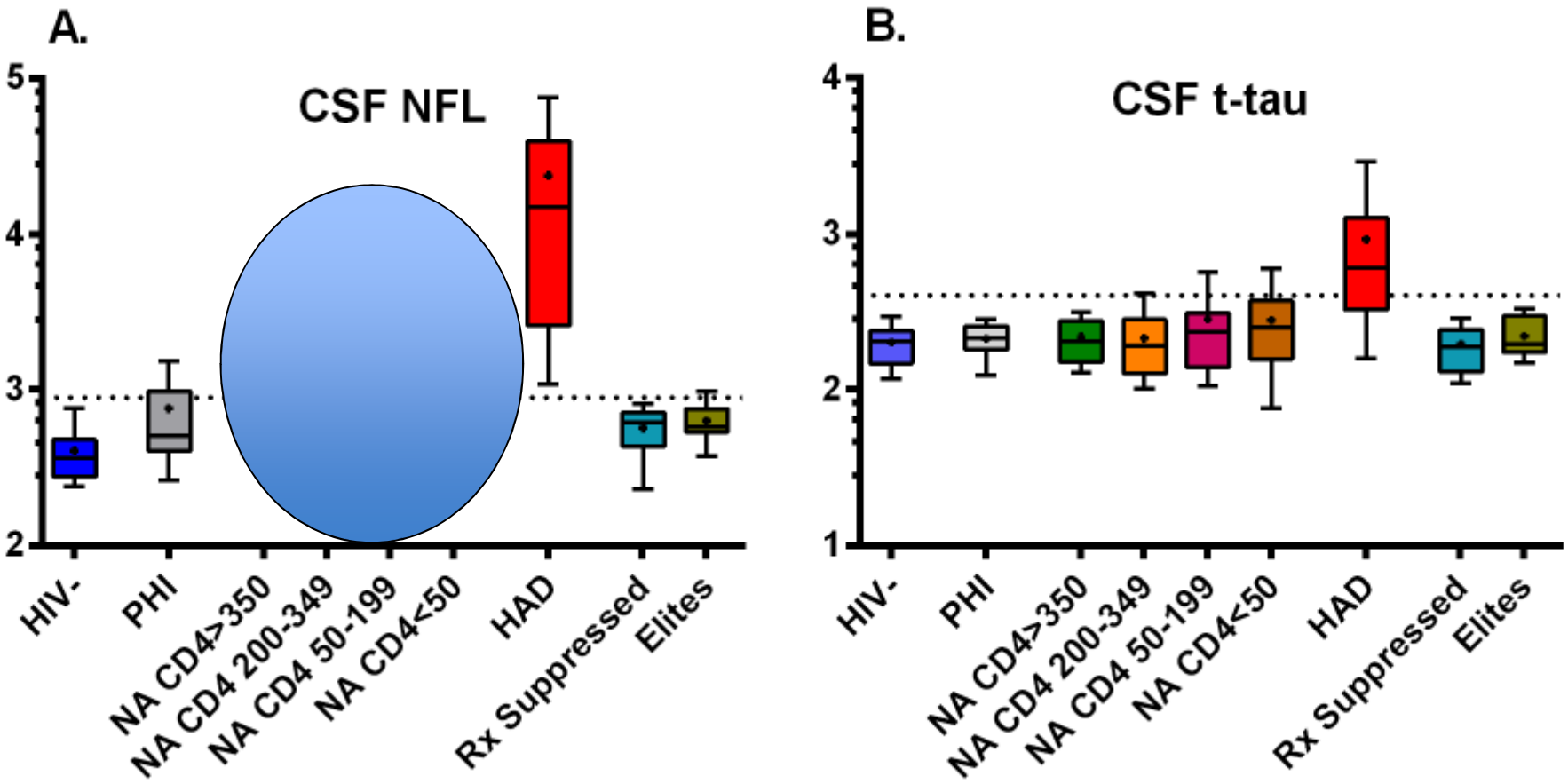
The Legacy effect

Irreversible neuronal damage before HAART initiation:

- CSF biomarkers of neuronal damage increase with decreasing CD4 cell count
- **Nadir CD4** cell count (and HIV DNA) is associated with:
  - Incident neurocognitive disorders
  - BBB damage
  - failure of PI monotherapies (including CSF escape)

Heaton RK, et al. Neurology 2010; Robertson KR, et al. AIDS 2007; Calcagno A, et al. JNV 2014; Antinori A, et al. AIDS 2015.

The Legacy effect (2)



Peterson J, et al. PlosOne 2014

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

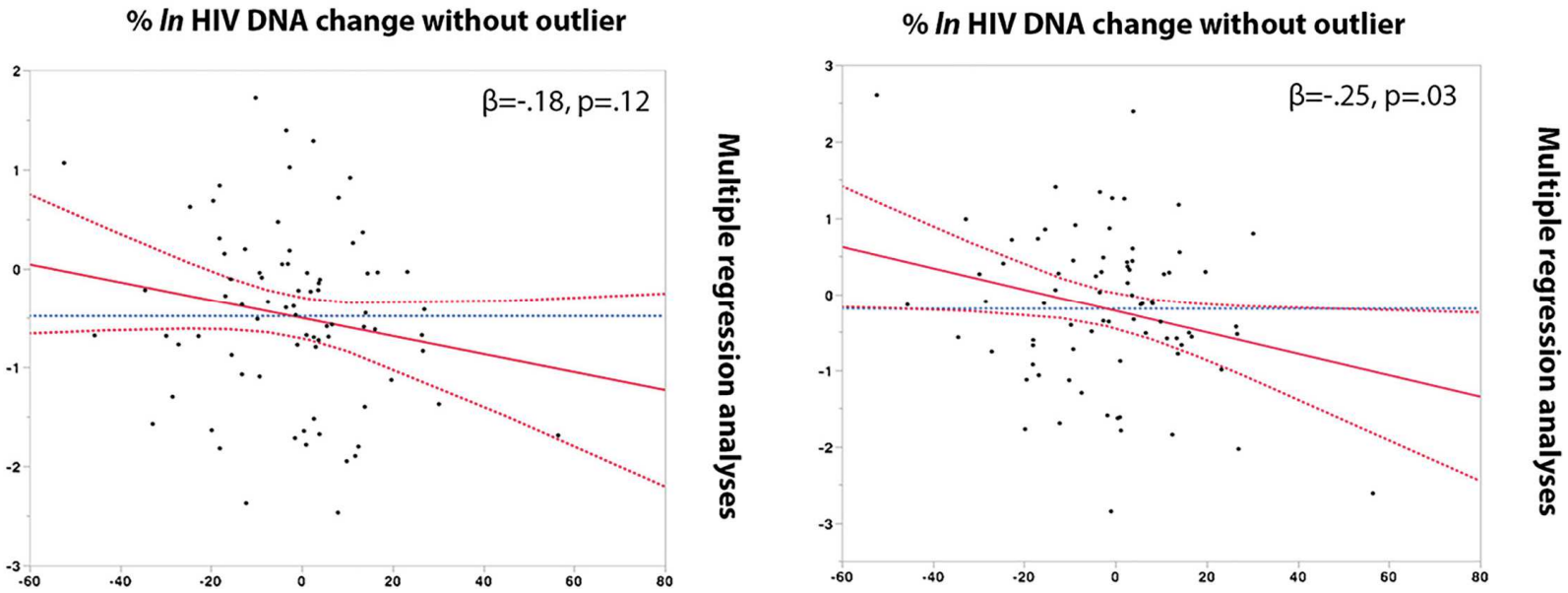
3: **HIV DNA in CD14+ reservoirs is associated with regional brain atrophy in patients naive to combination antiretroviral therapy.** Kallianpur KJ et al. AIDS. 2014

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

Peripheral Blood Mononuclear Cells HIV DNA Levels Impact Intermittently on Neurocognition



While the HIV DNA levels in PBMC are not associated with current non-demented HAND, **increasing HIV DNA levels were associated with a decline in neurocognitive functions associated with HAND progression**

Cysique LA. et al. PlosOne 2015

Maraviroc effect

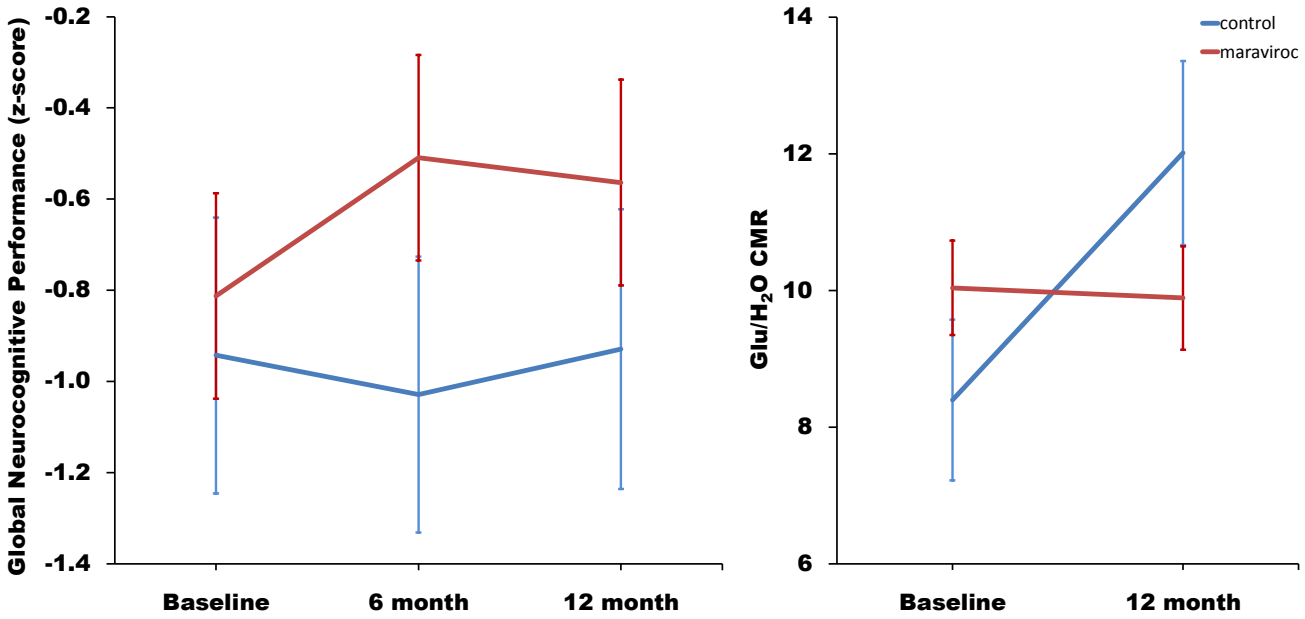
- Antiviral? CSF viruses often R5 tropic
  - Astrocyte infected via CXCR4
- Protective for SIV infection in macaques
- **Maraviroc intensification**
  - increase in MRS Naa/Cr (neuronal integrity)
  - reduction in CSF CXCL10 (IP-10)
  - better with higher MVC plasma conc
  - Reduction in CD16+ monocytes,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

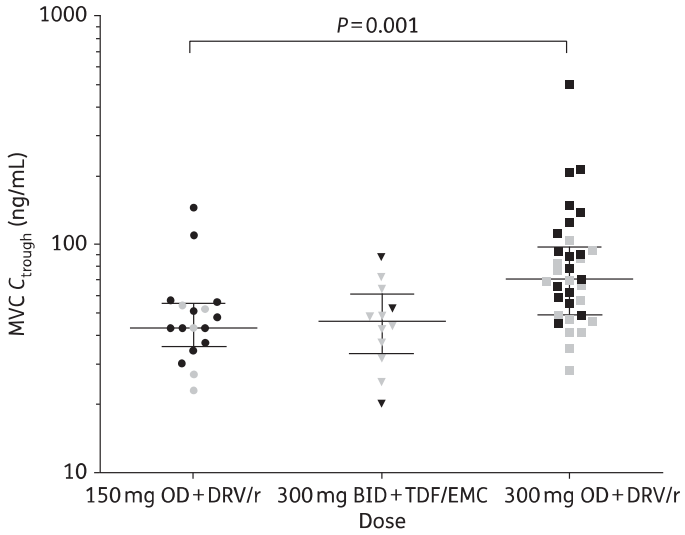
14 virally-suppressed (blood and CSF) HIV+ males on stable cART with recent progression to HAND

Open-label RCT of MVC-intensification

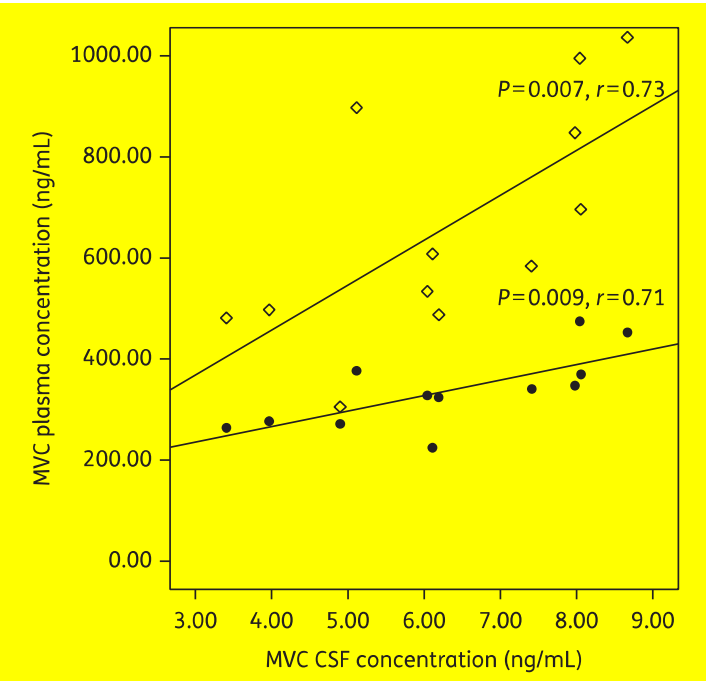


MVC DOSE!

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



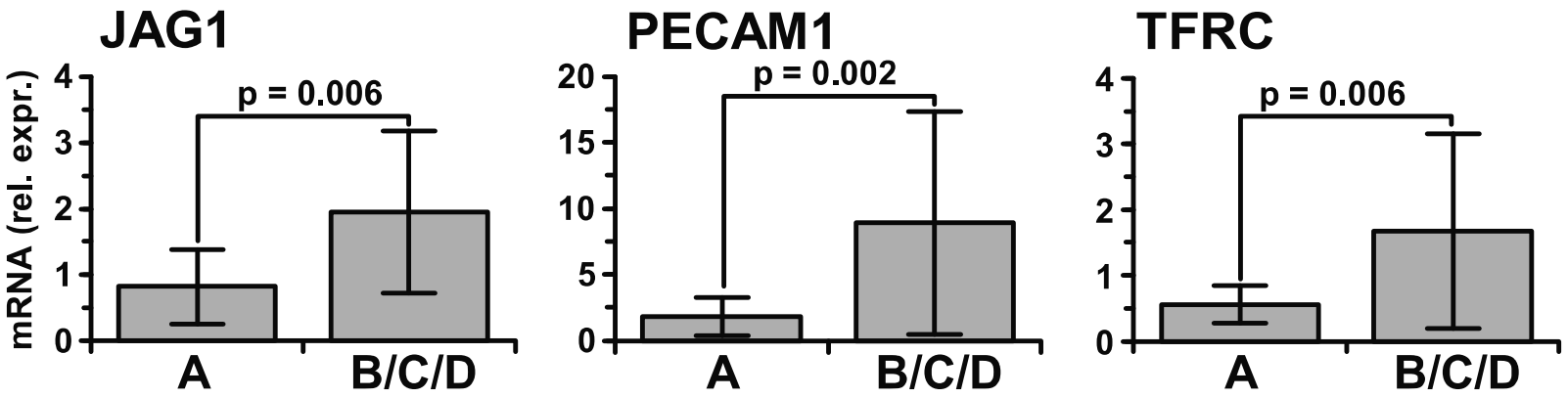
1. Plasma viral load control is paramount in controlling CNS replication in the majority of patients
   - Durable suppression

2. Low nadir CD4/high PBMCs HIV DNA is associated with a higher incidence of HAND
   - neurotargeted HAART?

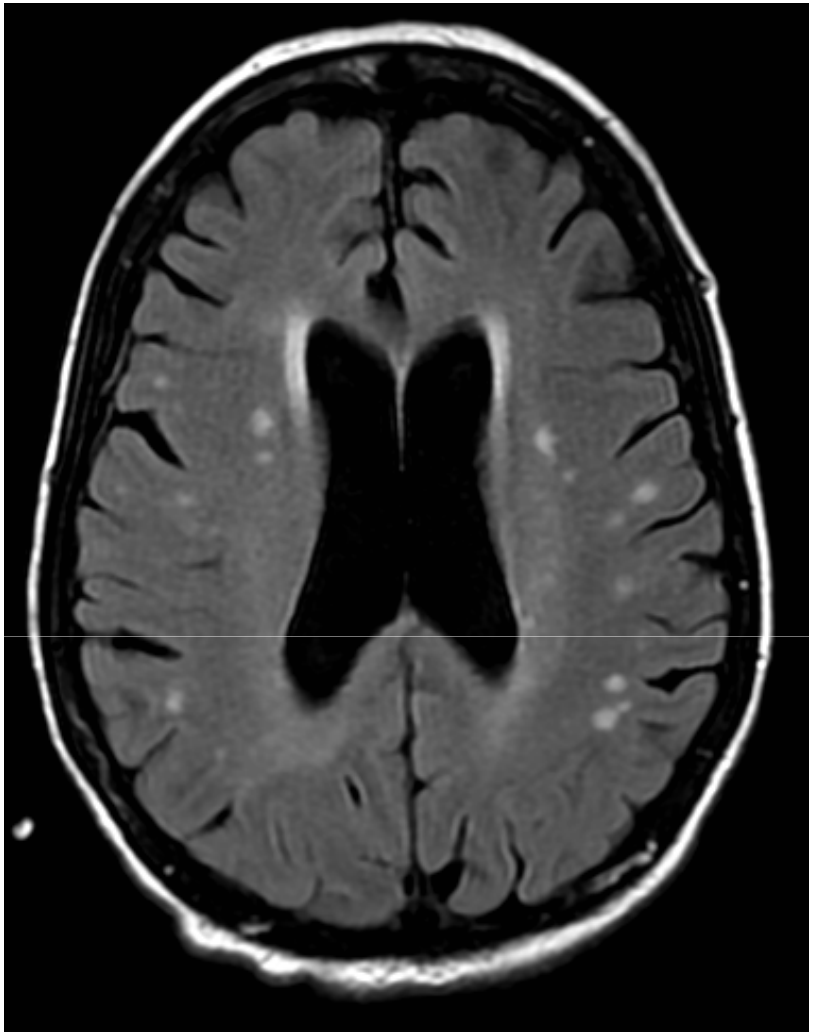
3. **Vascular abnormalities are predominant in CNS HIV infection**
   - Management!

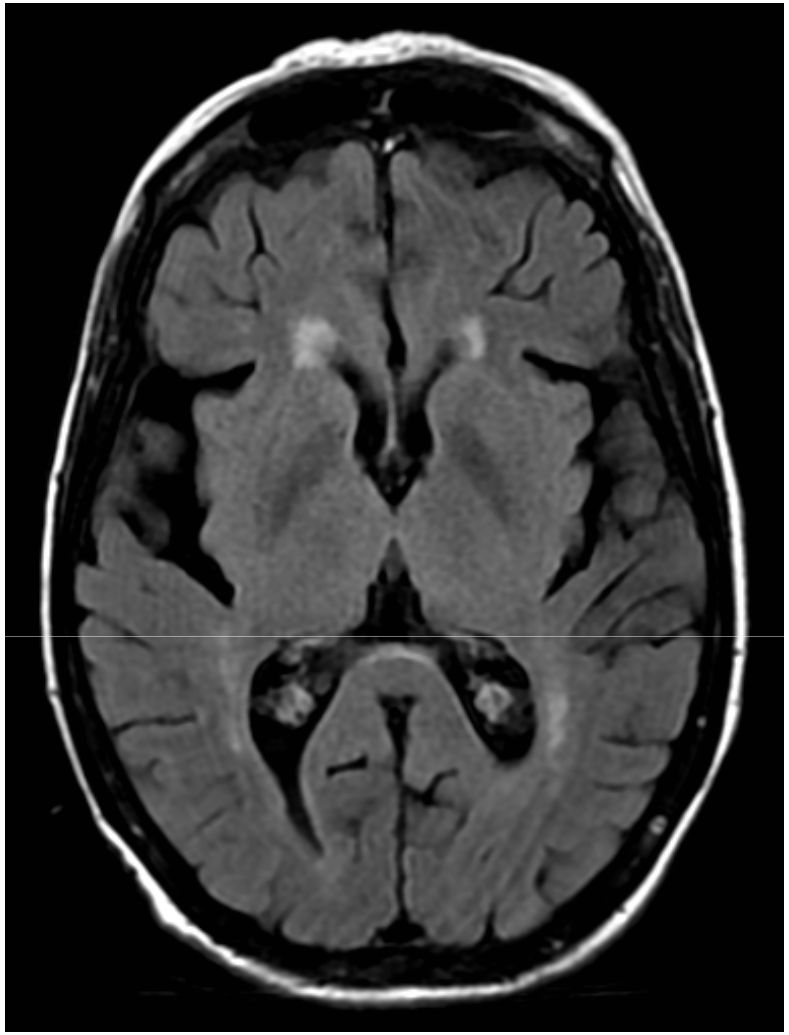
The National NeuroAIDS Tissue Consortium Brain Gene Array: Two Types of HIV-Associated Neurocognitive Impairment

Characteristic	Type I impairment	Type II impairment
NNTC Gene Array Group**	Group D	Group C
Last Global Impairment Score***	7.5±2.2	6.9±1.1
Neuropathological substrate	HIV encephalitis	Unknown
Related to brain HIV-1 replication	Yes	No
Influenced by HAART****	Decreased prevalence	Possibly no influence
Brain immune responses on array	Strong upregulation	Not upregulated, possibly deficient
Brain CD163 expression on array	Strong increase	Usually no increase
Neuronal mRNAs in neocortex on array	Broad downregulation	Not downregulated
Prevalence before 1995	At least 20%	Unknown
Prevalence 2011	Less than 10%	At least 35%

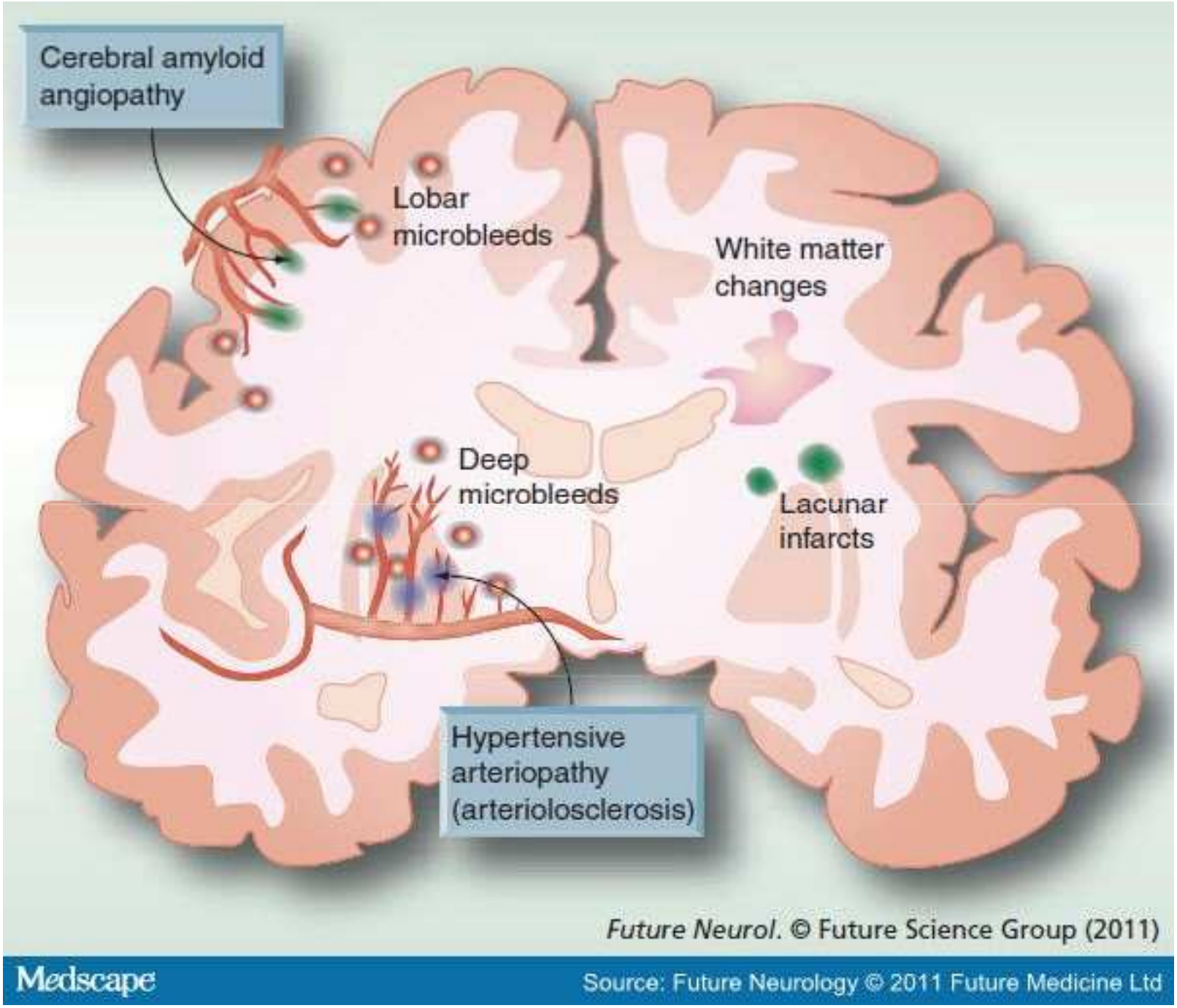


Gelman BB, et al. PlosOne 2012



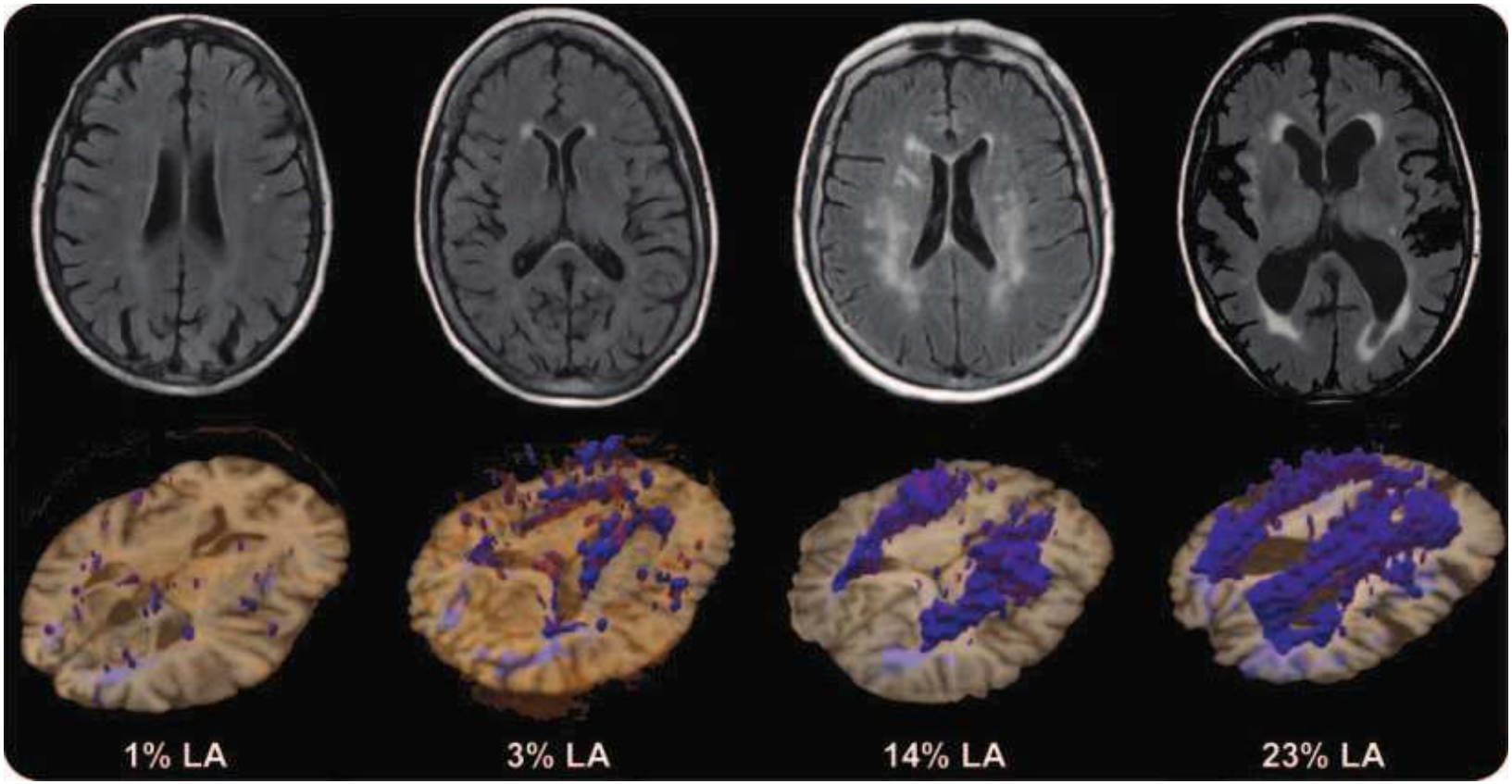


Multiple long TR hyper-intensities, no alteration in diffusivity, non-contrast enhancement


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

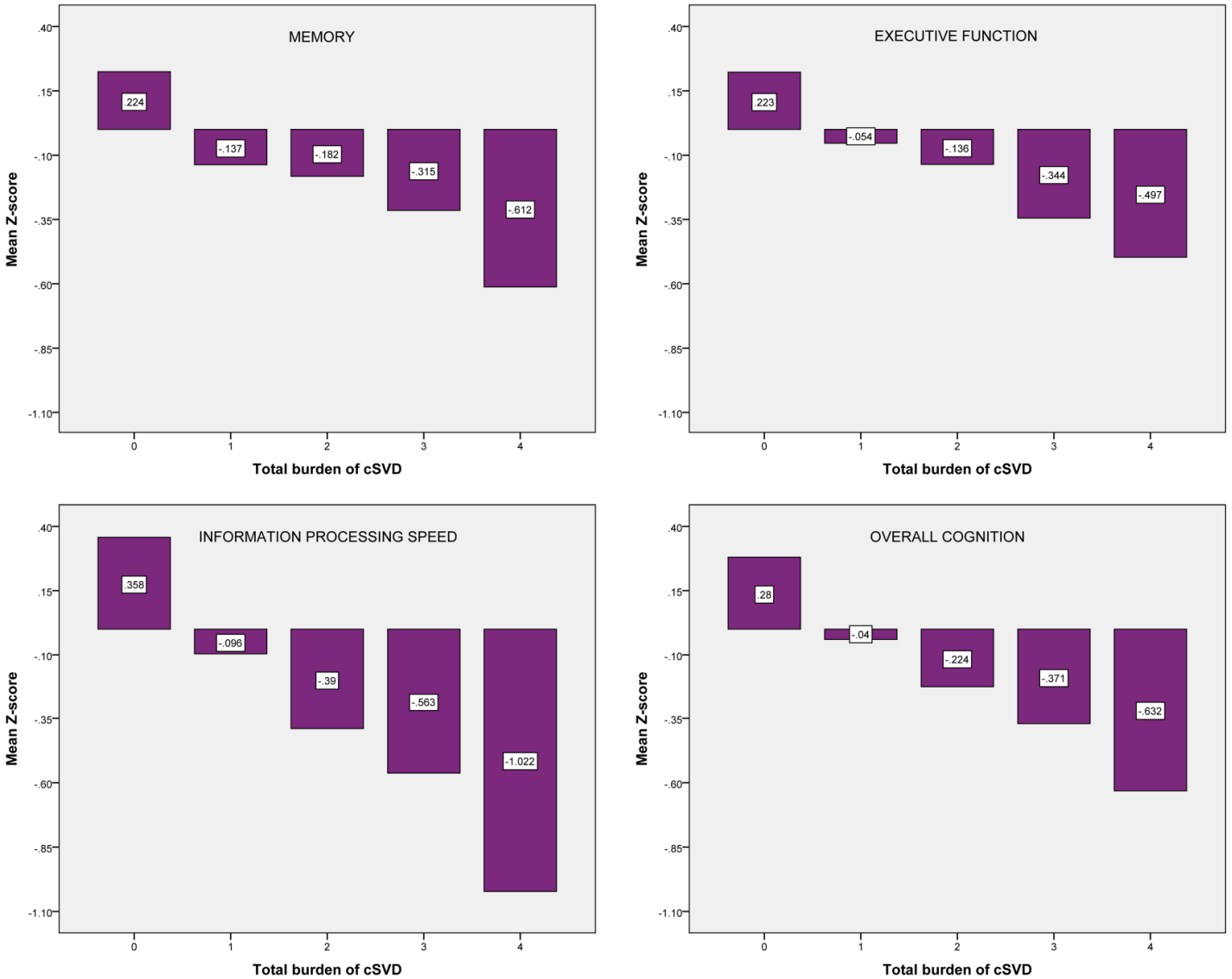
CSVD on MRI

White matter lesions (WMLs), asymptomatic lacunar infarcts, brain microbleeds (BMBs) and enlarged perivascular spaces (EPVS) have been identified as silent lesions due to cerebral small vessel disease (cSVD)



Price CC, et al. Neurology 2012; Huijts M, et al. Front Ageing Neurosci 2013

CSVD and NC function

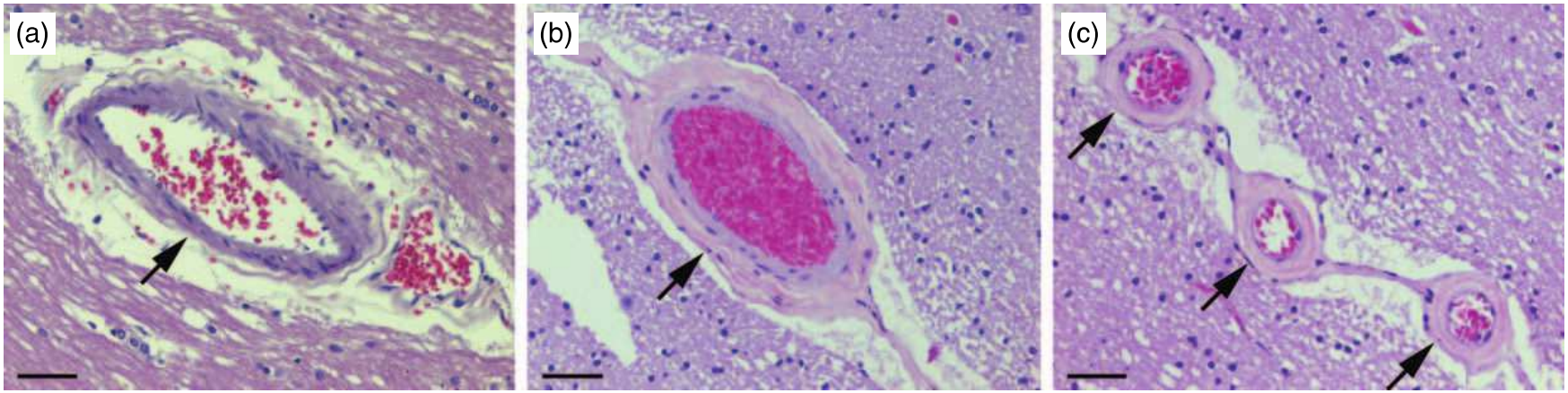


Huijts M, et al. Front Ageing Neurosci 2013

Management of cSVD (HIV-)

- HPT ----- (SBP <130 mmHg)
- LDL-Cholesterol ------ (LDL<100?)
- hyperhomocysteinemia ----- (folate and B12 vitamin)
- Vitamin E?
- ASA (325 mg)?

CSVD and PI use



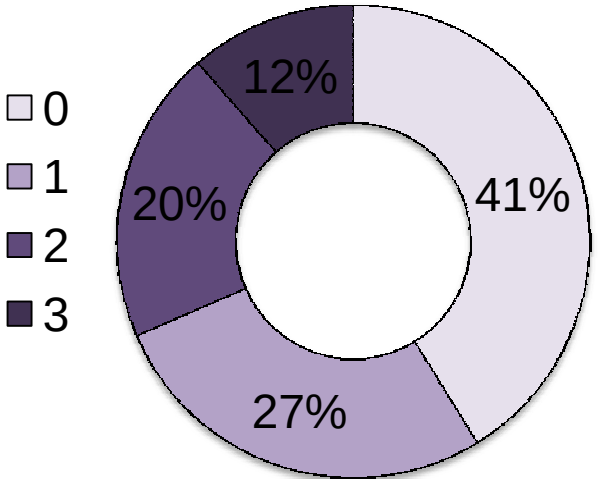
Mild CSVD **24.8%** and moderate/severe CSVD **47.4%** (137 autopsies, 1999-2011)

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

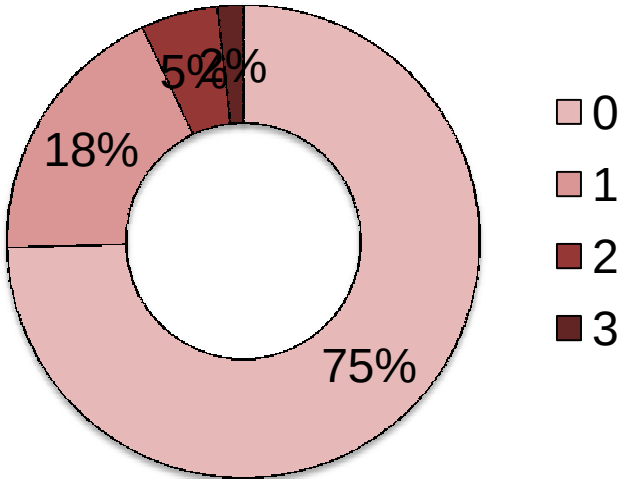
Soontornniyomkij V, et al. AIDS 2014

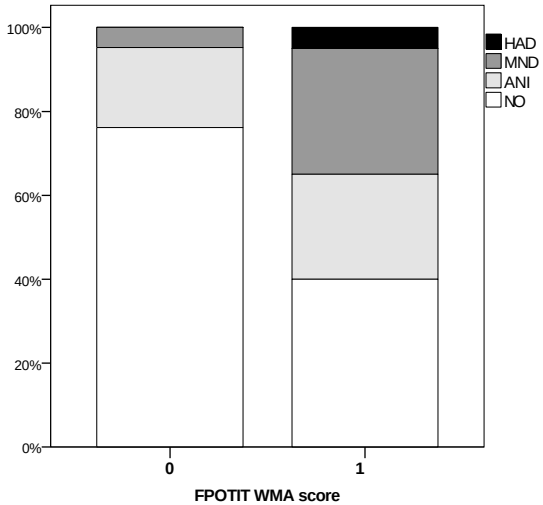
WMA grading

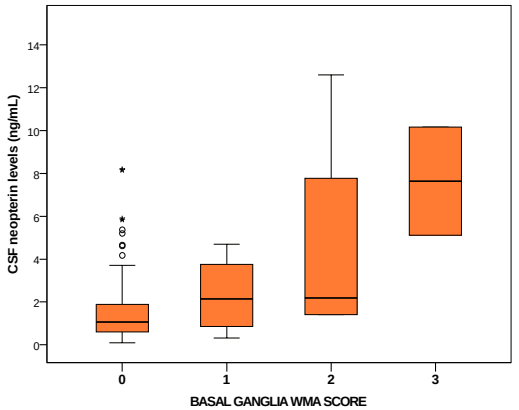
F, PO, T, IT WM abnormalities

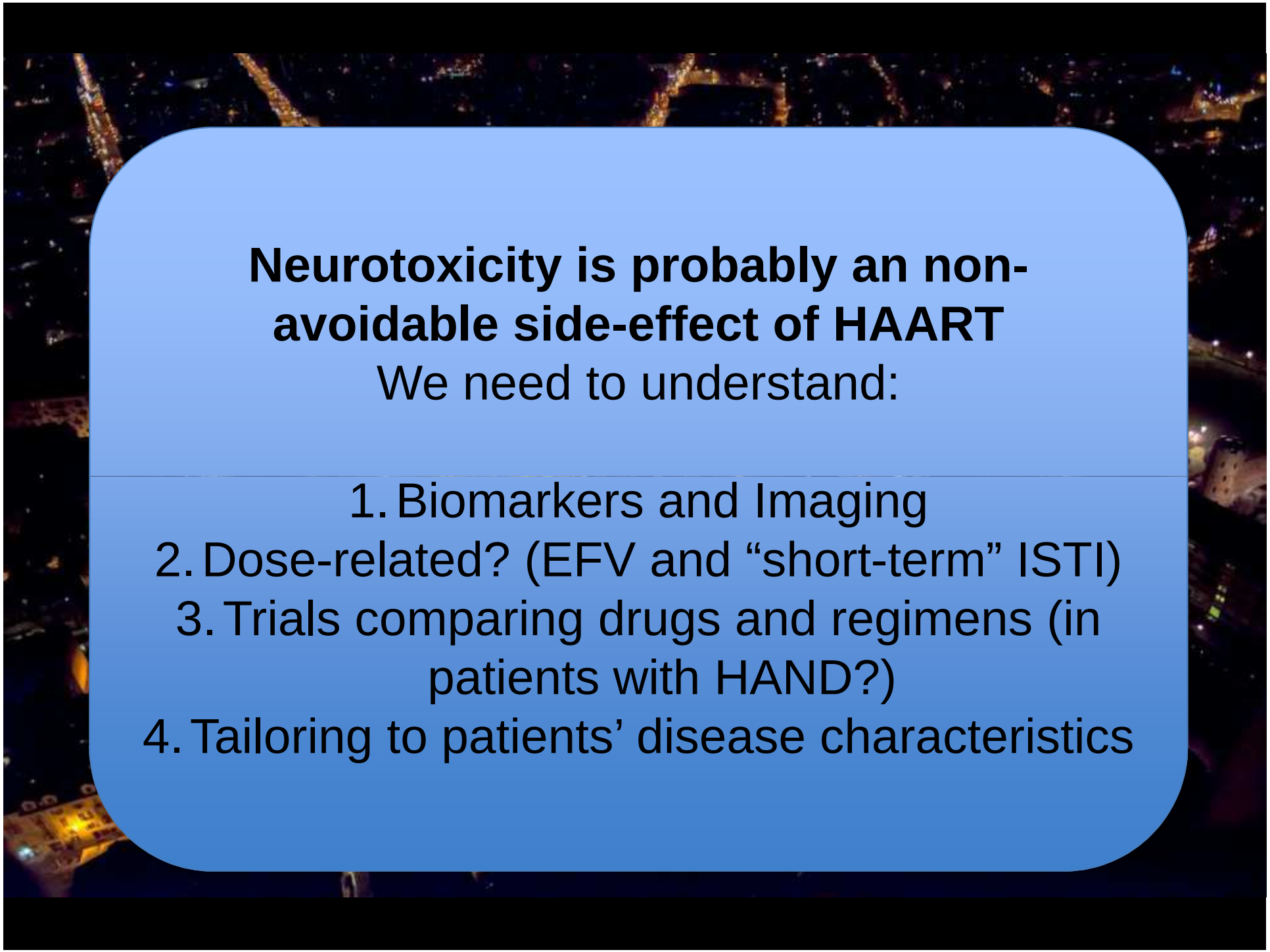


Basal ganglia WM abnormalities

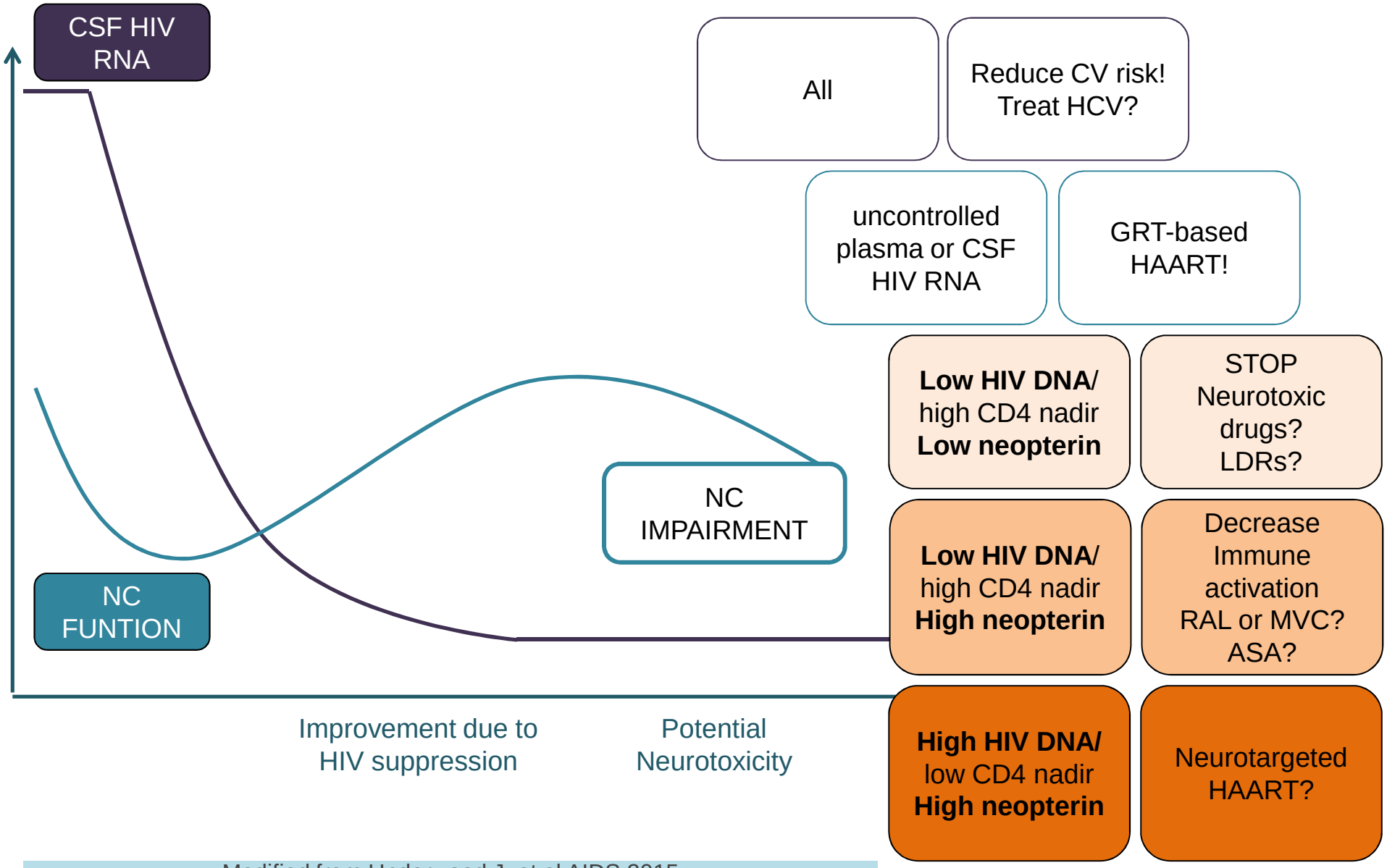







Neurotoxicity is probably an non-avoidable side-effect of HAART
We need to understand:
1. Biomarkers and Imaging
2. Dose-related? (EFV and “short-term” ISTI)
3. Trials comparing drugs and regimens (in patients with HAND?)
4. Tailoring to patients’ disease characteristics

Tailored Treatments?



Modified from Underwood J, et al AIDS 2015

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Alessandra Ariaudo
Fabio Favata

Prof. S Letendre

Cognitive rehabilitation

Neuropsychol Rev
DOI 10.1007/s11065-013-9225-6

REVIEW

Cognitive Neurorehabilitation of HIV-associated Neurocognitive Disorders: A Qualitative Review and Call to Action

Erica Weber & Kaitlin Blackstone & Steven Paul Woods

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 16 November 2015
doi: 10.3389/fnbeh.2015.00306

CrossMark

Evaluation of a Cognitive Rehabilitation Protocol in HIV Patients with Associated Neurocognitive Disorders: Efficacy and Stability Over Time

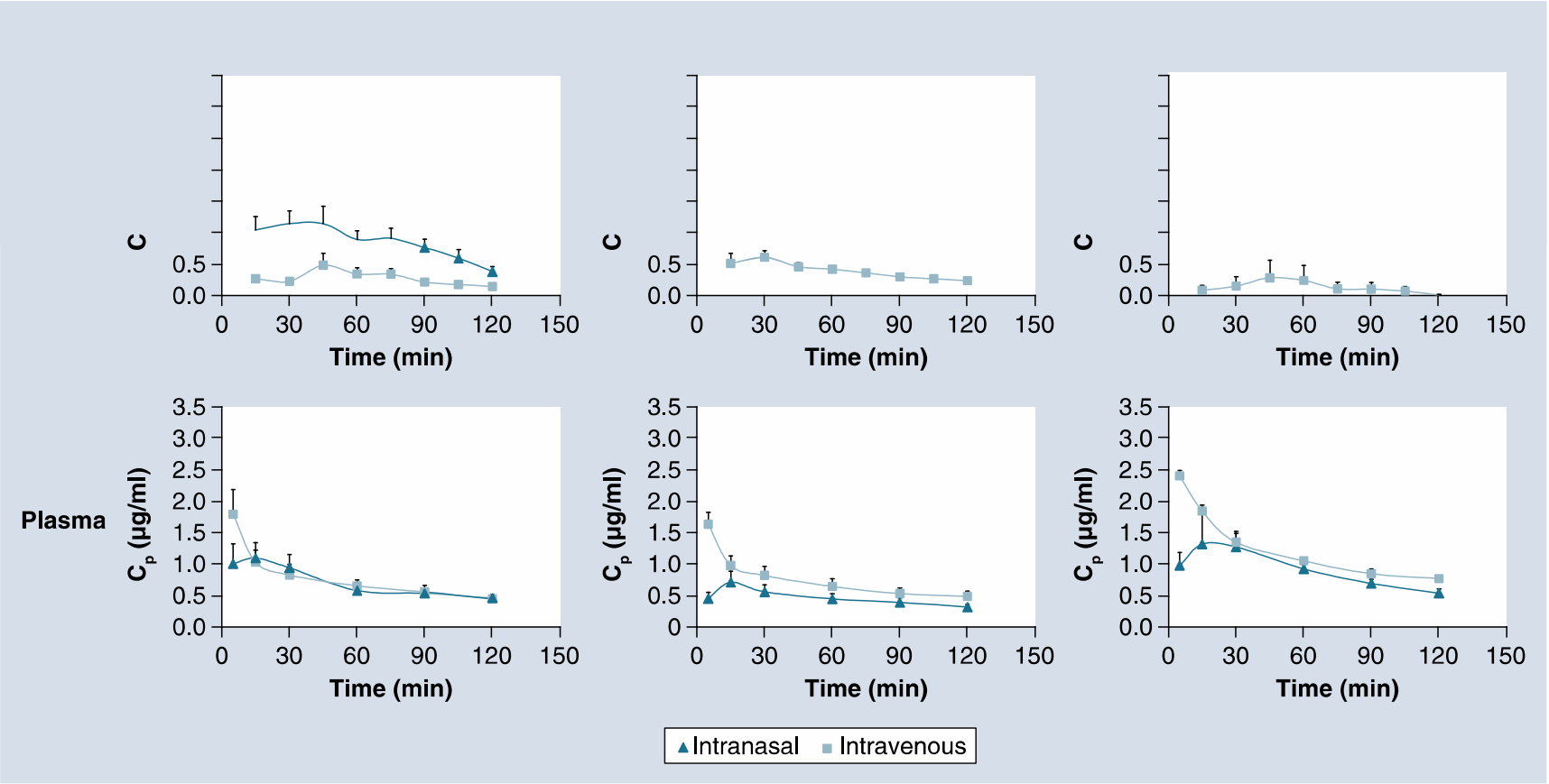
*Alessandro Livelli[1,2], Gian Carlo Orofino[1], Andrea Calcagno[3], Mariana Farenga[1], Donatella Penoncelli[1], Marta Guastavigna[1], Sinibaldo Carosella[1], Pietro Caramello[1] and Lorenzo Pia[2]**

Weber E, et al. Neuropsychol Rev. 2013; Livelli A, et al. Front Behav Neurosci. 2015

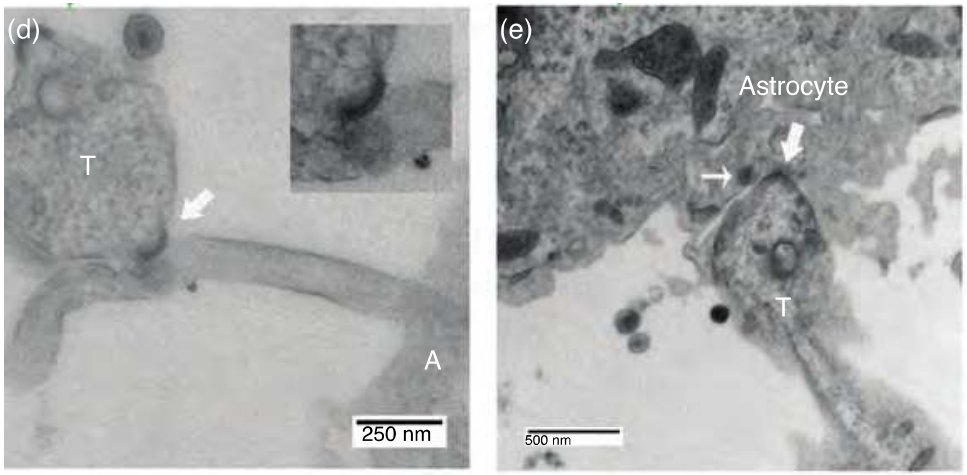
HCV Letendre

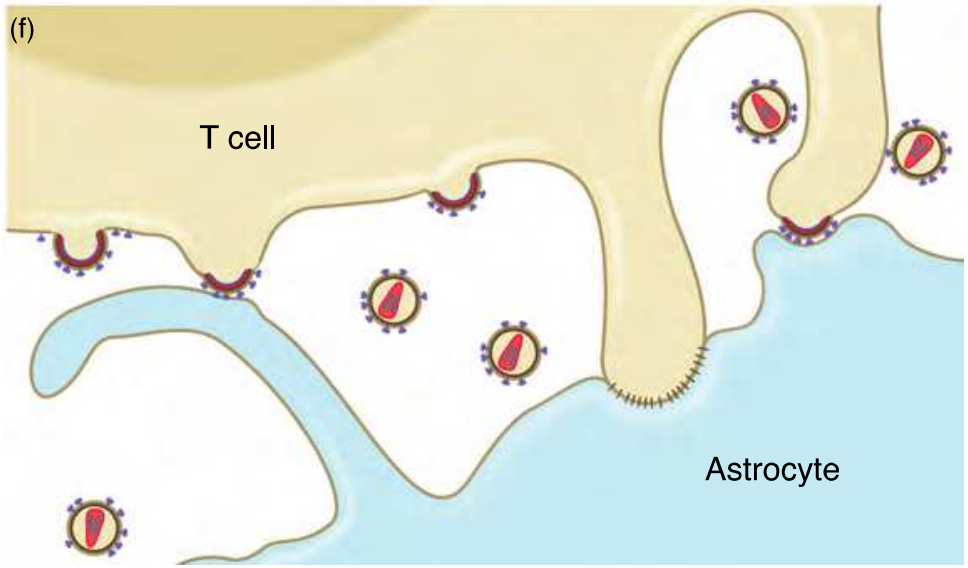
Nanopharmacology (2)

Intranasal administration of EFV-loaded micelles for anatomical targeting to the brain in HIV

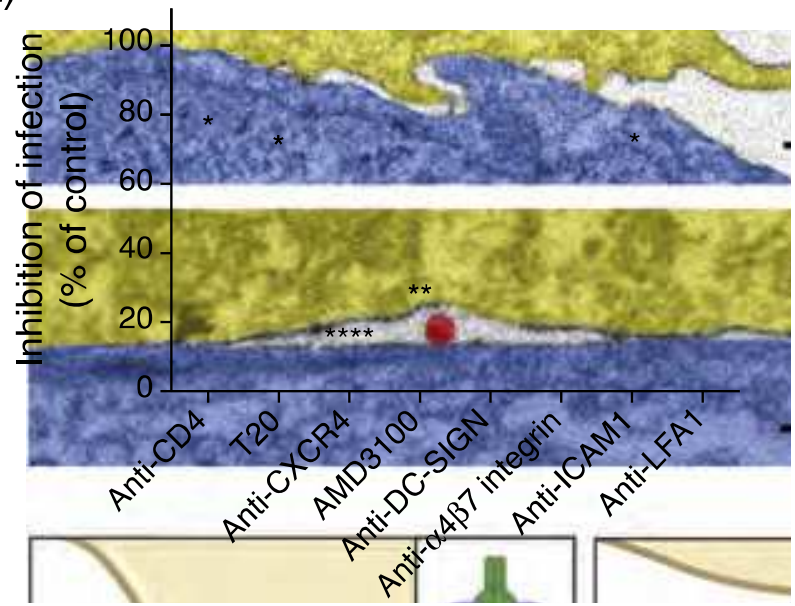


Astrocyte infection trough CXCR4

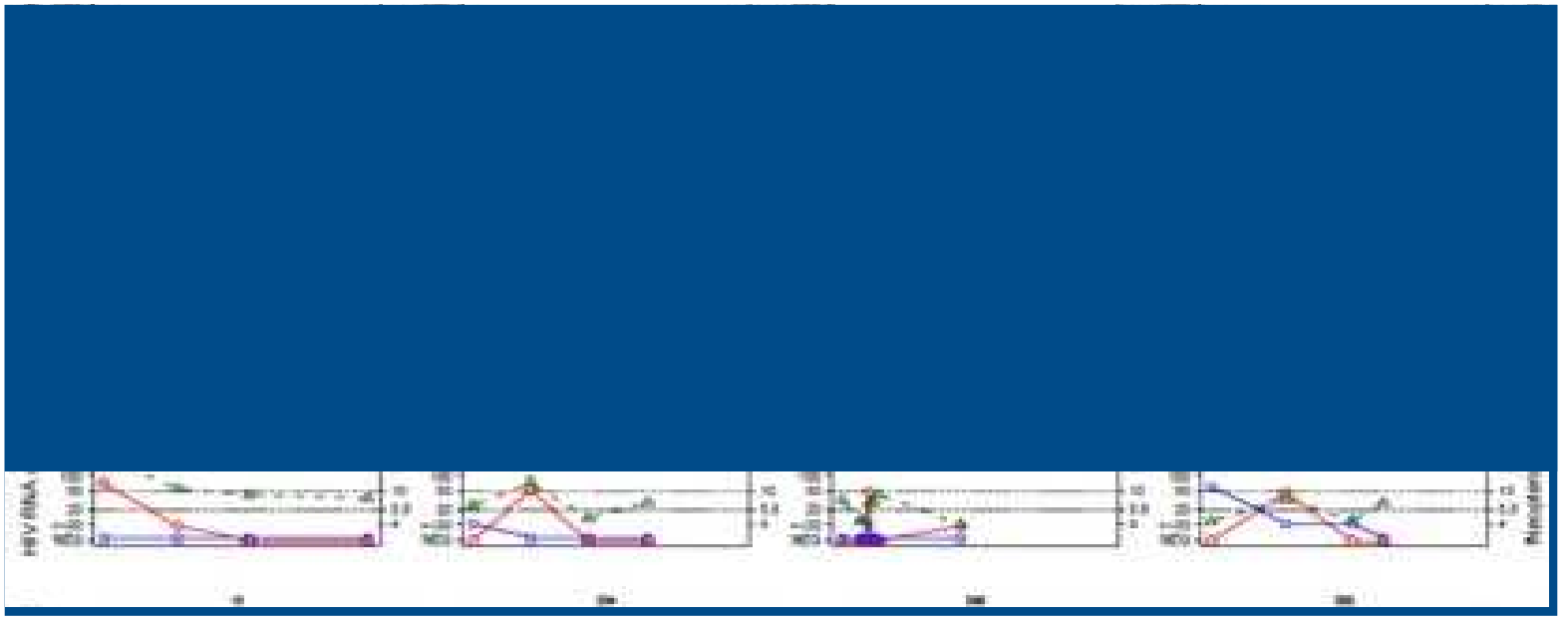




(a)



CSF escape and progression

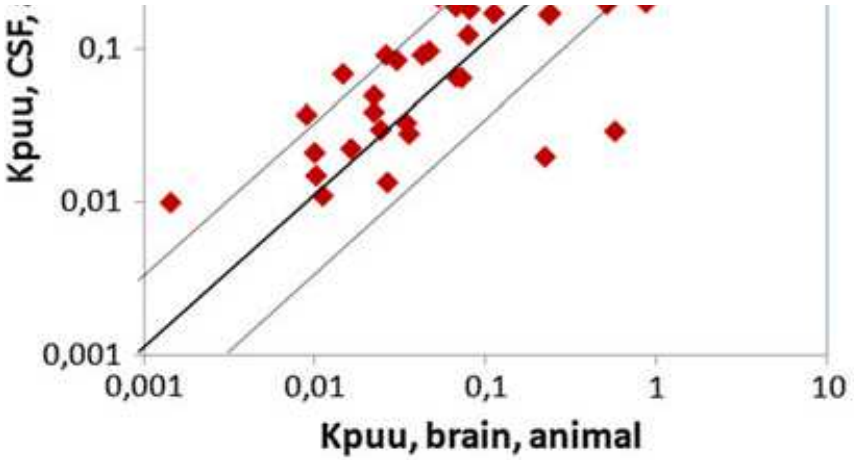


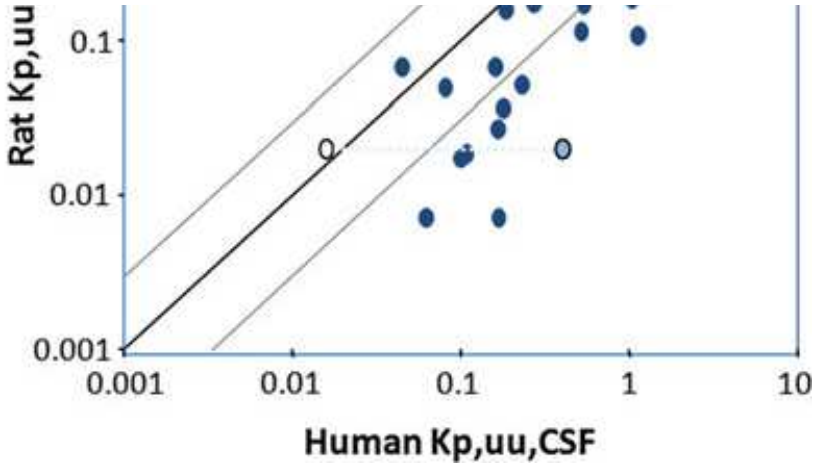
- **25%** of 56 **neurologically stable** patients on effective antiretroviral therapy had CSF HIV1 RNA >50 copies/ml on one or more occasions

CSF viral escape leading to subsequent treatment failure was not observed

Eden A, et al. CROI 2012 *unpublished*

CSF PK → Brain PK (2)



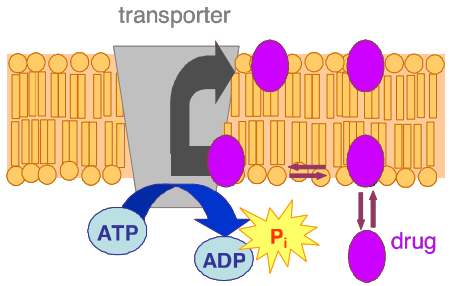


de Lange ECM, J Pharmacokinet Pharmacodyn (2013) 40:315–326

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

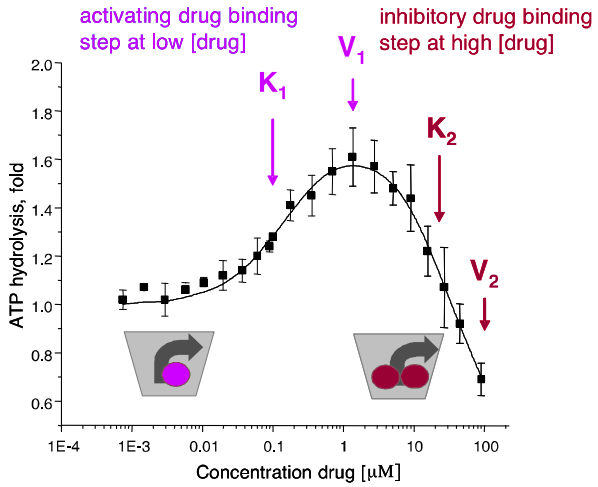
- **ATPase assay**

Plasma membrane vesicles

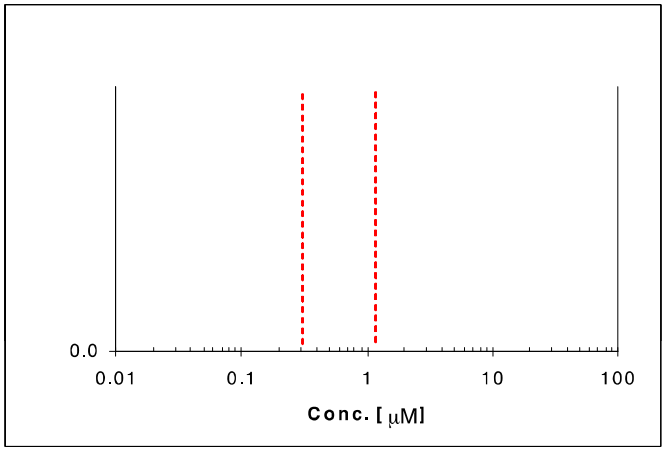


ATP hydrolysis → Pi release (UV spectroscopy)

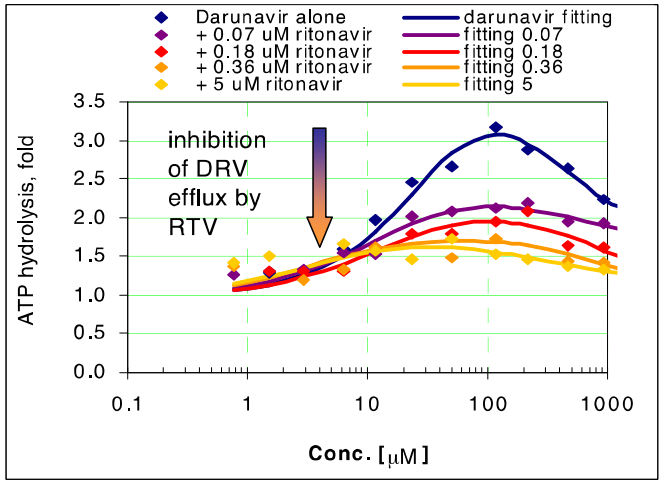
ATPase activity profile upon titration with increasing drug concentrations



P-gp activity profile for RTV

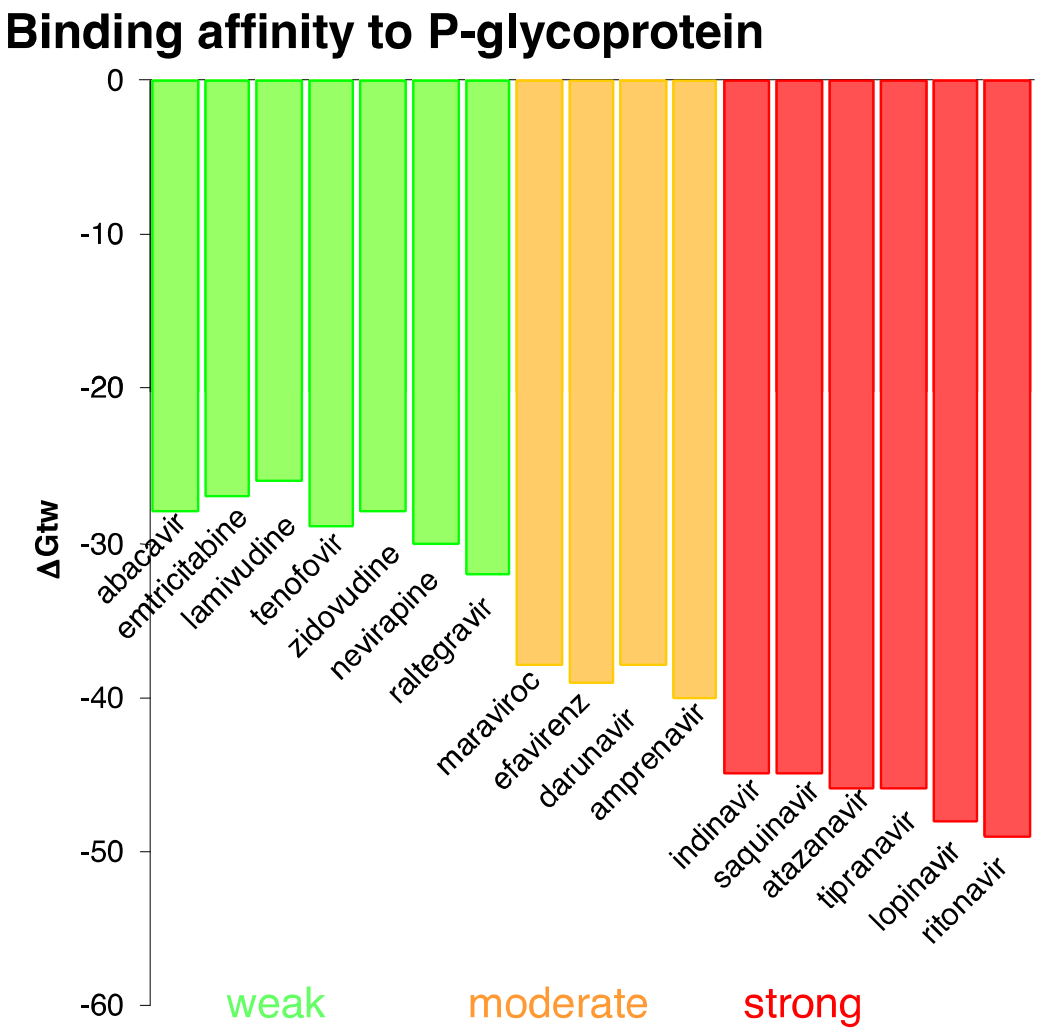


P-gp activity profiles for DRV ± RTV



Marzolini C, et al. EACS 2011

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. EACS 2011

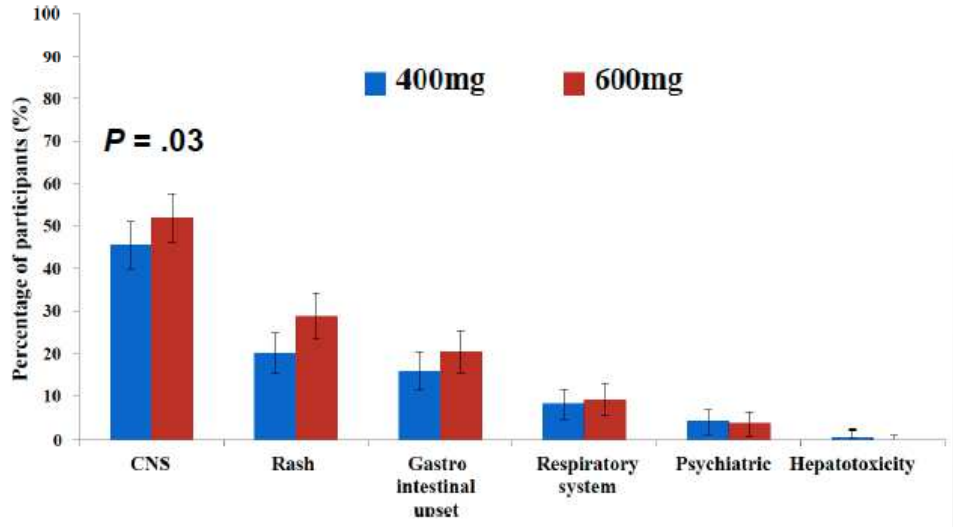
Methodological issues in measuring CNS PK

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)

Efavirenz dose

- 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



- **Unconfirmed association b**

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