Rethinking ARV Penetration and Effectiveness in the CNS

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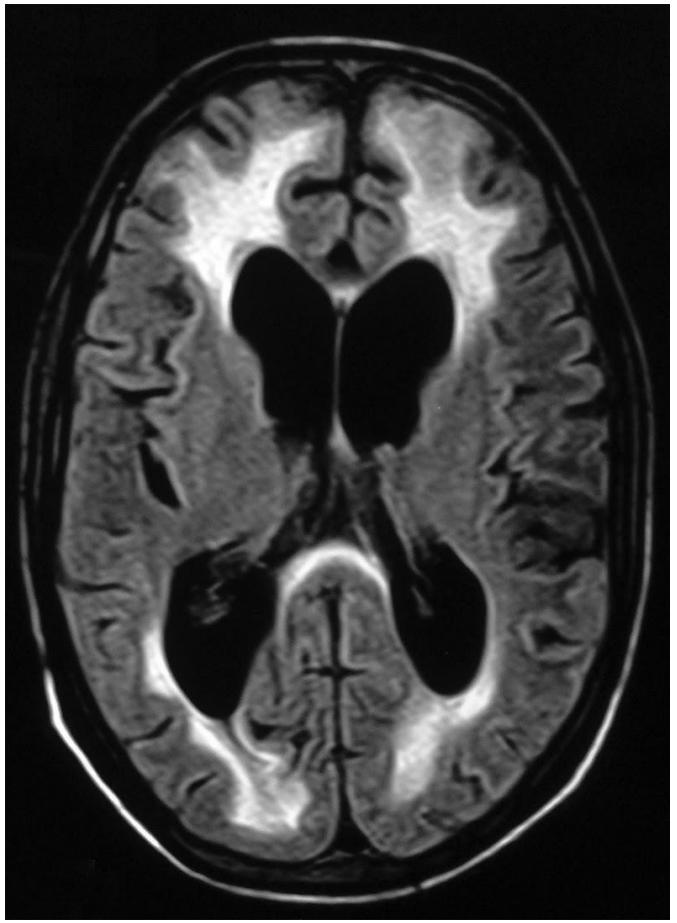
HIV ENCEPHALOPATHY & AIDS DEMENTIA COMPLEX

- Annual incidence (7%) → global risk (5-20%)
- 4-15% first HIV-associated disease
- Stages 0-4
- Histologic findings (atrophy, cortical/subcortical, multinucleated giant cells infiltrates, etc.)
- Poor survival without HAART (3-6 months)



HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

- Exclusion diagnosis:

  NO Delirium,

  NO other pre-existing cause,

  NO untreated depression,

  NO active substance abuse

- Acquired impairment in cognitive functioning, involving at least **two ability domains**

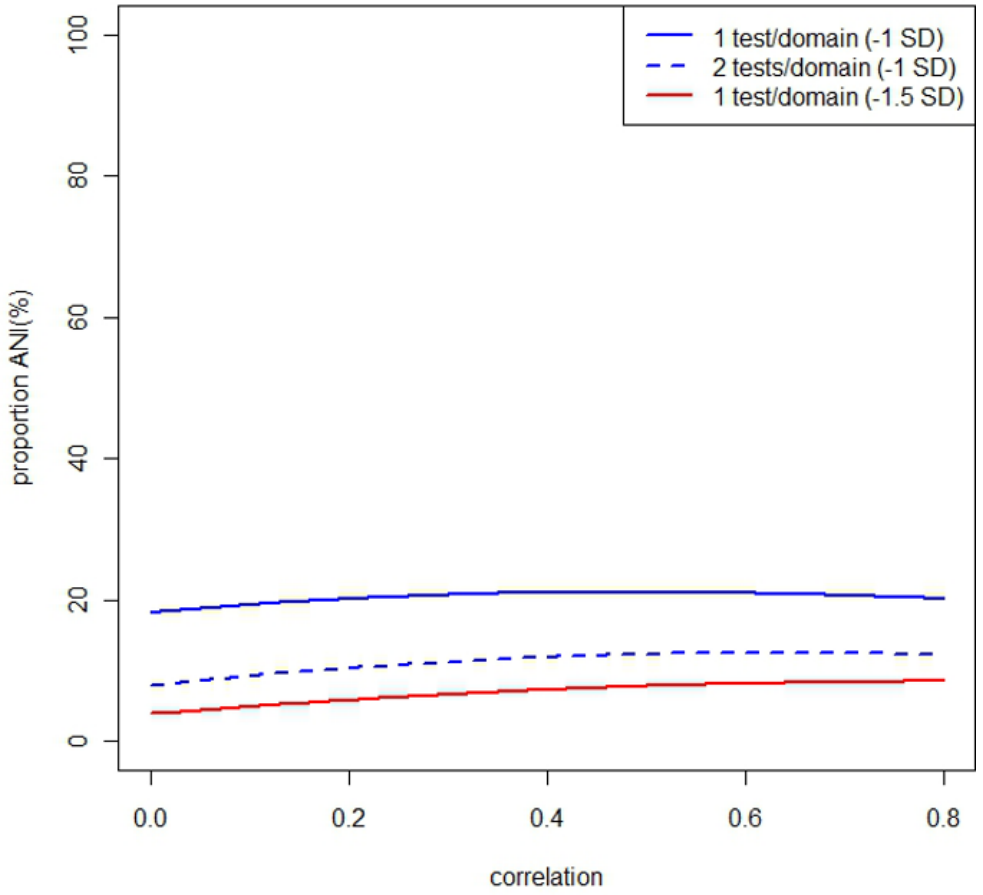
- Interference with day-to-day functioning (work, home life, social activities)

	IADL Abnormal
ANI Asymptomatic	No
MND Moderate	Moderate
HAD Dementia	Severe

HAND = HIV-associated neurocognitive disorders
ANI = Asymptomatic neurocognitive impairment
MND = Mild neurocognitive disorder
HAD = HIV-associated dementia
IADL = Instrumental activities of daily living

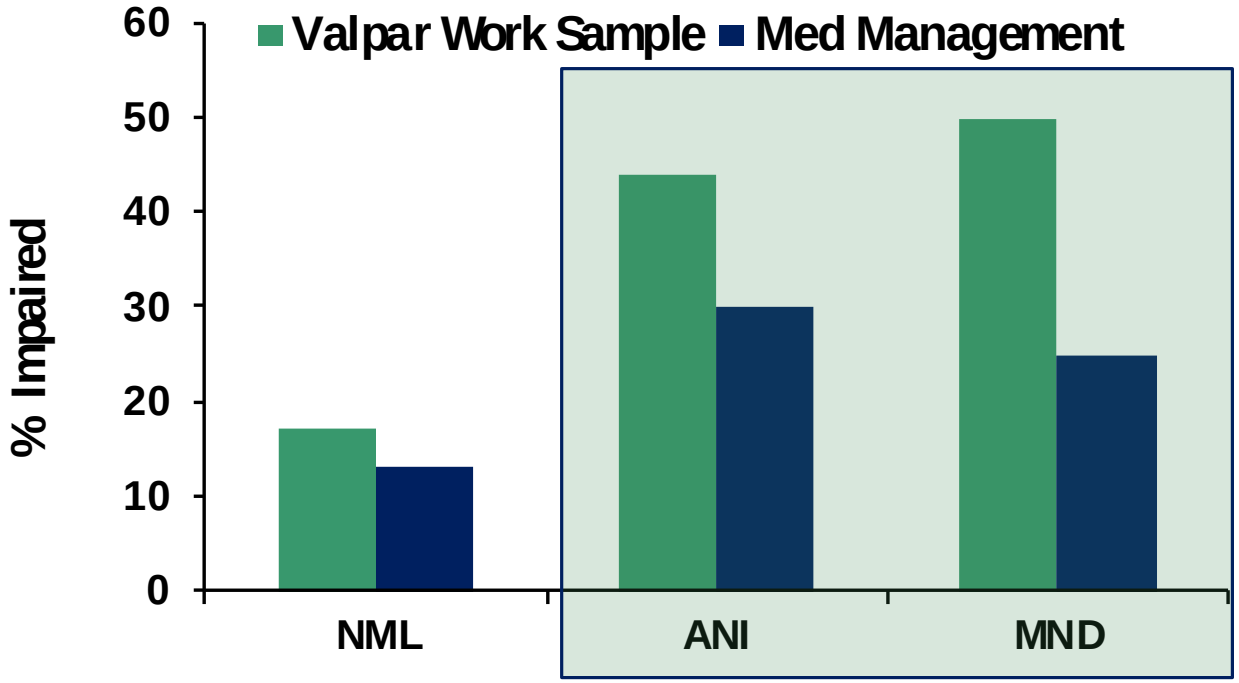
Antinori A, et al. Neurology 2007

OVERESTIMATION?



Gisslen M, et al. BMC Inf Dis 2011

UNDERESTIMATION?



Blackstone K et al. JINS 2012

INSTRUMENTAL ACTIVITIES OF DAILY LIVING


Use of the telephone


Shopping


Food preparation

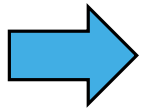

Housekeeping


Laundry


Mode of transportation

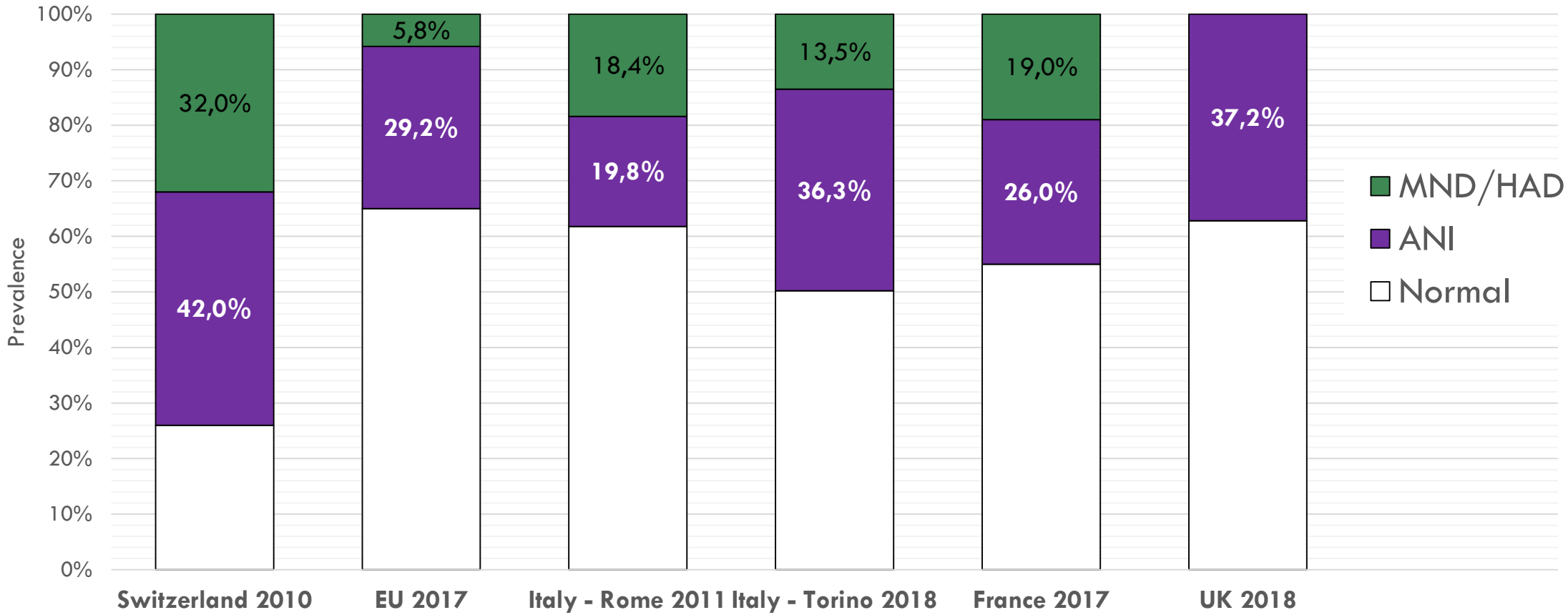

Handling own medications


Handling finances



Travels independently on public transportation or drives own car
Arranges own travel via taxi, but does not otherwise use public transportation
Travels on public transportation when assisted or accompanied by another
Travel limited to taxi or automobile with assistance of another
Does not travel at all

HAND PREVALENCE IN RECENT STUDIES IN EUROPE



Simioni S, et al. AIDs 2010; Haddow LJ, et al. AIDS Behav 2017; Balestra P, et al. 6th IAS 2011; Trunfio M, et al. HIV Medicine 2018; Vassallo M, et al. JNV 2017; Rackstraw S, et al. HIV Glasgow 2018, P200.

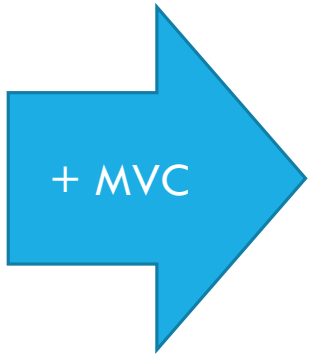
A CLINICAL CASE AND SEVERAL OPEN QUESTIONS

- Female, 50 yy old
- HIV+ since 1988
- HCV cured (DAAs)
- Lipodistrophy and hypercholesterolemia
- Hypertension
- Smoking 10/day
- 2017 complaining of memory and attention deficits → HAND (ANI at full NC tests)
- On DTG + DRV/r twice daily
- CD4 1238/mm^3 (ratio 1)
- CD4 nadir 248/mm^3
- HIV RNA <20 copies/mL since 5 years
- RAMS: D67N, K70KR, M184MV, K219Q, V108VI (RT) and L90M (PRO)
- MRI: White matter hyperintensities

A CLINICAL CASE AND SEVERAL OPEN QUESTIONS (2)

CSF (04.2018)

- No cells, normal glucose and proteins
- **HIV RNA 120 copies/mL**
- No RNA amplification for RAMs, R5-tropic
- Normal t-tau and p-tau, low 1-42 Beta-amyloid
- Normal BBB
- Intrathecal IgG synthesis (41%)
- No CMV/EBV/JCV



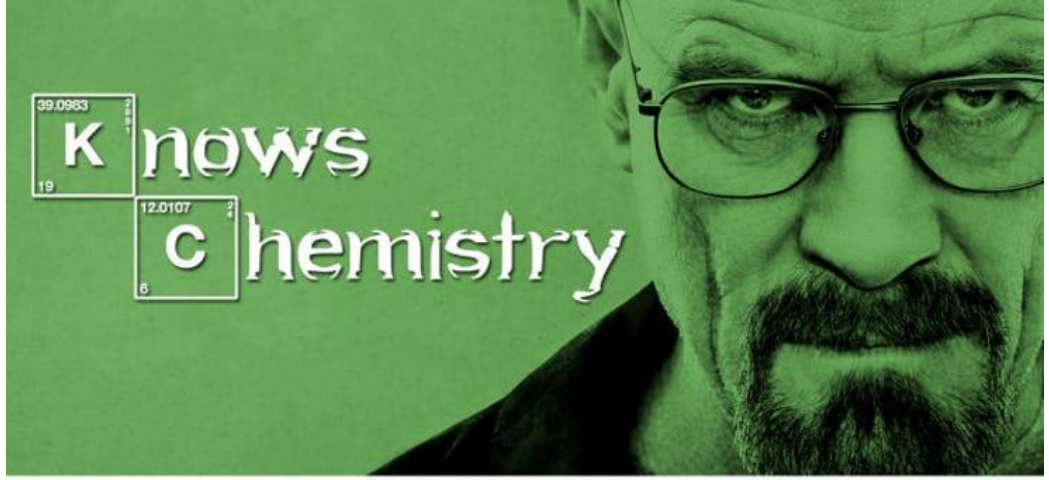
CSF (12.2018)

- No cells, normal glucose and proteins
- **HIV RNA 80 copies/mL**
- RT RAMs (D67N, T69N, K70R, K219Q)
- Normal t-tau and p-tau, normal 1-42 Beta-amyloid
- BBB and IgGs *ongoing*
- No CMV/EBV/JCV

OPEN QUESTIONS

1. Is this HAND **and** CSF escape?
2. Is this HAND **because** of CSF escape?

3. Why IgG production in the CNS?
4. Does CSF penetration matter?
5. Any idea on the best antiretroviral treatment for this patient?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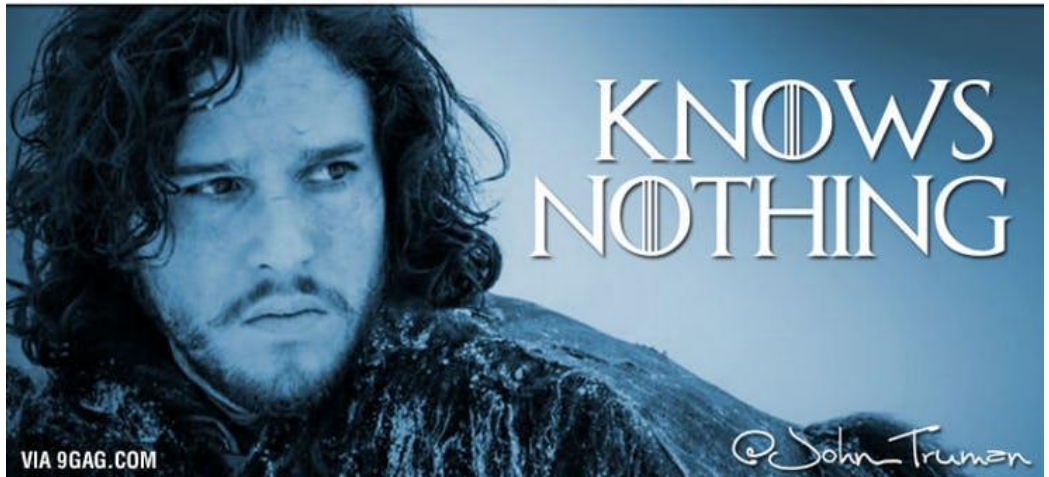
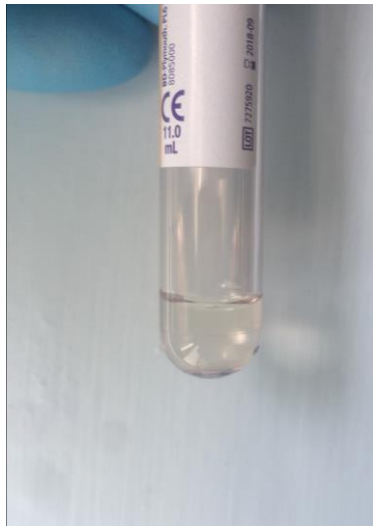
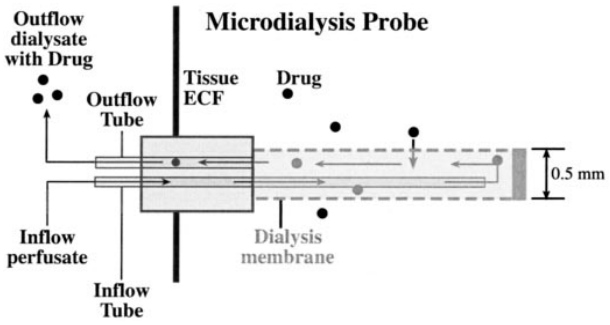

KNOWS
NOTHING
VIA 9GAG.COM
John Truman

MEASURING ARVS EXPOSURE IN THE CNS

Cerebrospinal fluid



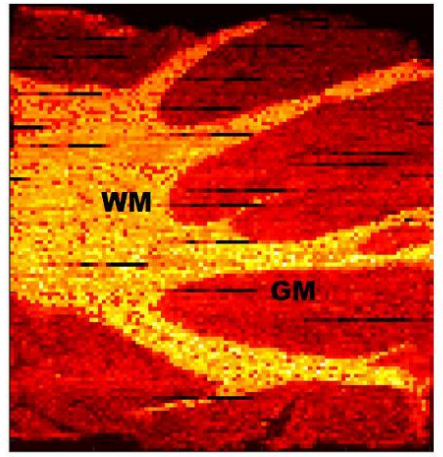
Brain extracellular fluid microdyalisis



Brain tissue homogenate

Mononuclear cells extracted from tissues

IR-MALDESI



In vivo

ex vivo

Autopsy, Brain biopsy

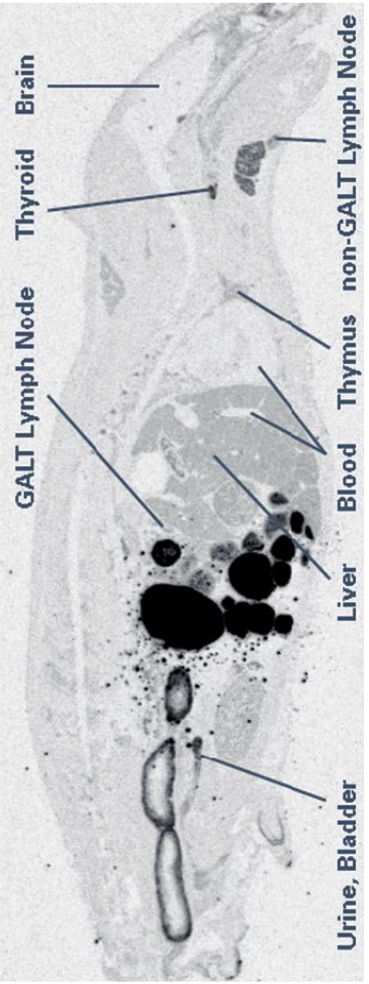
Fletcher C, et al. PNAS 2014; Srinivas et al, CROI 2018 #472

«OLD» DATA ON CSF → BRAIN PARENCHYMA

For several compounds CSF may be a valid surrogate of CNS concentrations (3 fold error but proportionality)

In macaques AZT concentrations showed CSF/serum (0.27 ±0.23) similar to brain/blood ratios (0.13 ±0.06)

In rats CSF/plasma ratios 0.05 (0.10 unbound) vs. brain/blood radioactivity 0.25



Liu, X., et al. Drug Metab. Dispos 2009; Fox E, et al. The J of Pharm and Exper Ther 2002; Walker DK, et al. Xenobiotica, 2008.

CENTRAL NERVOUS SYSTEM PENETRATION EFFECTIVENESS 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		

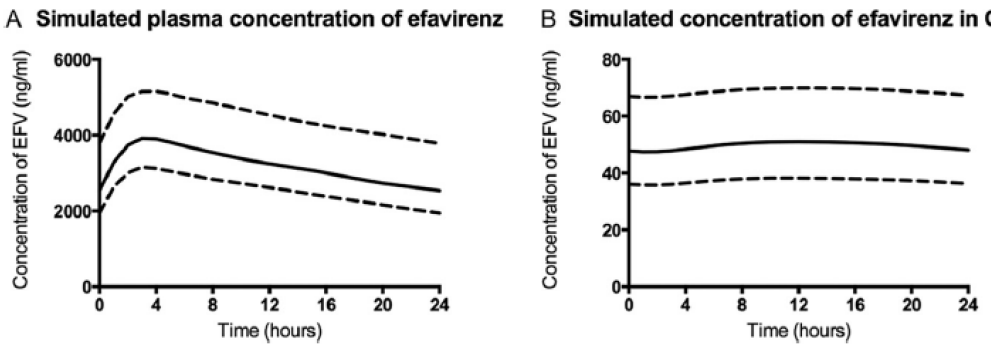
Hammond ER, et al. Am J Epidemiology 2014

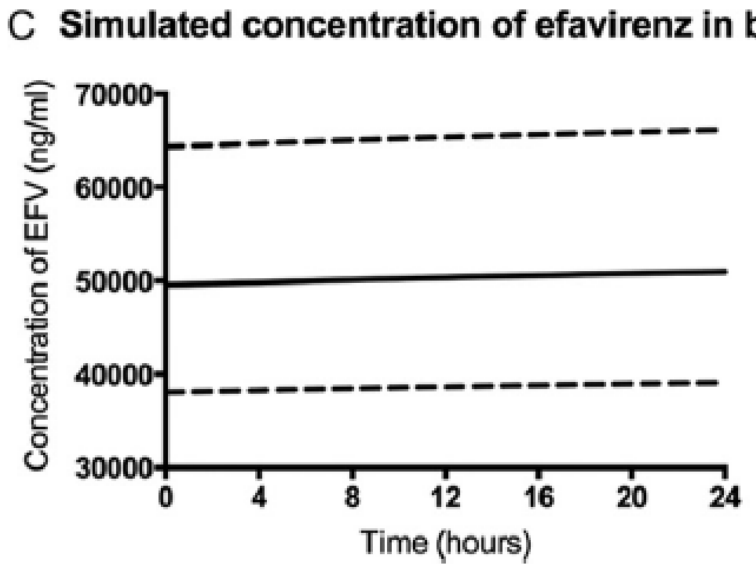
PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELLING

EFV CNS distribution was calculated using a permeability-limited model on a virtual cohort of 100 patients.

Simulation data were then compared with human data from the literature and with rodent data.

Wistar rats were administered efavirenz (10 mg/kg of body weight) once daily over 5 weeks.





Curley P et al, AAC 2017; Thompson CG, et al. AAC 2015

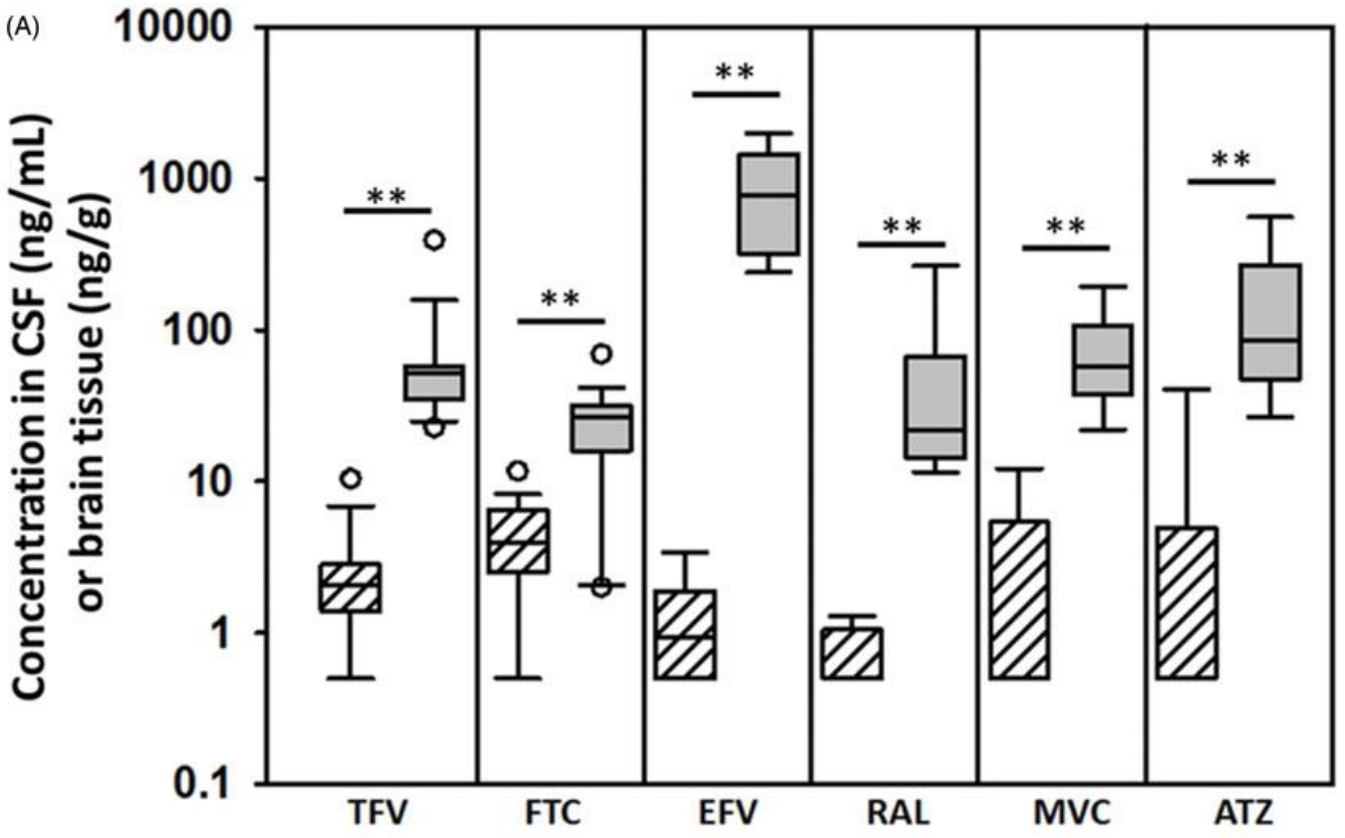
Predicted Cmax	
Plasma	3184
CSF	49.9
Brain	50343
Tissue to plasma	**15.8**

Observed Cmax in Rodents	
Plasma	69.7
Brain	702.9
Tissue to plasma	**9.5**

Macaque	
Cerebellum to plasma	**12.7**

CSF AND BRAIN CONCENTRATIONS IN ANIMAL MODELS

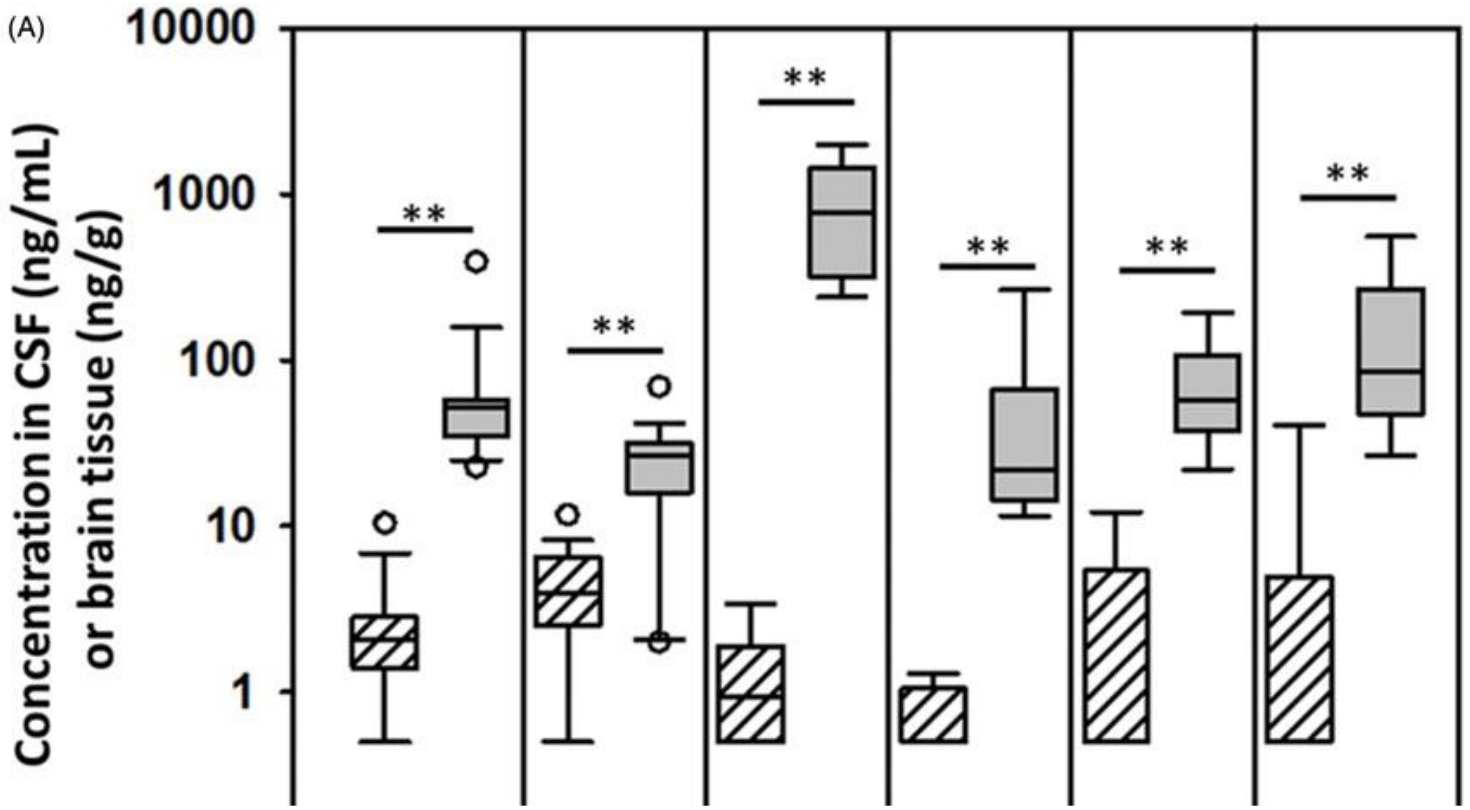
1. CSF underestimates brain tissue concentrations



Srinivas et al, Xenobiotica 2018

CSF AND BRAIN CONCENTRATIONS IN ANIMAL MODELS

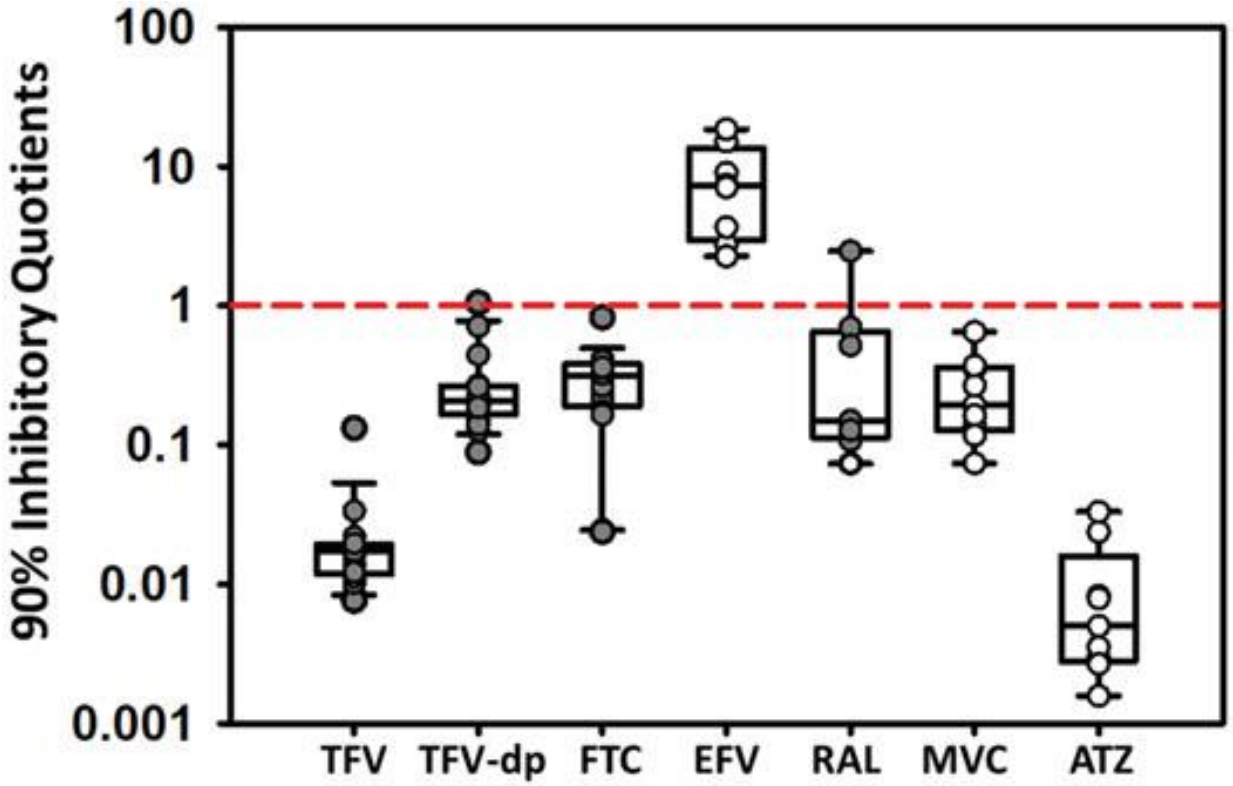
2. There is no correlation between individual CSF and brain tissue concentrations (except for EFV)



Srinivas et al, Xenobiotica 2018

CSF AND BRAIN CONCENTRATIONS IN ANIMAL MODELS

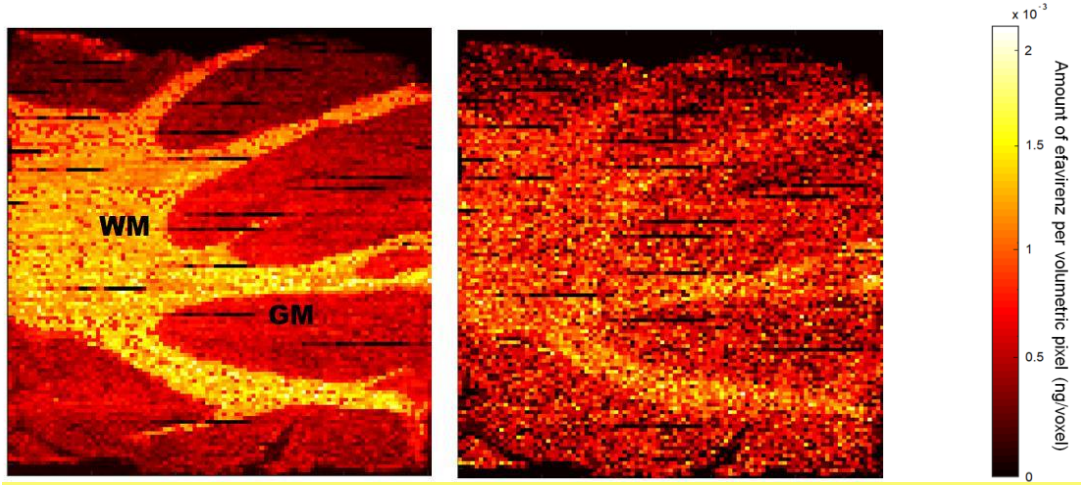
3. IC_{90} is seldom exceeded in brain tissue (in macaques)



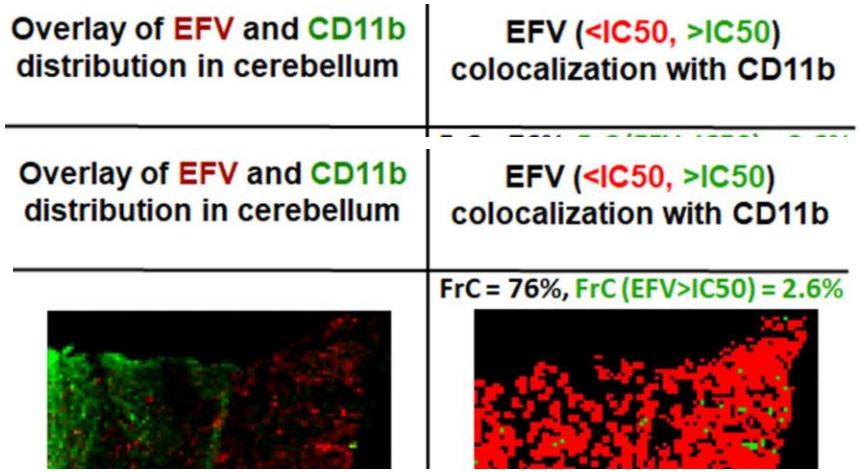
Srinivas et al, Xenobiotica 2018

BRAIN CELL DISTRIBUTION

- 4 male rhesus macaques on TDF/FTC/EFV/RAL
- 10 µm thick frozen slices of discrete cerebellum regions analysed with infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI)
- TFV, FTC, and RAL **were not detected** by MALDESI and were <100 ng/g by LC-MS/MS (range of concentrations were 9.4-61.2 ng/g).
- EFV concentrations by IR-MALDESI had a standard deviation of 663 ng/g for all samples and was **86% lower in RT-SHIV-infected than uninfected brain tissue** (median = 1596 and 723 ng/g, respectively).



EFV up to 3-fold higher in the WM vs. GM



22-59% of CD11b+ microglial cells with EFV and only 3.3% with EFV>0.5 ng/g

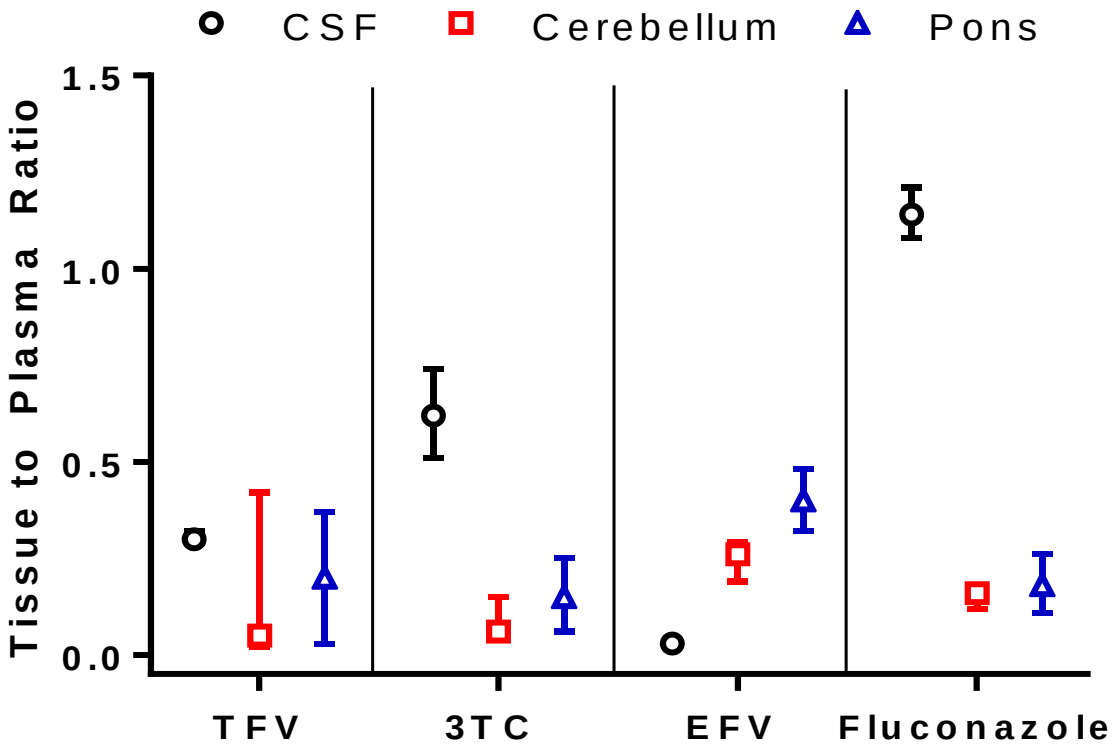
Srinivas et al, Xenobiotica 2018


HAVE YOU
SEEN ME?

BRAIN TISSUE CONCENTRATIONS IN HUMANS

	n	Overall Mean	WM (mean)	GP (mean)	CGM (mean)
Concentrations Similar to Historical CSF Concentrations					
Atazanavir (ATV)	2	< 25	< 25	< 25	< 25
Efavirenz (EFV)	2	38.6	45.2	34.8	35.9
Emtricitabine (FTC)	4	181.3	230.4	173.2	140.3
Lamivudine (3TC)	3	196.9	205.5	209.8	175.4
Concentrations in White Matter Higher than Historical CSF Concentrations					
Lopinavir (LPV)	4	153.3	410.6	< 25	< 25
Concentrations Higher than Historical CSF Concentrations					
Tenofovir (TDF)	6	206.0	220.0	212.1	185.8

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



Bumpus N, et al. CROI 2015 #436; Nicol MR, et al. CROI 2018 #474

Pgp Inhibitors	PgP inducers
amiodarone	ASA
atorvastatin	cisplatin
azithromycin /clarithromycin	cyclosporine
carbamazepine	dexamethasone
carvedilol	erythromycin
chloroquine	insulin
Tacrolimus/cyclosporin ++	nifedipine
verapamil ++/diltiazem	phenobarbital
fenofibrate	phenytoin
fluoxetine /paroxetina	rifampin
grapefruit juice	St. John's Wort
garlic	tacrolimus
green tea (catechins)	tamoxifen
ivermectin	verapamil
Lanso/ome/pantoprazolo	
loperamide	
progesterone	
tamoxifen ++	

Cynomolgus monkeys

Nelfinavir with zosuqidar

brain to plasma:

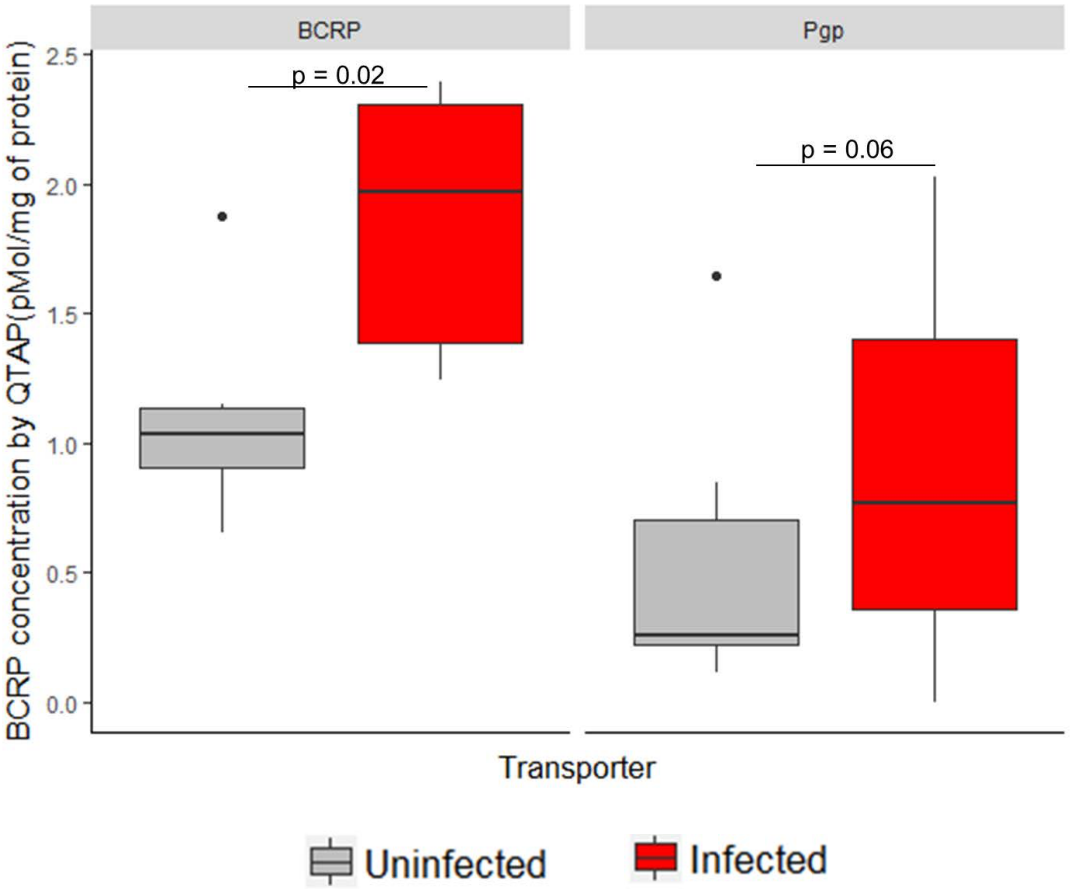
- **huge effect 4.4% →640%**

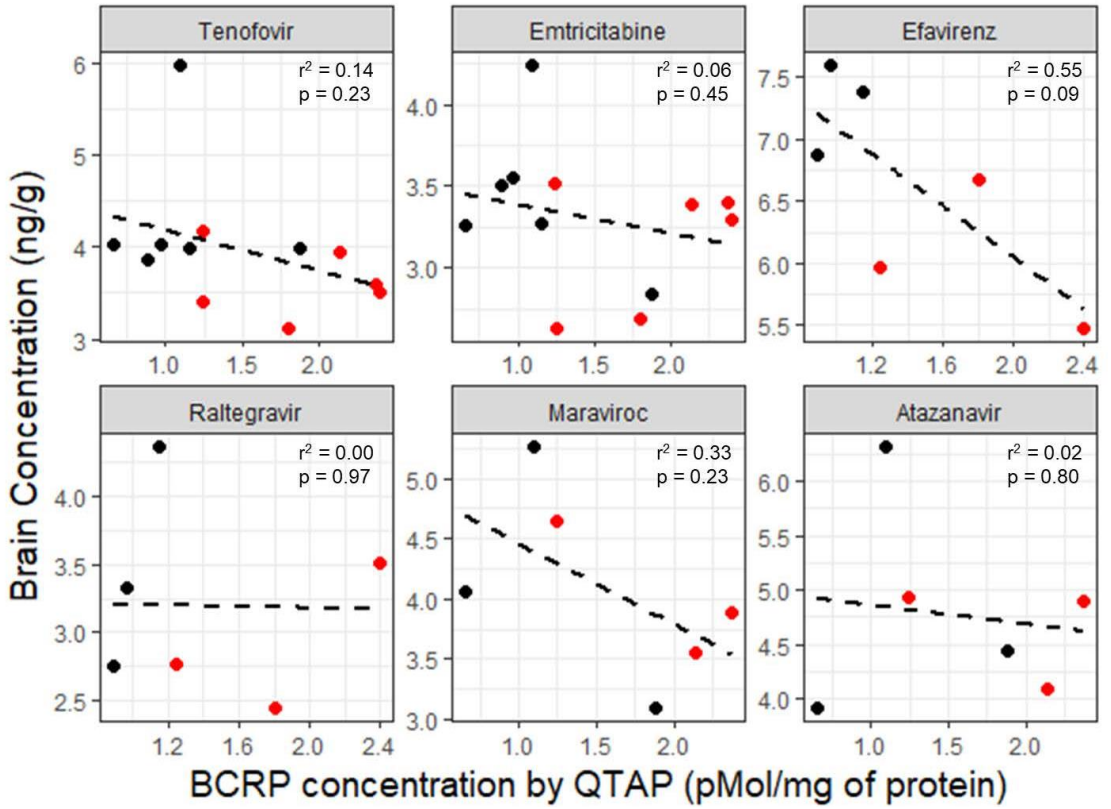
CSF to plasma:

- no effect 0.6% → 0.7%

Kannan P, et al. Clinical Pharm and Ther 2009; Kaddoumi A, et al .Drug Met and Disp 2007; 35 (9): 1459-1462

BCRP/PGP AND BRAIN CONCENTRATIONS IN MACAQUES

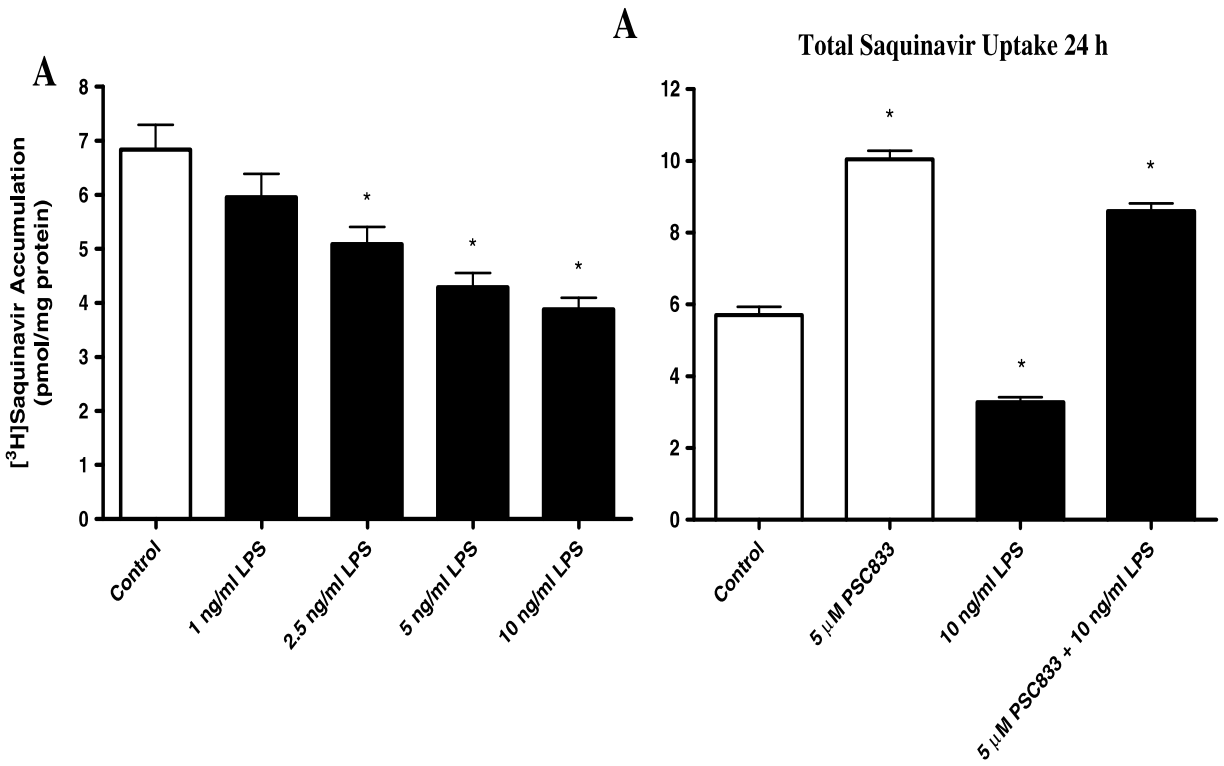




Srinivas et al, IAS 2017, Abstract WEAB0105

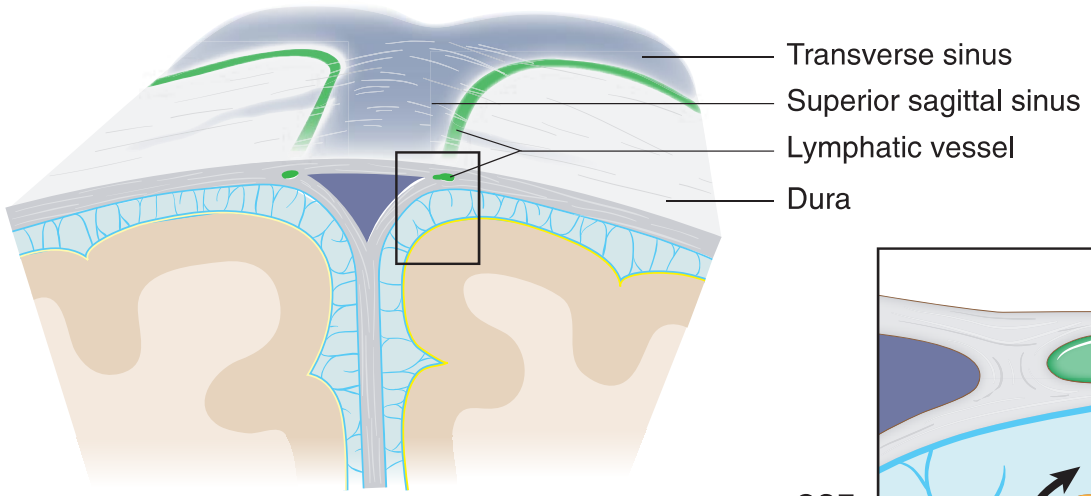
TRANSPORTERS INDUCTION BY INFLAMMATION

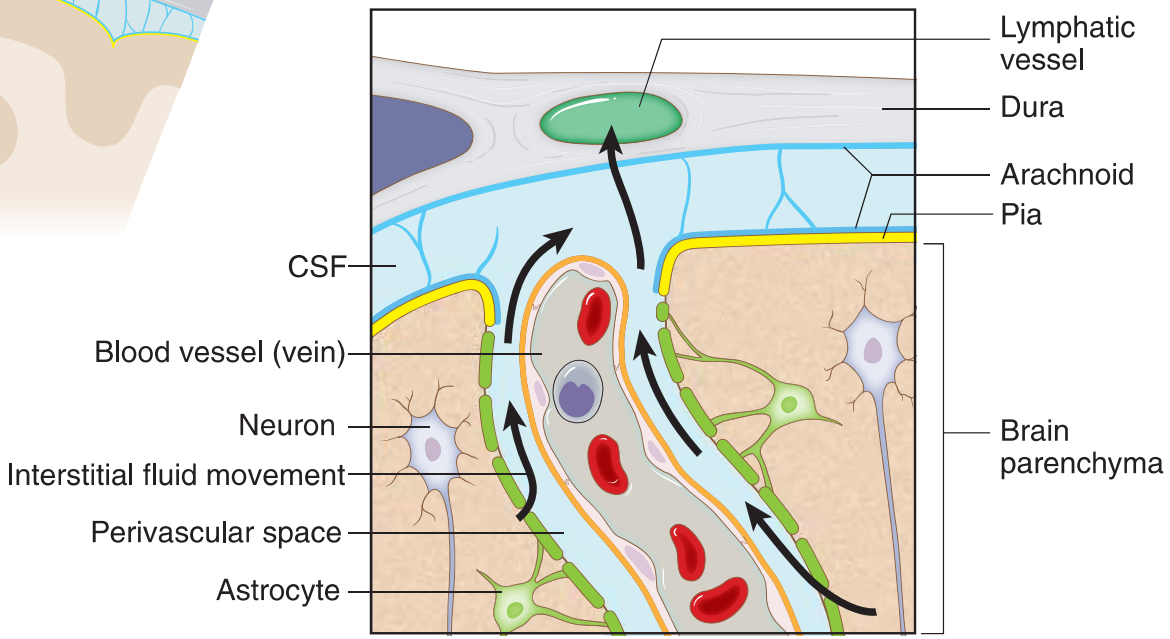
- Increased expression of P-gp in hypertrophic GFAP-positive astrocytes in brains from MS patients
- HIV infection increases P-gp expression in lymphocytes, GALT and brain endothelial cells
- PgP^{high} CD4+ cells and antiviral efficacy
- P-gp expression affects intracellular concentrations and activity of PIs



Kooij G, et al Journal of Autoimmunity 2010; 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

CNS "FUNCTIONAL" LYMPHATIC VESSELS



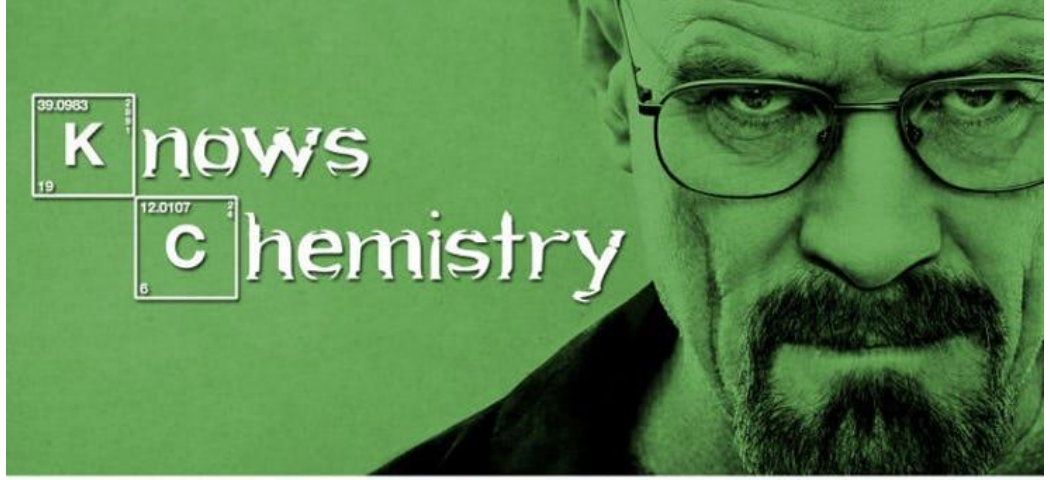


Opinion

Revisiting the Mechanisms of CNS Immune Privilege

Antoine Louveau,[1] Tajie H. Harris,[1] and Jonathan Kipnis[1,*]

Louveau A, et al. Nature 2015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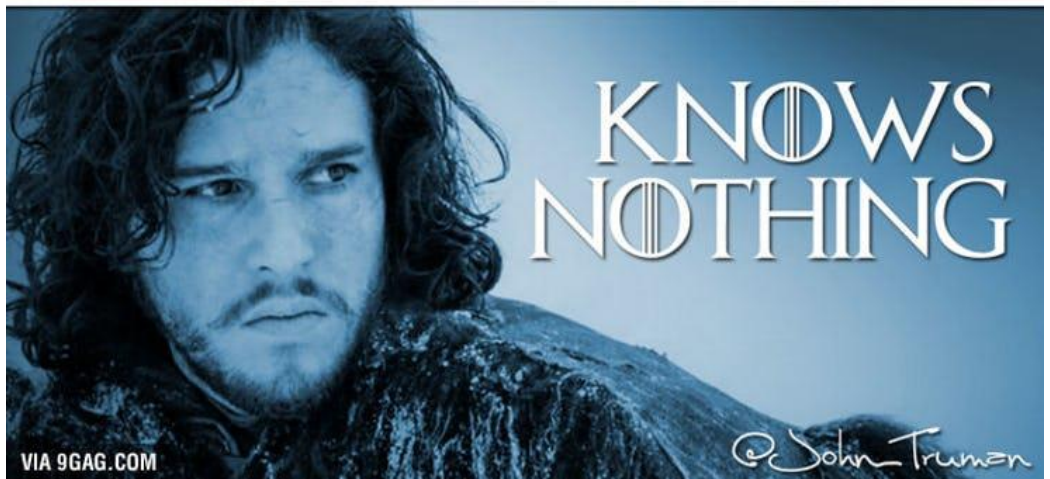
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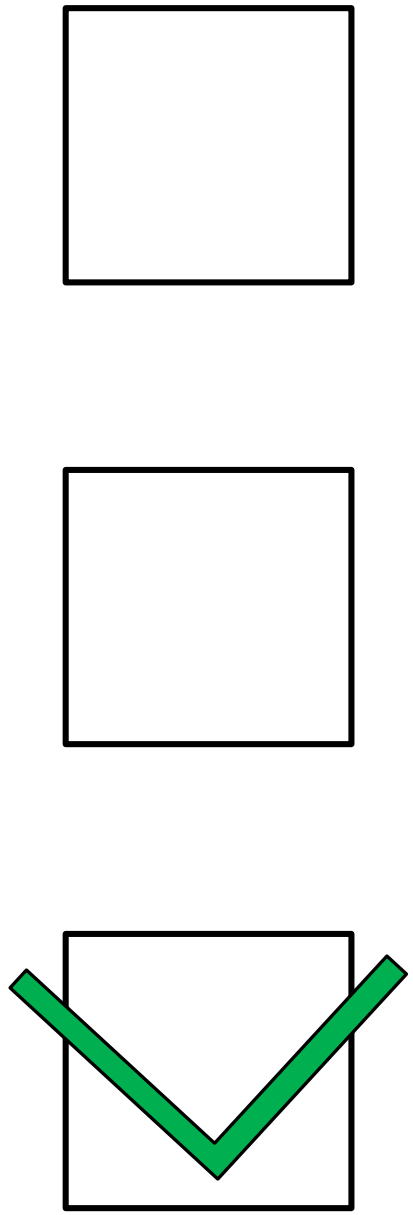
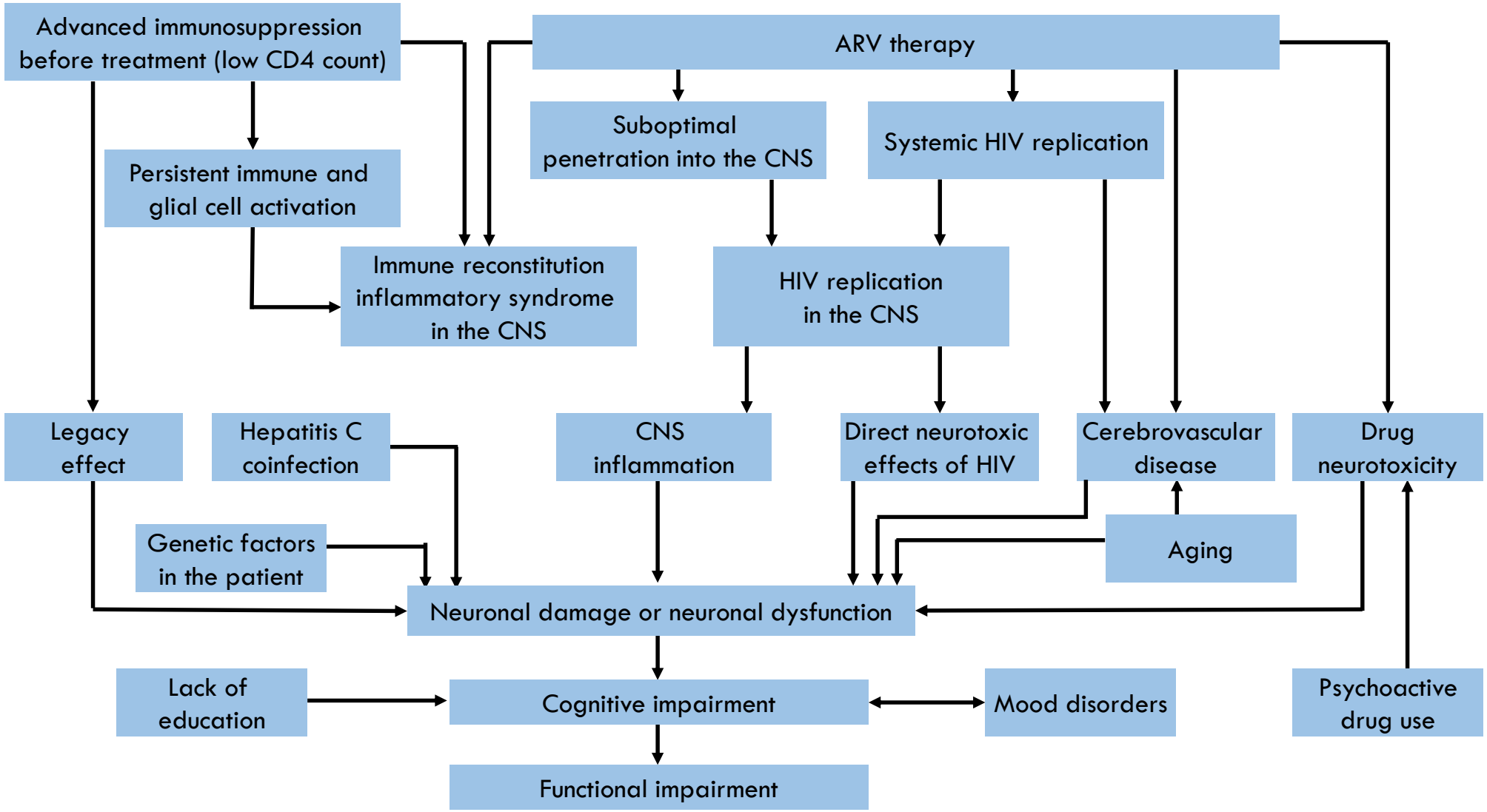
VIA 9GAG.COM
John Truman

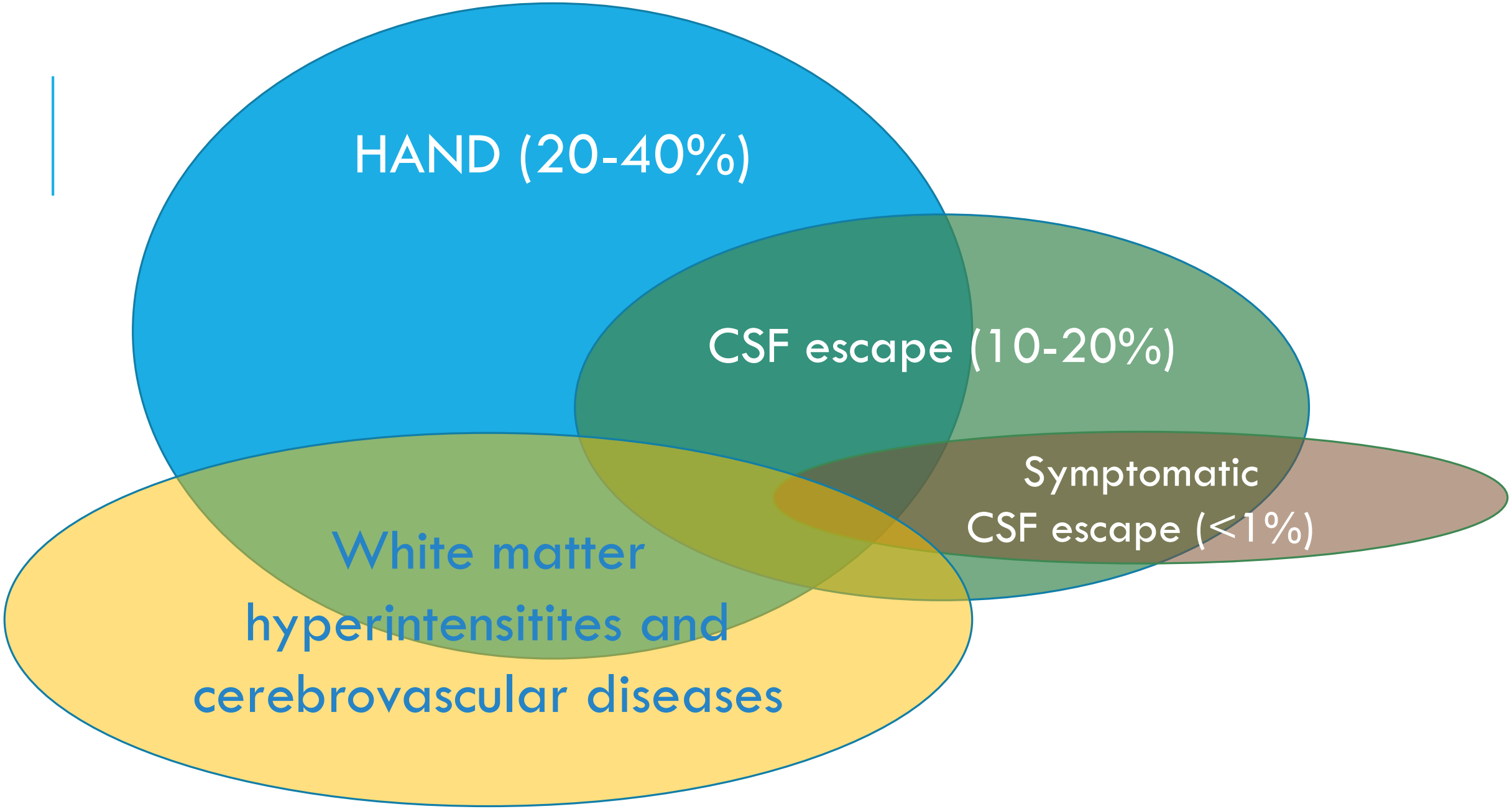


HAND is a complex phenotype

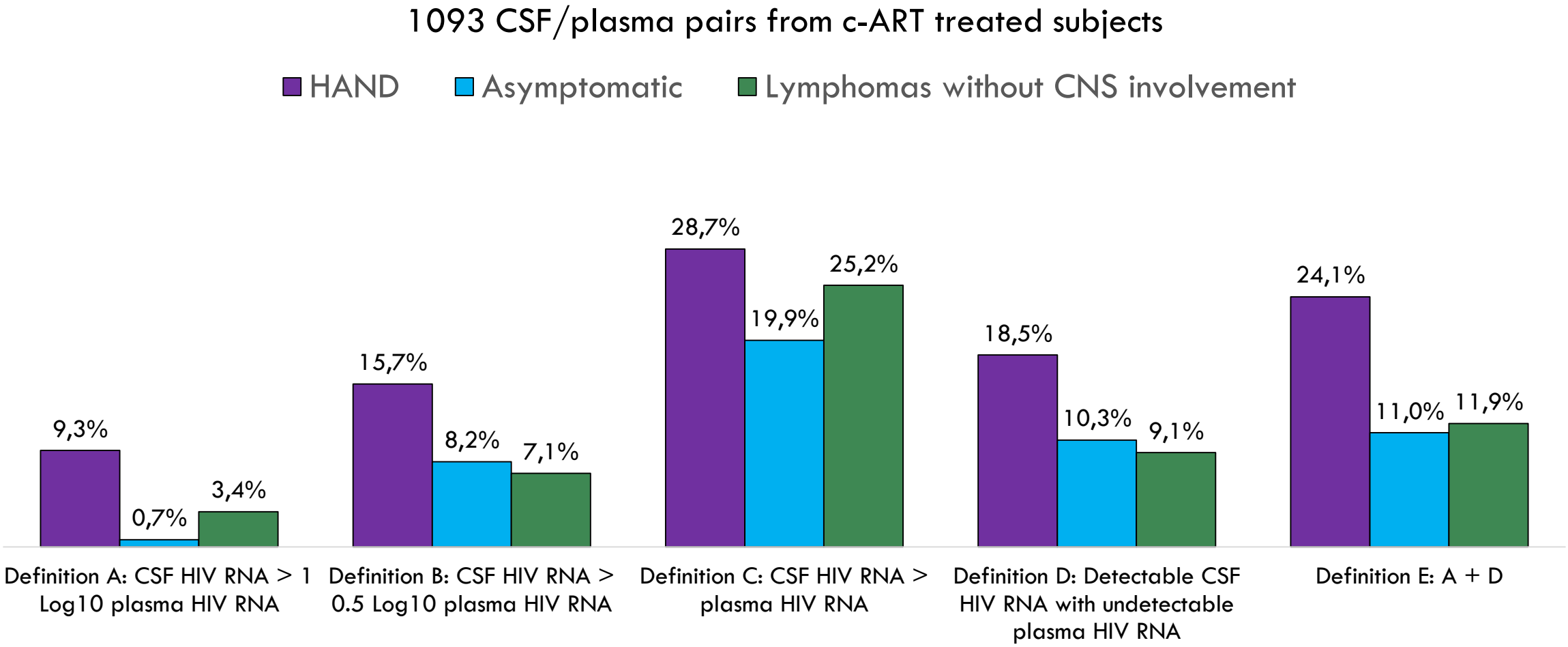
RISK FACTORS



Nightingale S, et al. Lancet Neurology 2014


HAND (20-40%)
CSF escape (10-20%)
Symptomatic
CSF escape (<1%)
White matter
hyperintensitites and
cerebrovascular diseases

CSF ESCAPE – ACCORDING TO DEFINITIONS AND UNDERLYING CONDITIONS



Trunfio M, et al. AIDS 2018

SYMPTOMATIC CSF-ESCAPE

Data from:

- 5 case series and sevrael case reports → n=102
- Recently from an Italian case series → n= 46

Usually low nadir CD4 count

Acute or subacute neurological symptoms

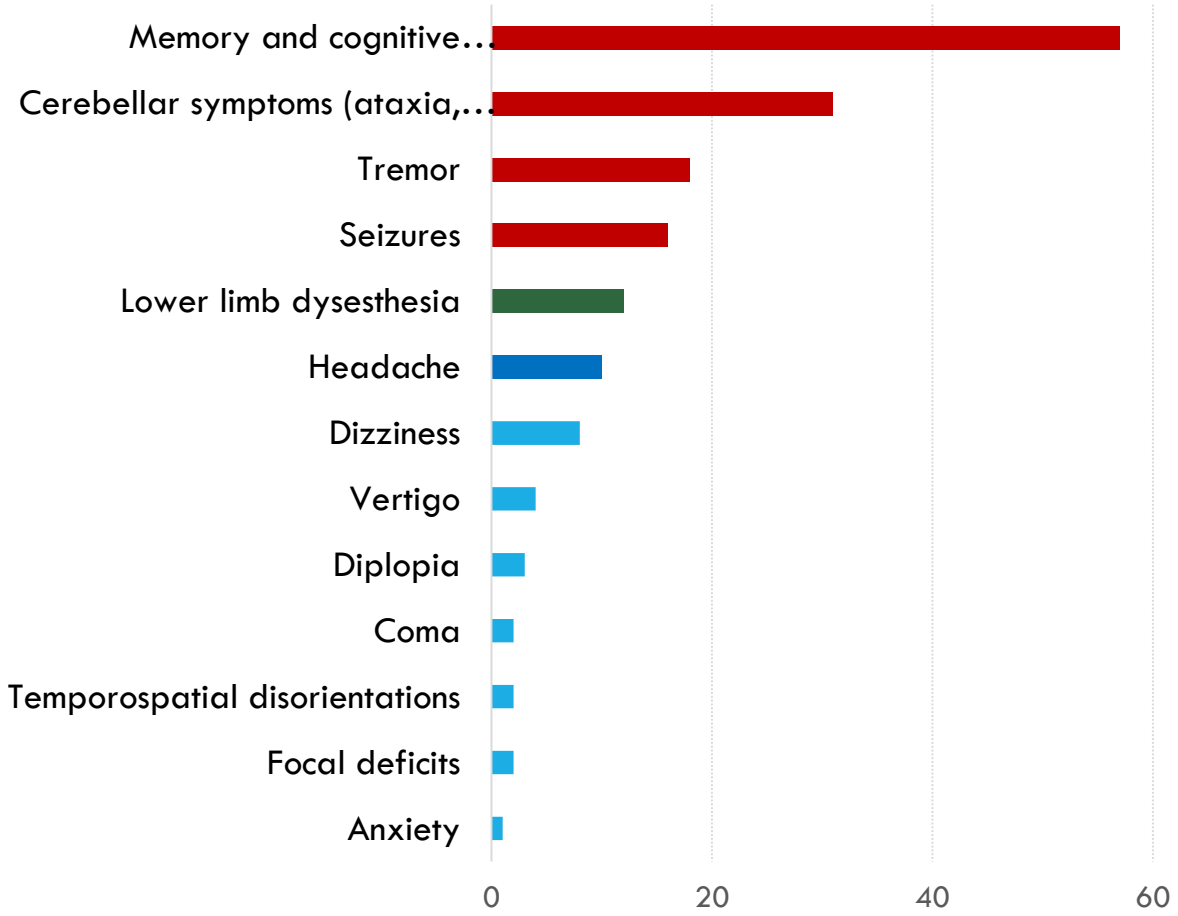
T-2 hyperintense lesions at brain MRI

Often resistance associated mutations (RAMs) in the CSF

Resolution/Improvement after HAART change (considering RAMs and CSF penetrating drugs)

Canestri A, et al. CID 2010; Peluso MJ, et al. AIDS 2012; Wendel KA, et al. CID 2003; Gutmann C, et al. AIDS 2010; Watanabe K, et al. Intern J STD & AIDS 2010; van Lelyveld SFL et al. CID 2010; Bingham R, et al. Intern J STD & AIDS 2011; del Palacio Tamarit M, et al. AIDS Res and Human Retrov 2011; Bogoch II, et al. J Infect 2011; Pasquet A, et al. AIDS 2012; Khouri MN, et al. JNV 2013; Bierhoff M, et al. Antivir Therapy 2013; Mangioni D, et al. CID 2014; Imaz A, et al. AIDS Res and Human Retrov 2014; Perez-Rodriguez MT, et al. CMI 2015; Martins J, et al. AIDS 2016; Vassallo M, et al. AIDs 2016; Trunfio M, et al. JNV 2017; De Zan V, et al. EACS 2017, Patel JNV 2018; Mukerji, et al. JAIDS 2017

Symptoms in published cases of CSF escape



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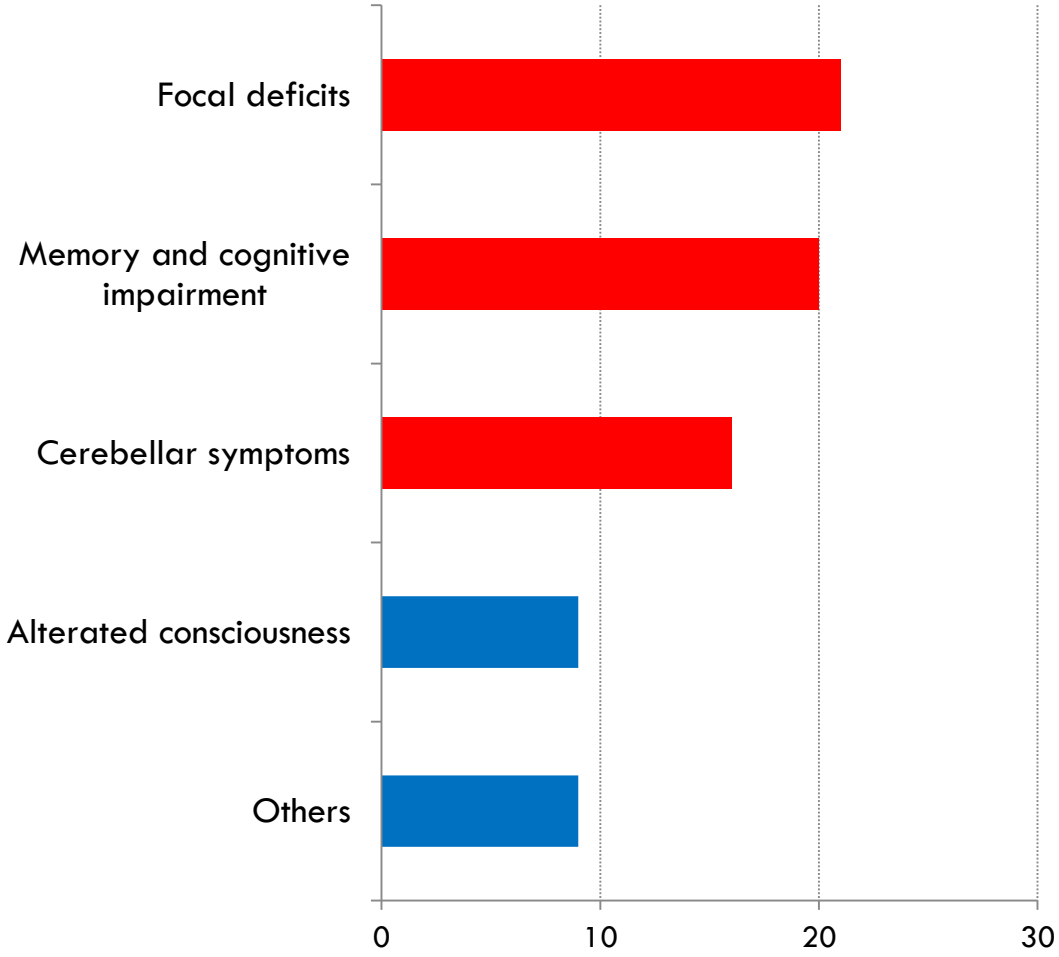
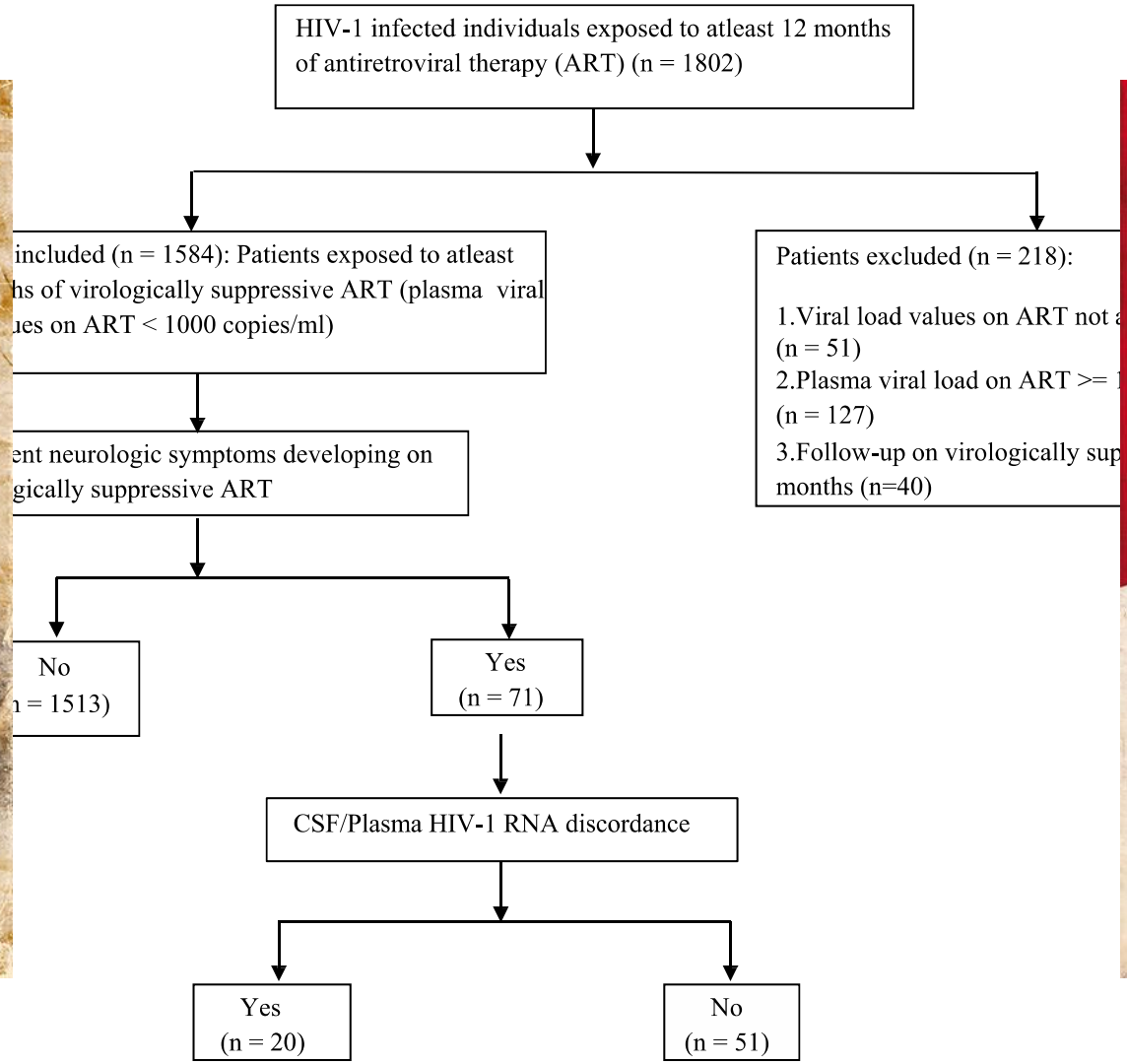


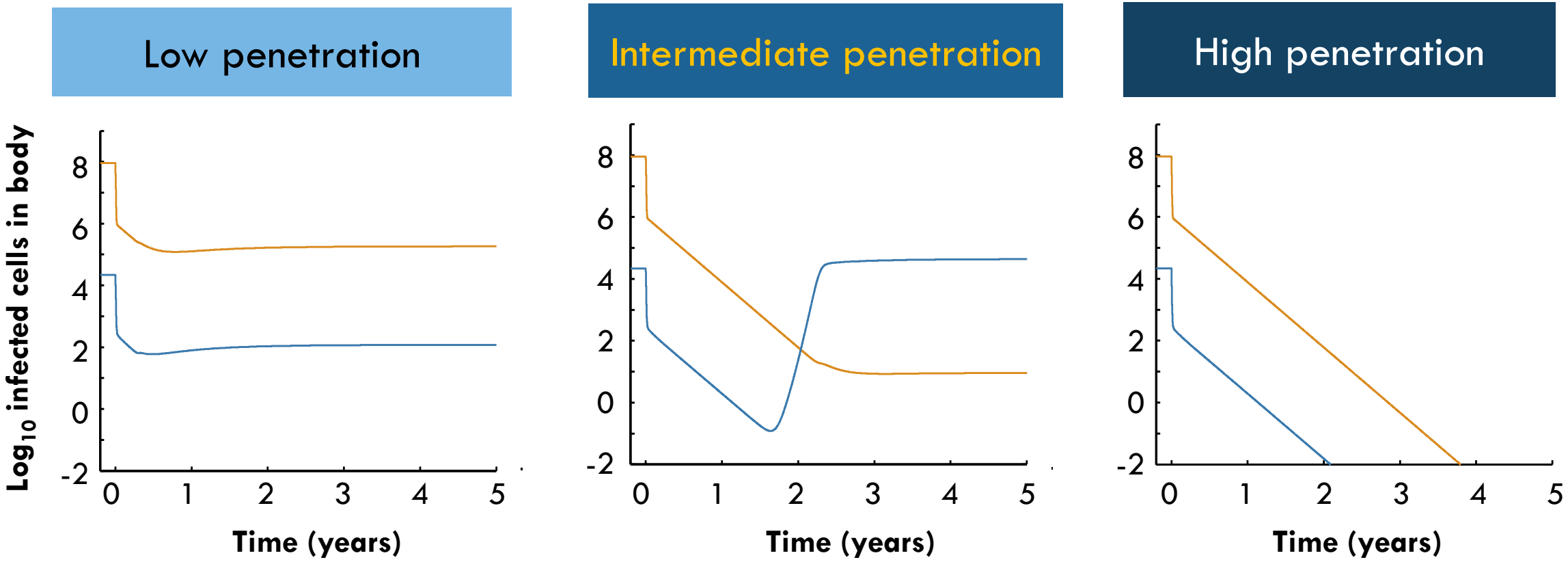
De Zan V, et al. EACS 2017

Discordant CSF/plasma HIV-1 RNA in individuals on virologically suppressive antiretroviral therapy in Western India



Dravid AN, et al. Medicine 2018 97:8(e9969); Patel AK, et al. JNV 2018

SANCTUARIES AND PK



Lorenzo-Redondo R, et al. Nature 2016

LYMPHOCYTE DOMINANT ENCEPHALITIS

17/30 SIV-infected macaques

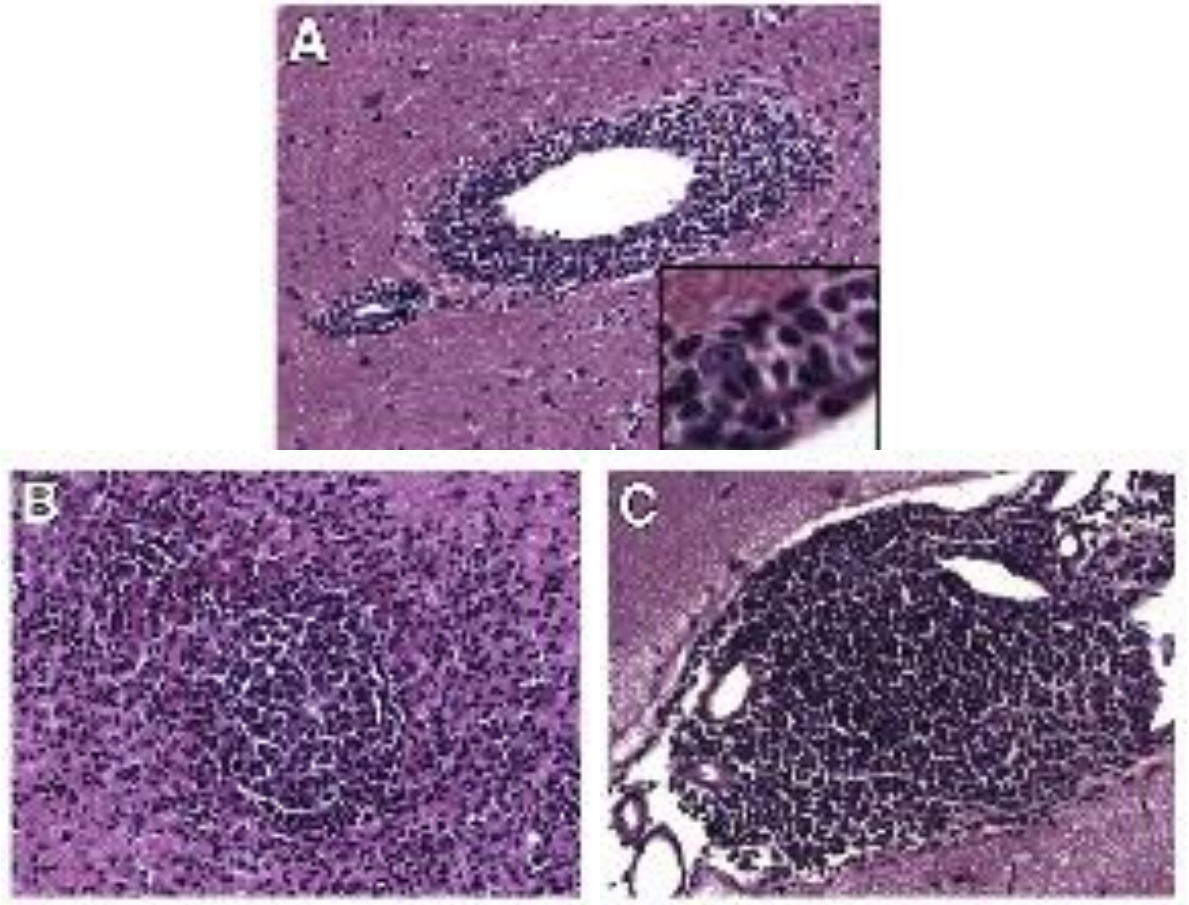
Asymptomatic

- (different from SIV encephalitis)

CNS infiltrates: CD20+ B cells and CD3+ T cells

Associated with low levels of SIV RNA on brain tissue

More frequent in animals with episodes of CSF SIV RNA

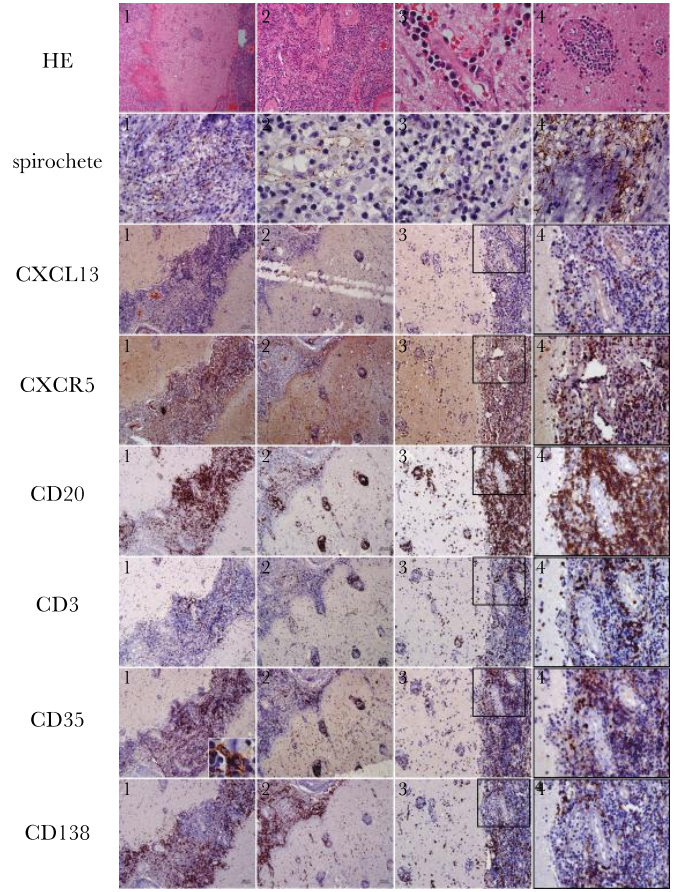


Mangus LM, et al. The Am J Pathology 2017

NEUROSYPHILIS AND ECTOPICAL GERMINAL CENTERS

Central portion of the mass contained a necrotizing inflammatory material infiltrated with epithelioid cells, inflammatory cells, severe endarteritis with endothelial cell swelling and hyperplasia

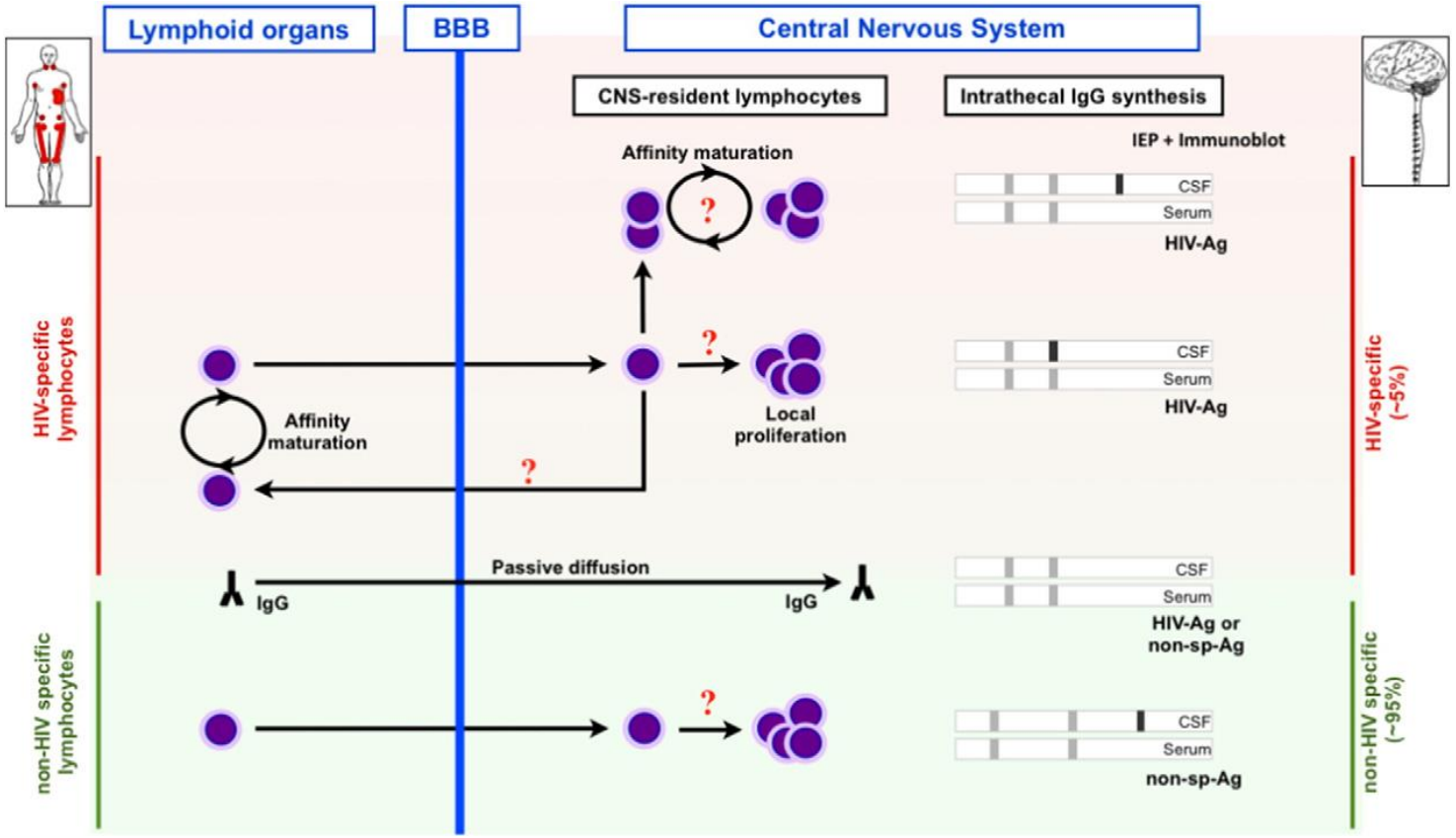
Syphilitic gumma was disclosed with abundant lymphocytes, plasma cells (CD138) and **follicle-like structures → ECTOPICAL GERMINALCENTERS**

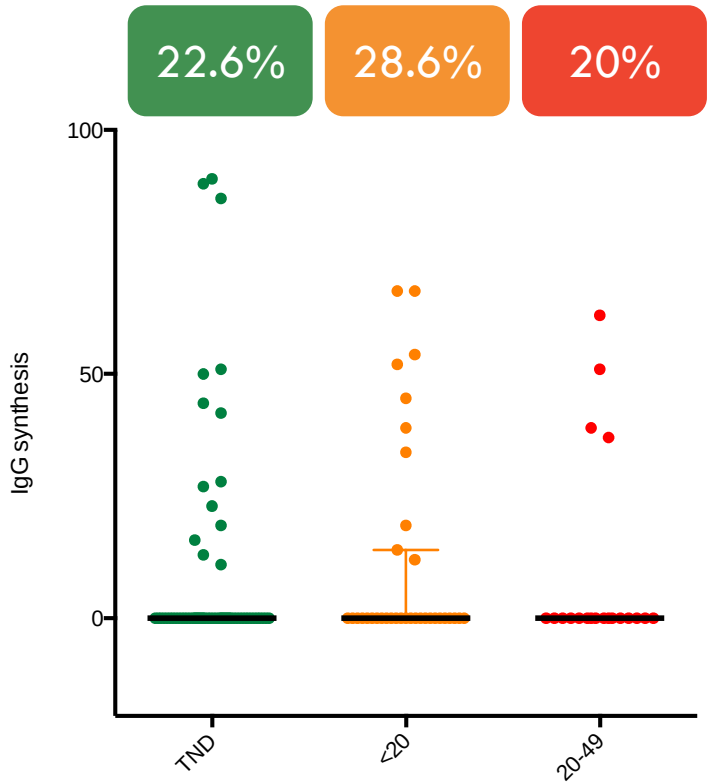


Yu Q, et al. JID 2017

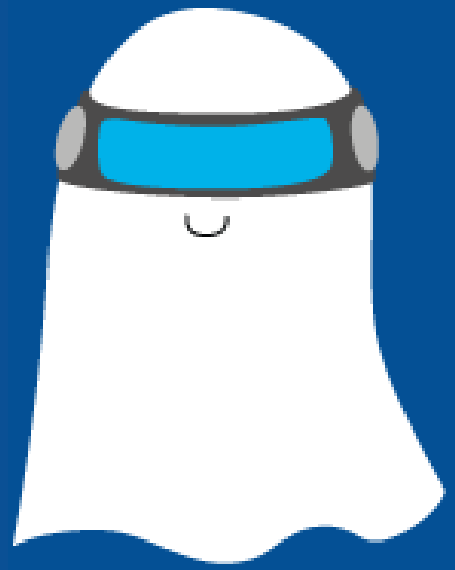
IgG production in the CNS?

117 patients from from the Turin NeuroHIV database
CSF HIV RNA <50 copies/mL under HAART
No CNS inflammatory disease





Bonnan M, et al. J Neuroimmunology 2015



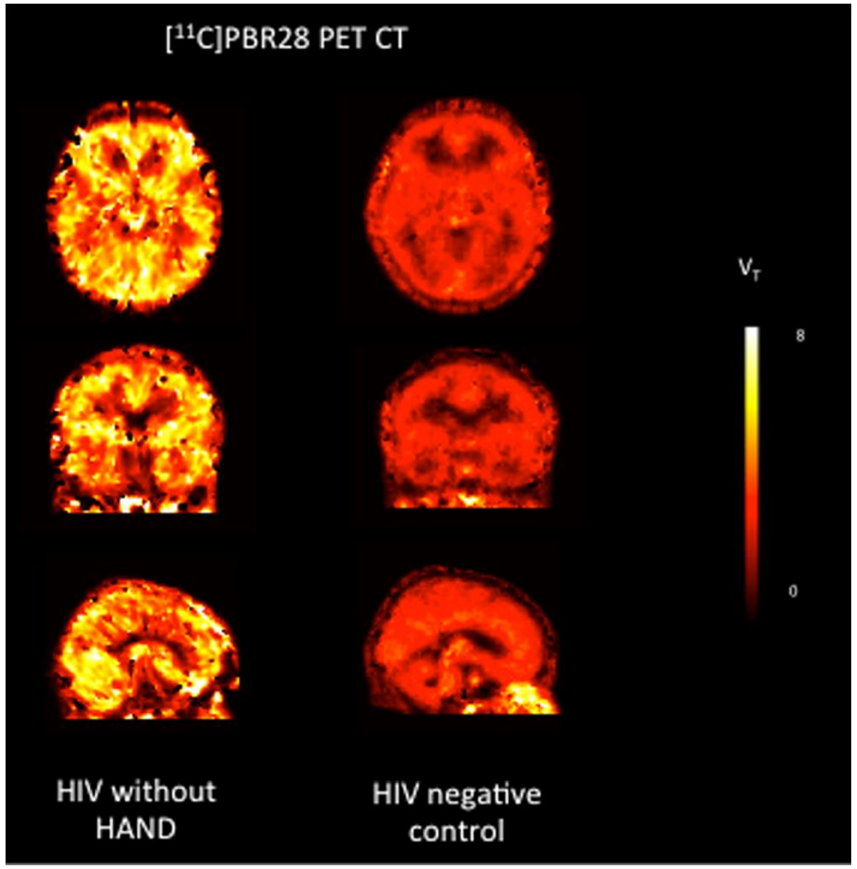
NEW DRUGS PK + NEW STRATEGIES

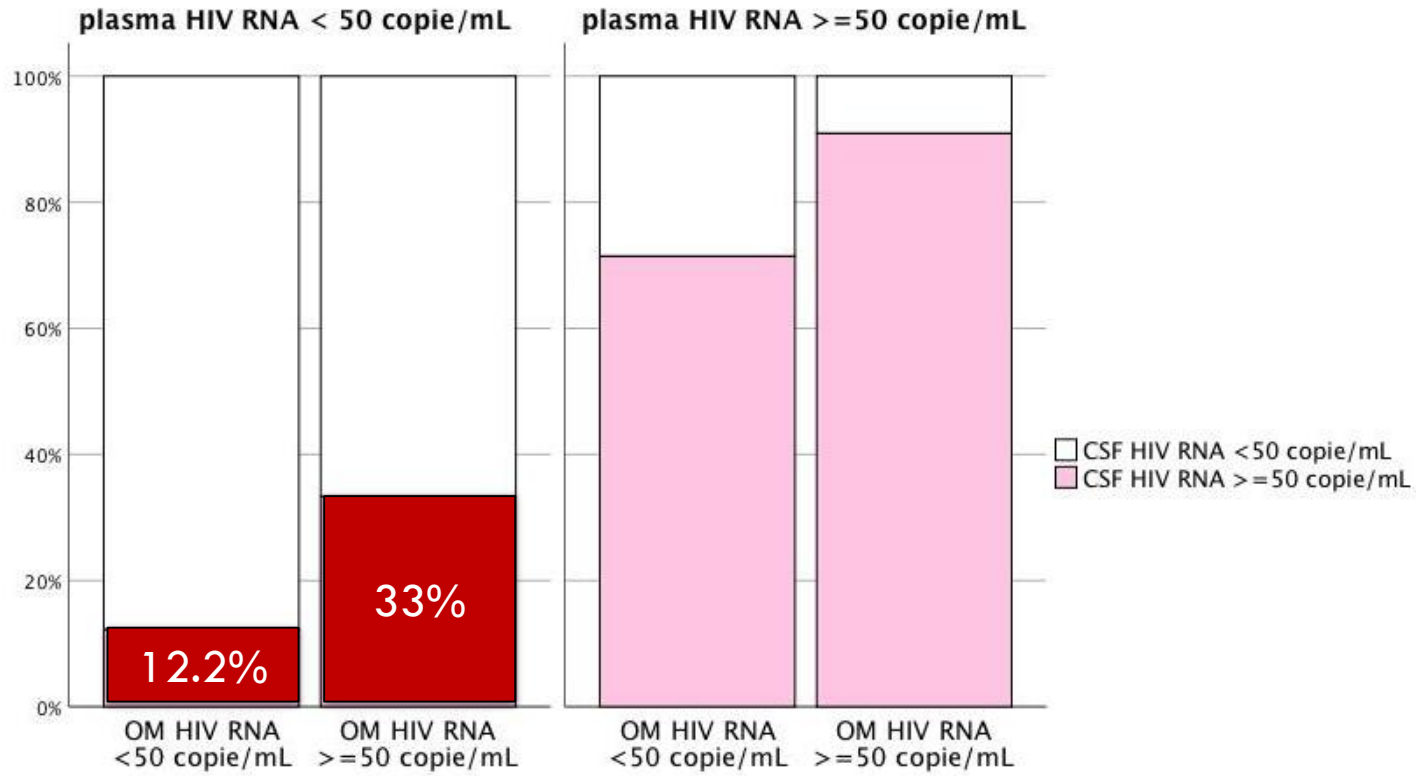
	CSF to plasma ratio	Comment
Tenofovir with TAF	3.4% Higher ratio	**High rates of CSF HIV RNA suppression**
Darunavir/cobicistat	1.1% Similar to DRV/r	
Rilpivirine	1.4%	
LA Rilpivirine	1/1.3%	
Elvitegravir/cobicistat	0.3%	
Dolutegravir	0.4/0.5%	
LA Cabitegravir	0.3%	

Less Late Presentation?

Ma Q, et al. CROI 2018, #473; Bartels H, et al. J Antimicrob Chemother 2017; Mora-Peris B, et al. JAC 2014; Letendre et al. HIV Glasgow O346; Ma Q, et al. CROI 2018, #473; Letendre S, et al. CID 2014

NON-INVASIVE MONITORING





Vera JH, et al. Eur J Nucl Med Mol Imaging 2017; Bertero L, et al. AIDS 2019

Vascular cognitive impairment and HIV-associated neurocognitive disorder: a new paradigm

Lucette A. Cysique[1,2,3] & Bruce J. Brew[2,3,4,5]

Received: 28 October 2018 / Revised: 15 November 2018 / Accepted: 16 November 2018

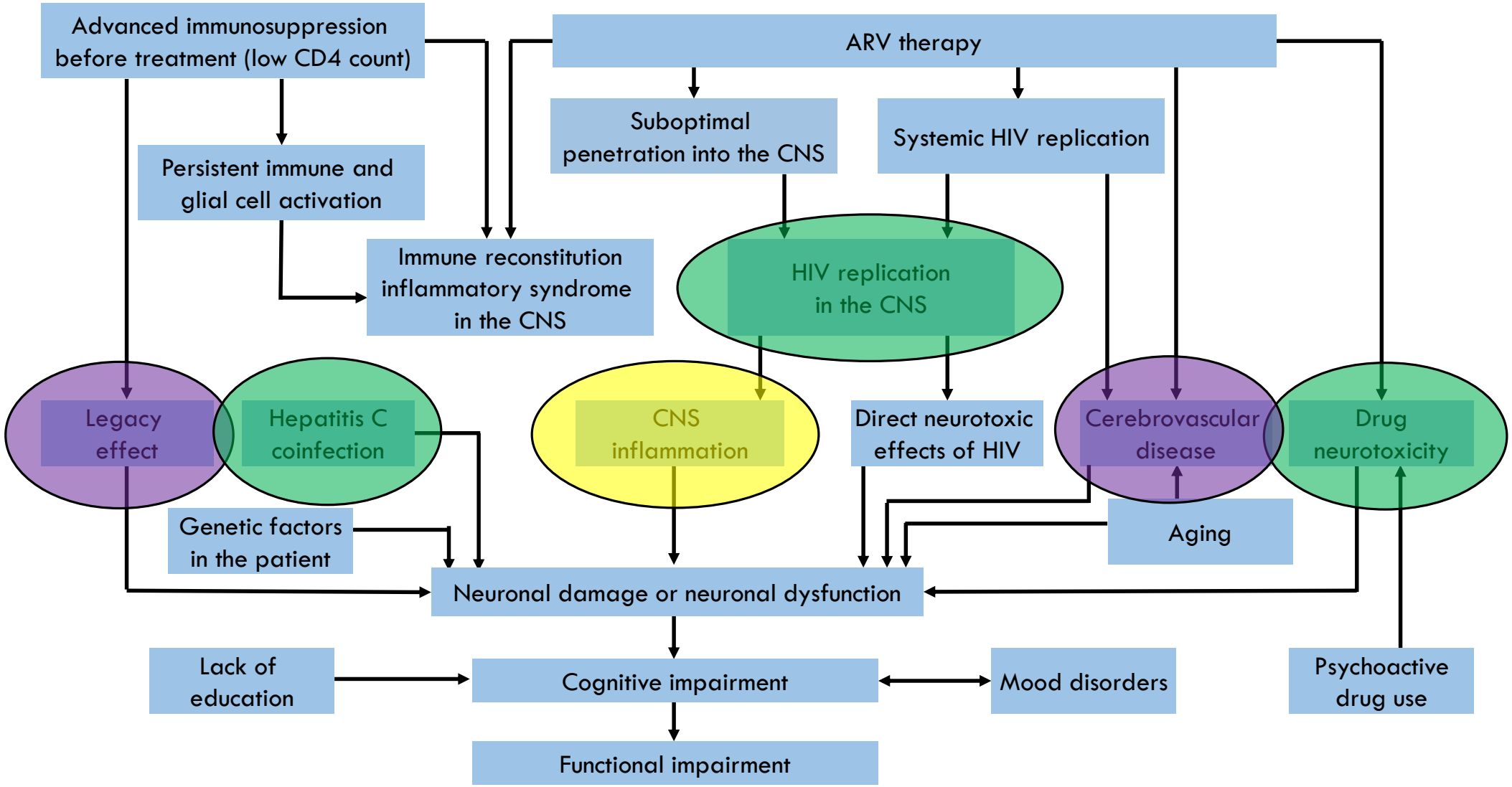
Abstract

In this review, we propose that vascular cognitive impairment (VCI), with relevance for the global HIV population, is fundamentally and clinically linked to the persistence of mild forms of HIV-associated neurocognitive disorders (HAND) in ageing people living with HIV infection (PLWH). After placing our review within the context of the general literature on HIV and ageing, we review non-VCI risks for dementia in ageing PLWH. We then present the recently updated VCI nomenclature and show that the neuropsychological and neuroimaging phenotypes of VCI and HAND are largely overlapping, suggesting that further research is needed to accurately distinguish them. We further link VCI and HAND at the mechanistic level by advancing the innovative proposal that the neuro-vascular unit (NVU) may represent the primary target of HIV-related brain injury in treated HIV infection. To this, we add the fundamental impact of mild and major VCI on the NVU. Importantly, we show that the potential contribution of vascular damage to overall brain damage in ageing PLWH is probably much higher than currently estimated because of methodological limitations, and because this research is only emerging. Finally, because all VCI risk factors are more prevalent, premature, and sometimes accelerated in the HIV population at large, we conclude that the probable total burden of VCI in the global HIV population is higher than in the general population and would need to be compared to chronic conditions such as type I diabetes and multiple sclerosis to account for the disease chronicity and lifelong treatment effects. Therefore, this review is also a call to action. Indeed, it is fully established that this amount of VCI burden is a major risk factor for dementia at aged 60+.

ACCORDING TO CHEMISTRY

ALCOHOL IS A SOLUTION

RISK FACTORS



Nightingale S, et al. Lancet Neurology 2014

TREATMENT OF HAND→ TREATMENT OF SPECIFIC PHENOTYPES

		CPE score	95% Inhibitory quotients	Monocyte efficacy score	Cardiovascular risk	*In vitro* neurotoxicity
NRTIs	Abacavir	3	na	3	++	+
	Emtricitabine	3	na	12.5	0	0
	Lamivudine	2	na	50	0	+
	Tenofovir DF	1	na	50	-	0
	Zidovudine	4	na	50	0	+
NNRTIs	Nevirapine	4	na	20	0	+
	Efavirenz	3	6.4	100	0	++
	Etravirine	2	5.1	na	0	+
	Rilpivirine	na	na	na	0	+
PIs	Atazanavir	2	0.4	na	-	+
	Atazanavir/r	2	2.8	na	-	+
	Darunavir/r	3	8.2-18.5	na	0?	0
	Lopinavir/r	3	1.5	na	++	+
INSTIs	Raltegravir	3	0.7	na	-	+
	Elvitegravir/r	na	na	na	0	+
	Dolutegravir	na	na	na	0	?
EIs	Maraviroc	3	na	na	0	-
	Enfuvirtide	1	na	50	0	na

[A] Source reference for table is Calcagno A, et al. Current HIV/AIDS Reports 2018

1) Tiraboschi J, et al. JAC 2012; 2) Nguyen et al, JAC 2013; 3) Mora-Peris, et al. JAC 2014; 4) Letendre S, et al. CROI 2013, Abst 178LB; 5) Hinckley S, et al. CROI 2016 #395

CONCLUSIONS

CSF does not seem to accurately predict brain PK

- CPE (largely based on physochemical properties) better?
- PBPK

Inflammation and transporter may affect brain parenchyma exposure

- Intracellular concentrations in target cells
- Pgp/BCRP inhibition?

We need to better define HAND phenotypes

- Tailored interventions

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