Pros and Cos of antiretroviral treatment on CNS

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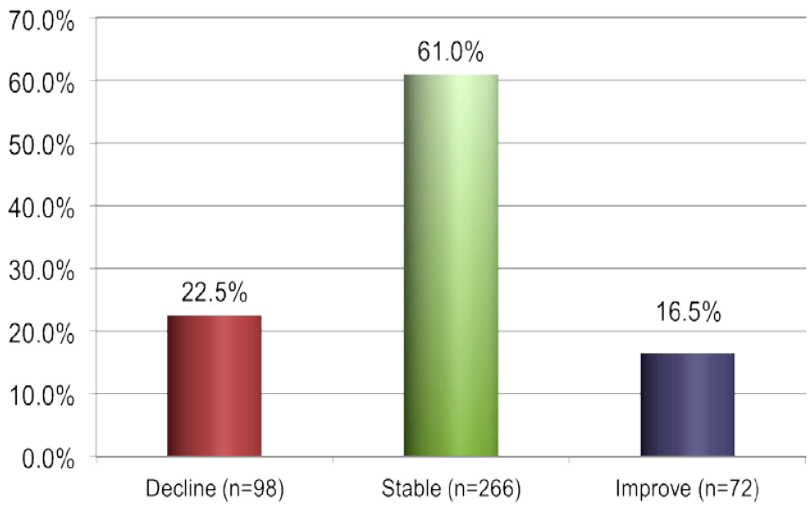
Does antiretroviral therapy have a role on CNS?

ART prevents neurocognitive decline

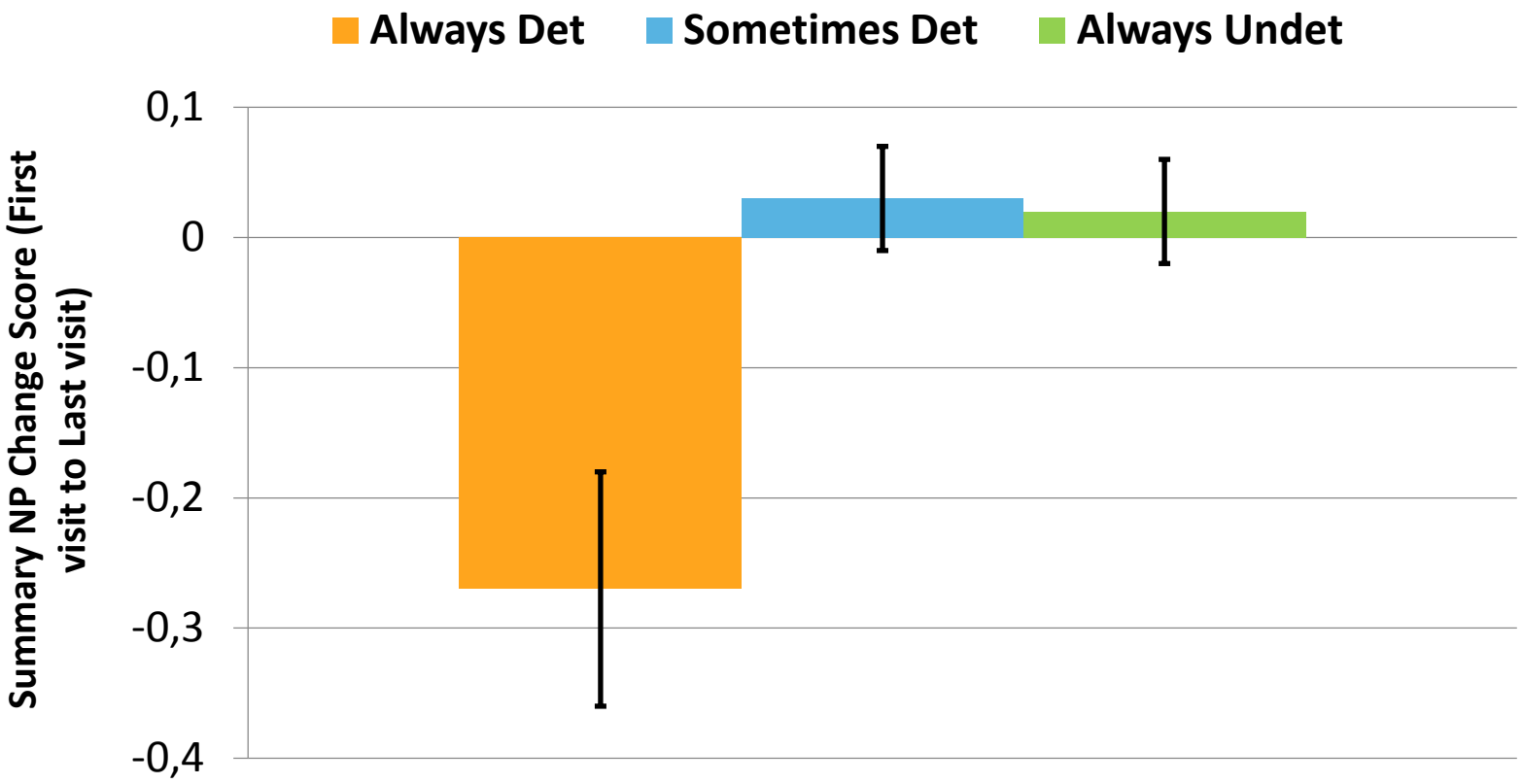
Risk factors associated with neurocognitive decline



Predictors of NC decline	Relative Risk	CI	p-value
Lower CD4	1.1	(1.02, 1.21)	.017
Comorbidities	2.4	(1.4, 4.0)	.0015
Off ART	1.6	(1.1, 2.5)	.025

Heaton RK et al. Clin Infect Dis 2015;60(3):473-80.

But there is something more than HIV suppression



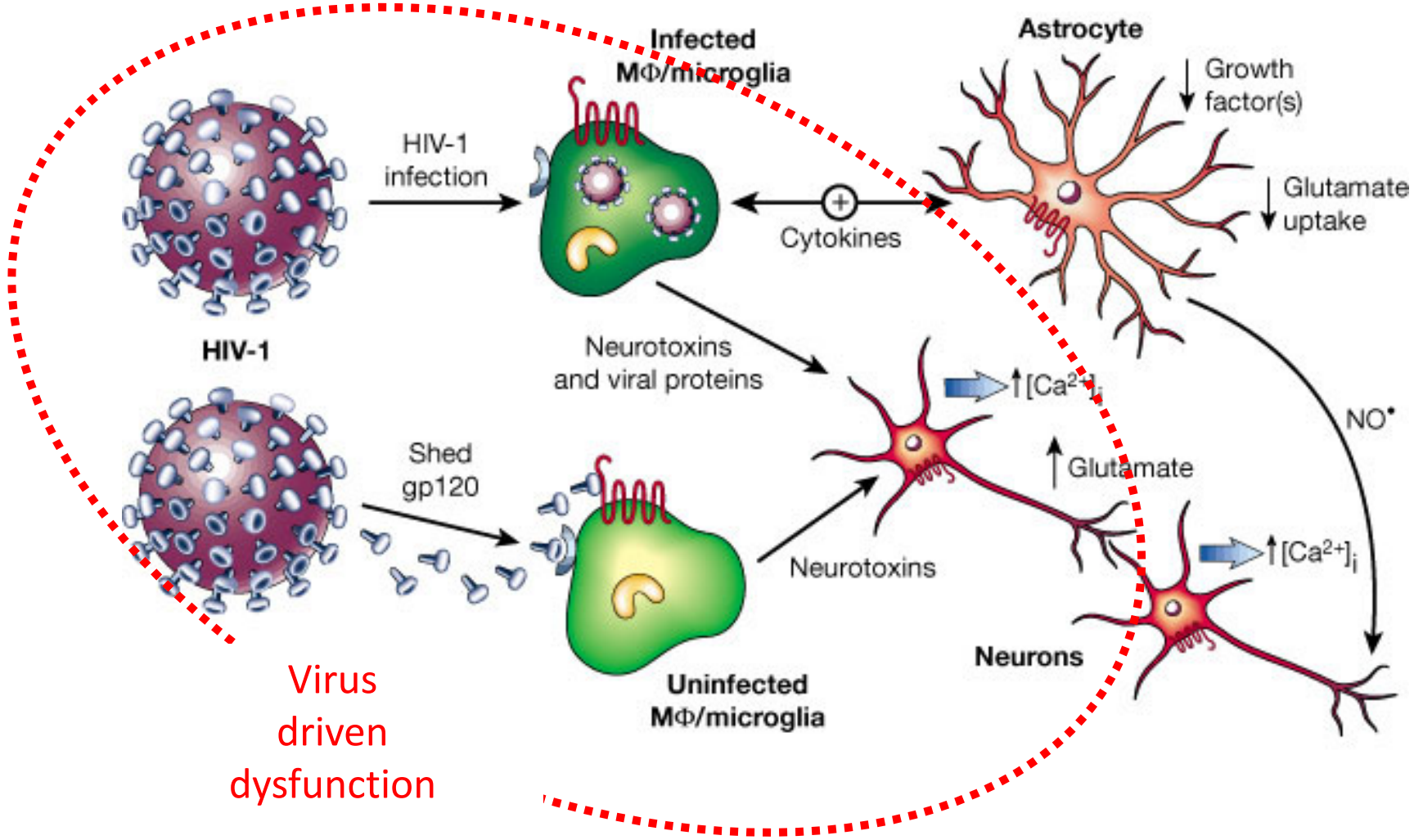
To be detectable all the time is associated with NC decline

Blips seem to have no impact in NC evolution

Heaton RK et al. Clin Infect Dis 2015;60(3):473-80.

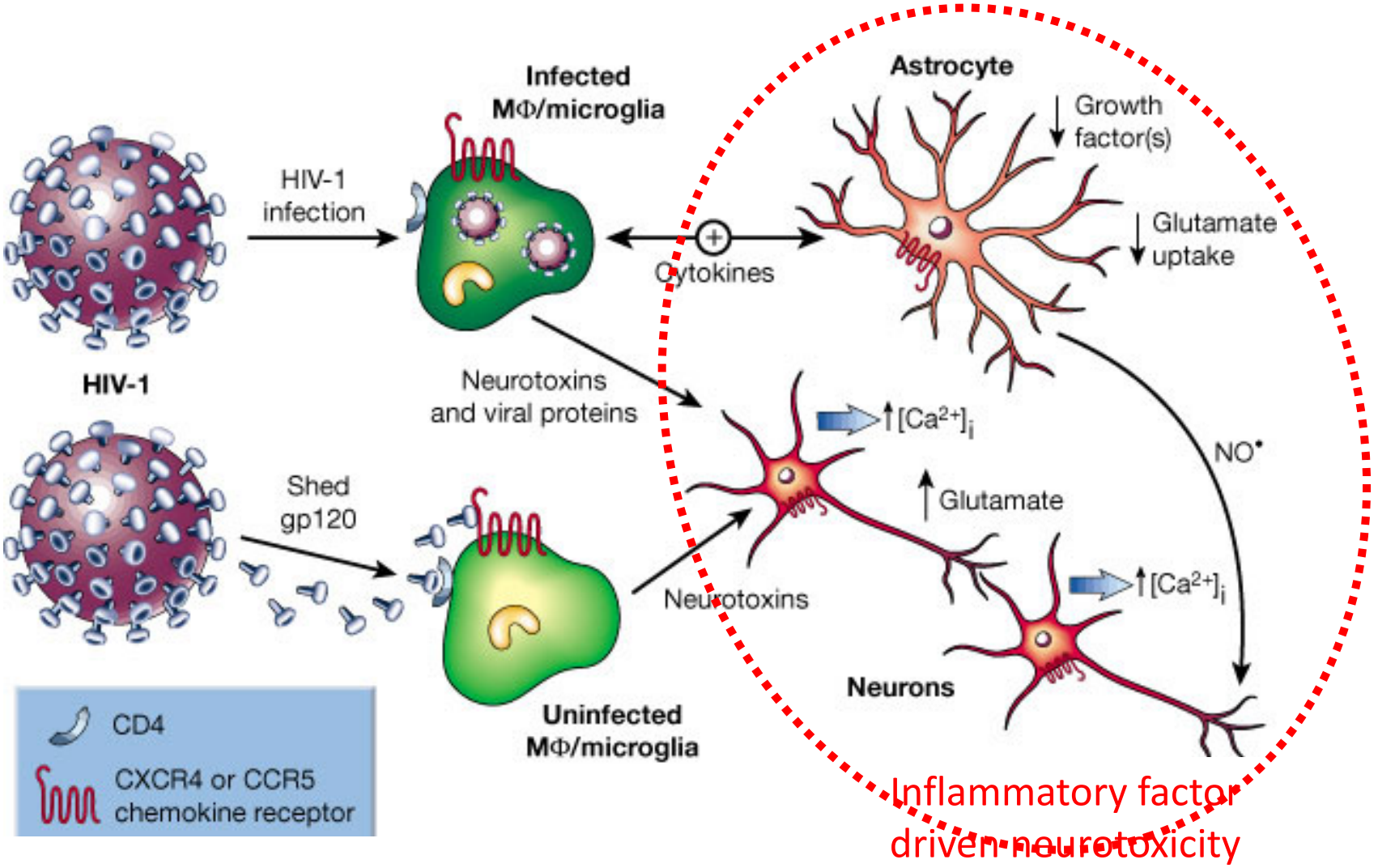
Why is difficult to stablish the role of antiretroviral therapy on CNS?

ART is not enough to stop all HIV-related neurotoxicity



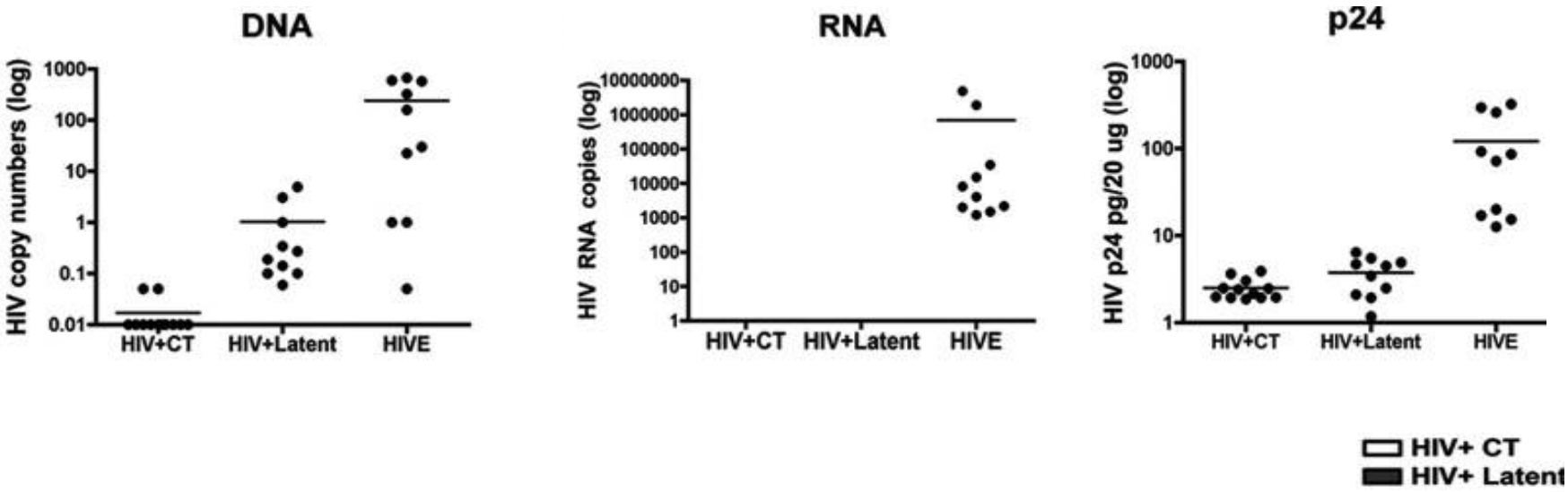
Kaul M, et al. Nature 2001; 410: 988-994.

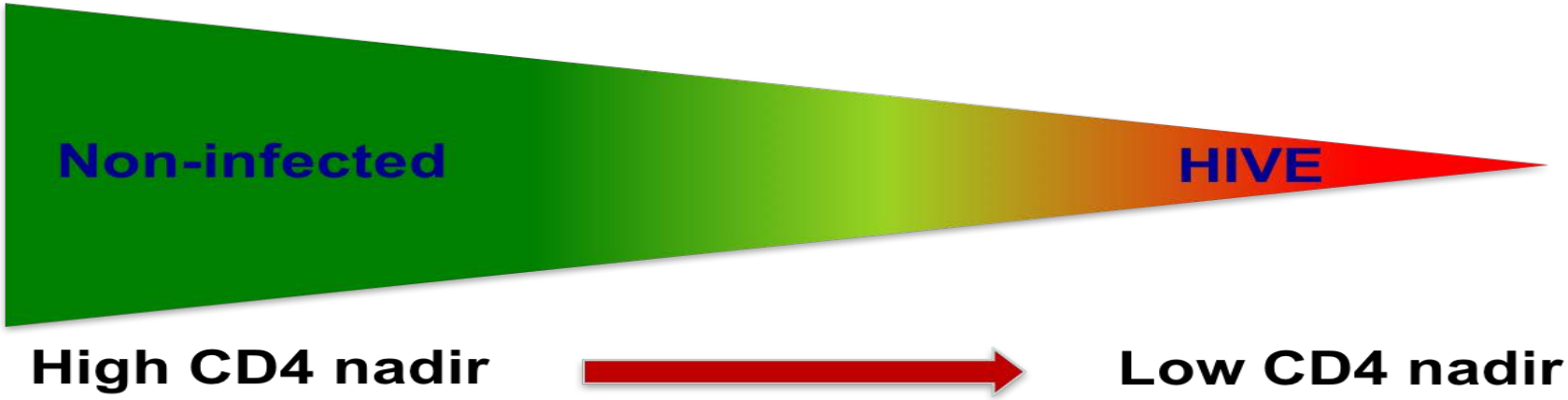
ART is not enough to stop all HIV-related neurotoxicity



Kaul M, et al. Nature 2001; 410: 988-994.

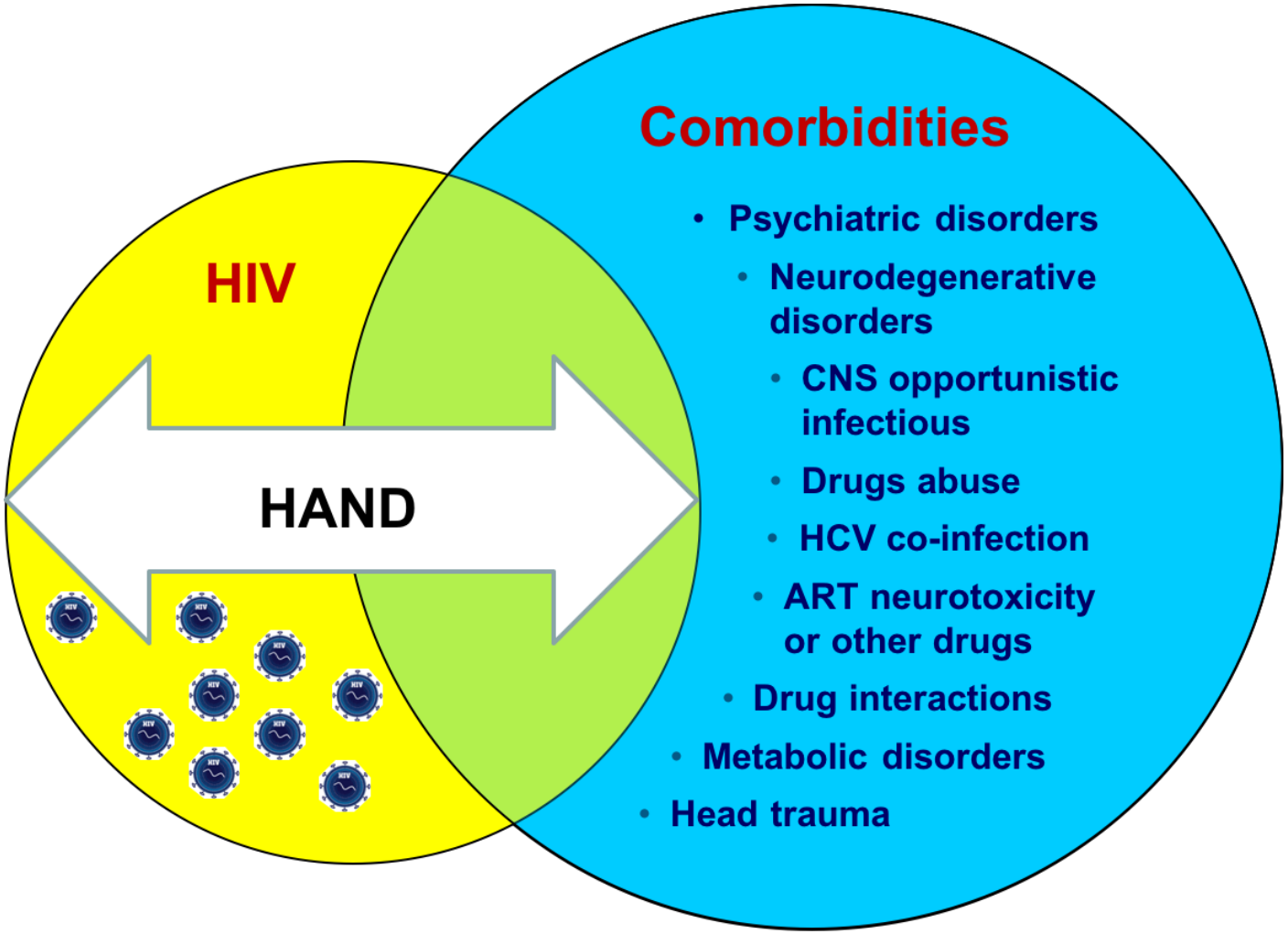
Intensity of CNS disease is not always the same





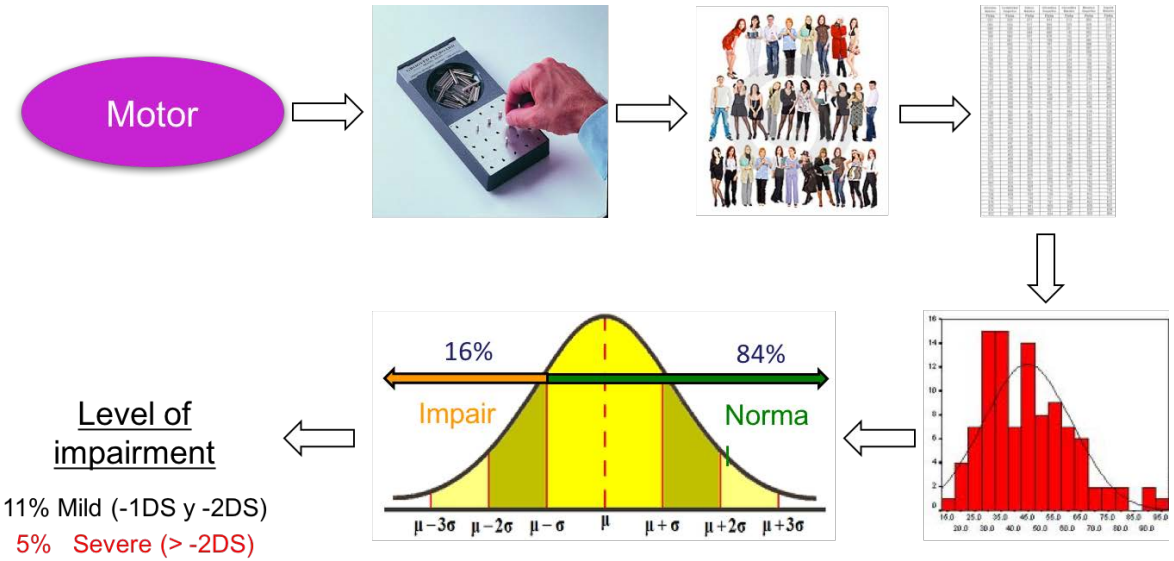
Desplats P et al. Neurology 2013;80(15):1415-23.

CNS comorbidities are not always the same



Adapted by Pérez-Valero I from Antinori A, et al. Neurology 2007, 69: 1789-1799.

And neurocognitive testing is inaccurate



Criteria	*Sensitivity*	*Specificity*	*PPV*	*NPV*
AAN	15/27 = 56%	10/12 = 83%	14/16 = 88%	10/22 = 45%
HNRC	18/27 = 67%	11/12 = 92%	18/19 = 95%	11/20 = 55%

Cherner M et al. J Neurovirol 2007;12:23-8.

The Ig® Nobel Prizes

Neurourology and Urodynamics 30:183–187 (2011)

The Effect of Acute Increase in Urge to Void on Cognitive Function in Healthy Adults

M.S. Lewis,[1,2] P.J. Snyder,[3,4] R.H. Pietrzak,[1,3] D. Darby,[1,5] R.A. Feldman,[6] and P. Maruff[1,5,*]

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[2]*Department Aged Psychiatry, Caulfield Hospital, Melbourne, Australia*
[3]*Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut*
[4]*Department of Neurology, Alpert Medical School of Brown University, Providence, Rhode Island*
[5]*Centre for Neuroscience, University of Melbourne, Melbourne, Australia*
[6]*Urology Specialists, P.C., Middlebury, Connecticut*

"Having an extreme urge to void exerted a large negative effect on attentional and working memory functions (d>0.8). These cognitive functions returned to normal levels after micturition"

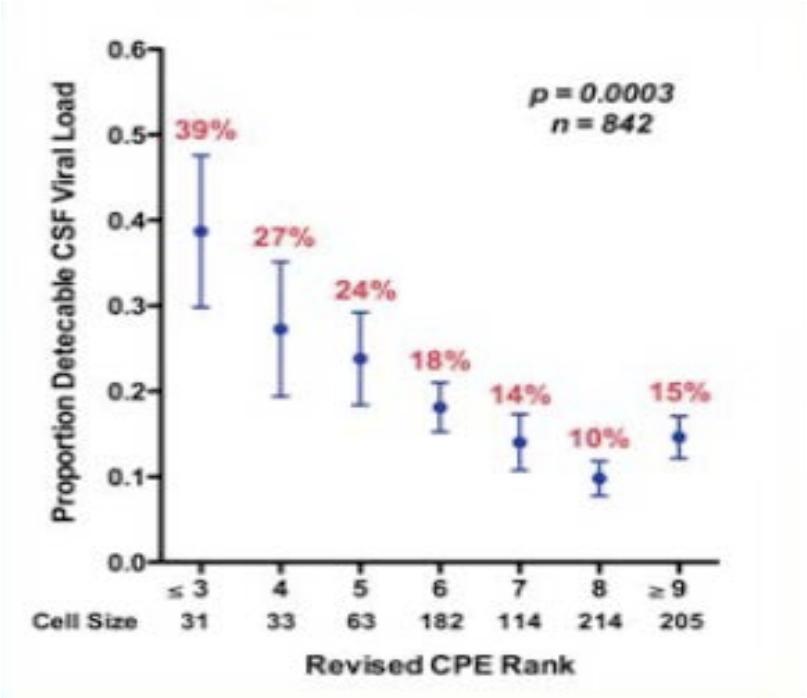
Do we need to use ART with high CNS penetration?

CPE demonstrated to control CSF replication

CPE Score 2010

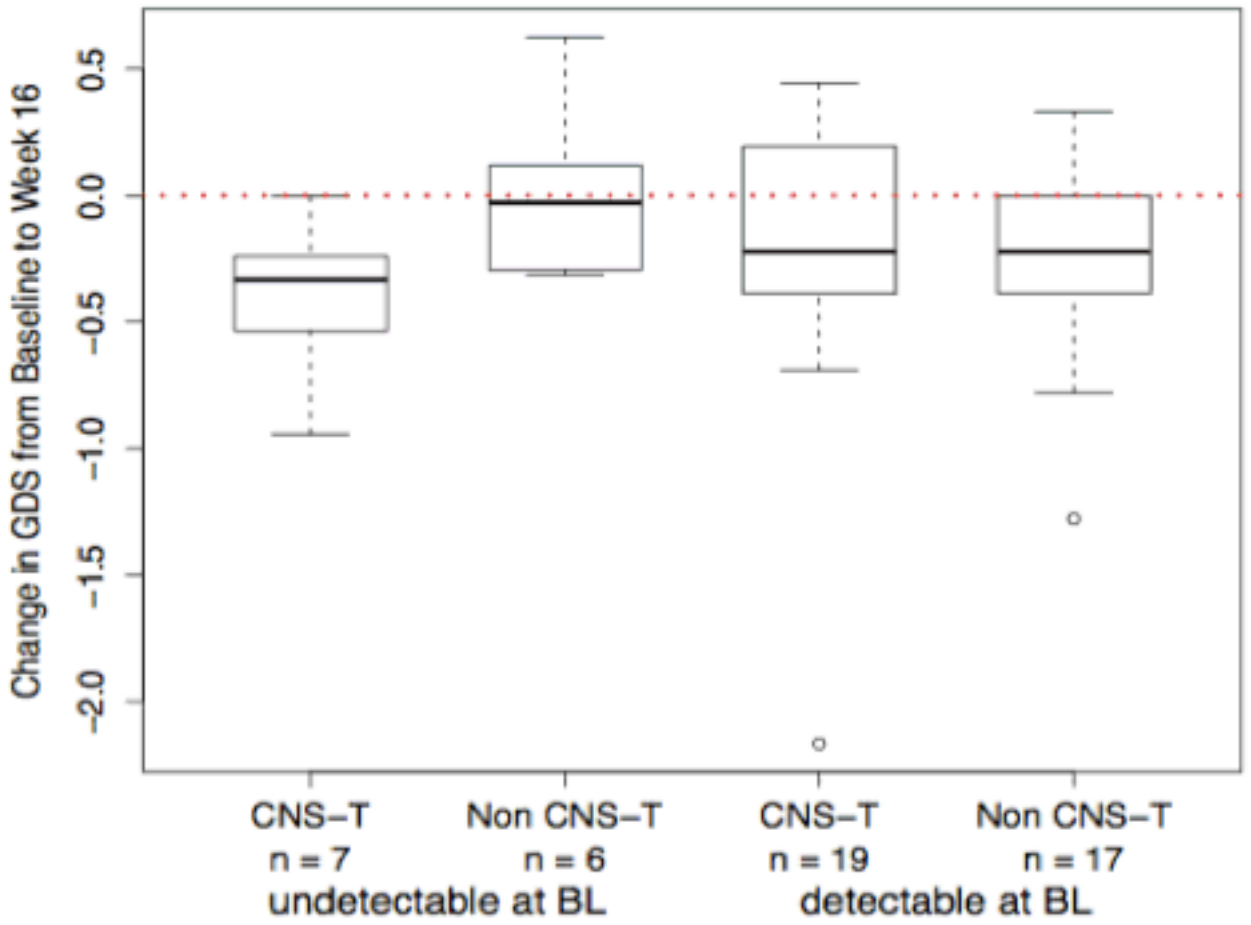
1	2	3	4
TDF DDC	**3TC** DDI D4T	**ABC** **FTC**	ZDV
	ETV	**EFV**	NVP
SQV/r TPV/r NFV	**ATV/r** ATV FPV	**DRV/r** FPV/r LPV/r	IDV/r
T20		MVC RAL	

Validation



Personal Slide Courtesy of S. Letendre

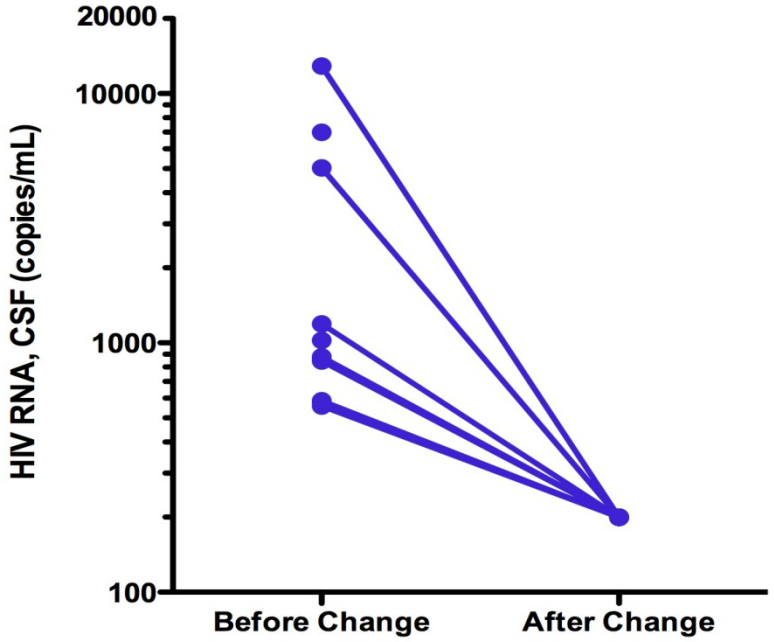
But it is unclear its role over NP function



Ellis et al. Clin Infect Dis 2014;58(7):1015-22.

Probably because only few patients need it

- 11 patients with new neurological symptoms and CSF HIV Escape* during ART
- Drug resistance mutations in CSF in 7 of 8
- ART modified
  - Drug resistance testing and estimated drug CNS distribution
- All patients clinically improved with reduction of HIV RNA in CSF

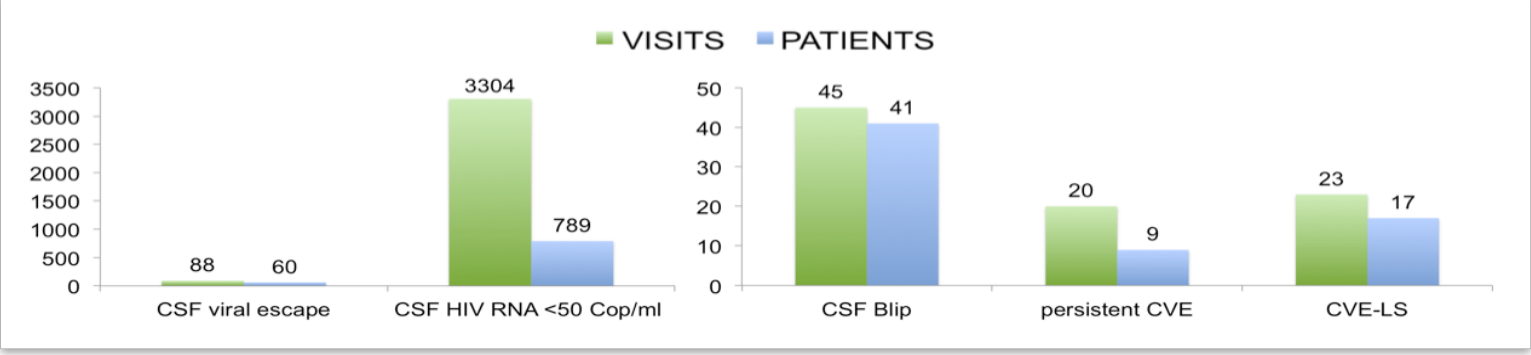


Defined as CSF RNA > 50 c/mL when plasma HIV RNA < 50 c/mL or CSF RNA > 1.0 $\log_{10}$ c/mL greater than plasma HIV RNA

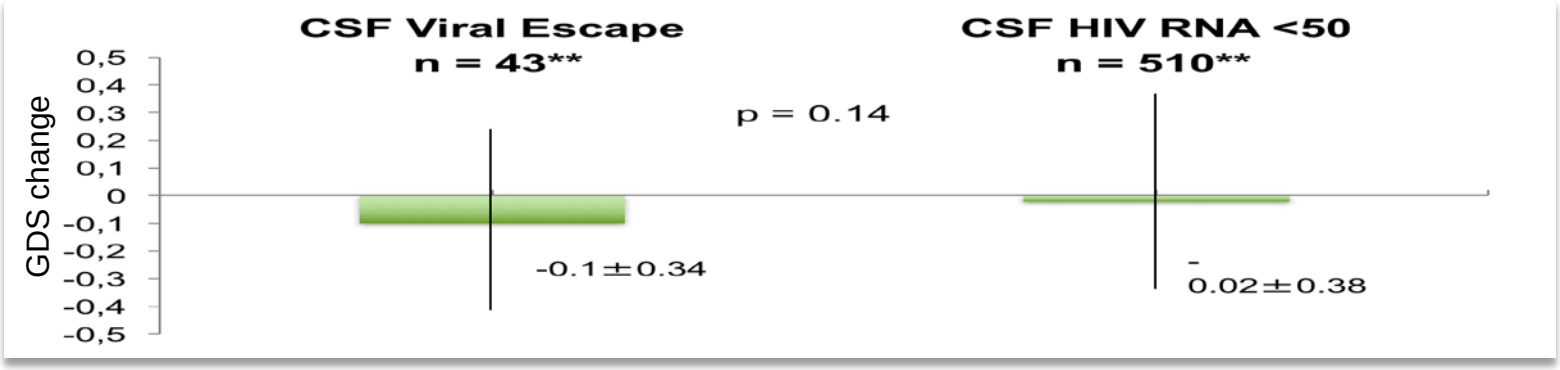
Canestri et al, Clin Infect Dis 2010, 50: 773–778

Current regimens have enough CNS penetration

Uncommon & transient



And it is not associated with NP decline



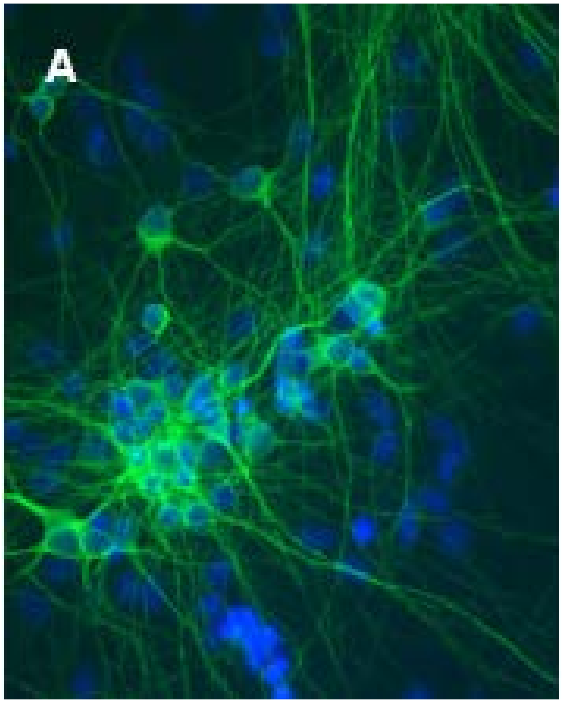
Perez Valero I et al. CROI 2013. Abstract 119

May be antiretroviral therapy a problem for CNS functioning?

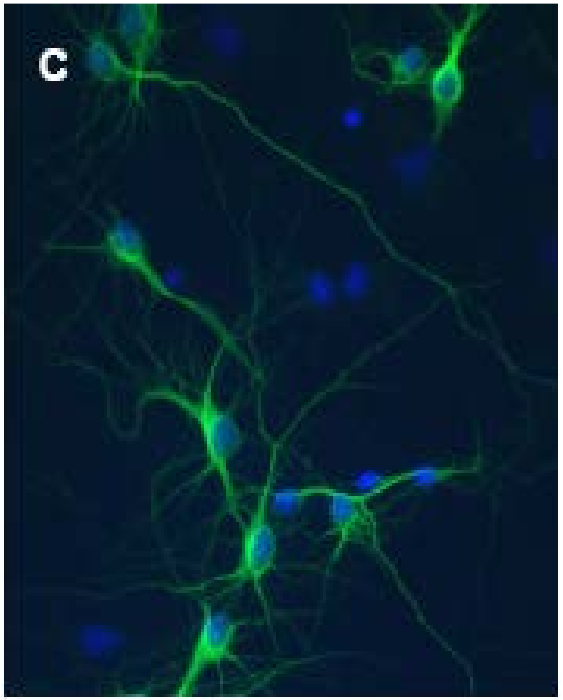
All antiretroviral drugs may be neurotoxic

HIV Neuropsychiatry

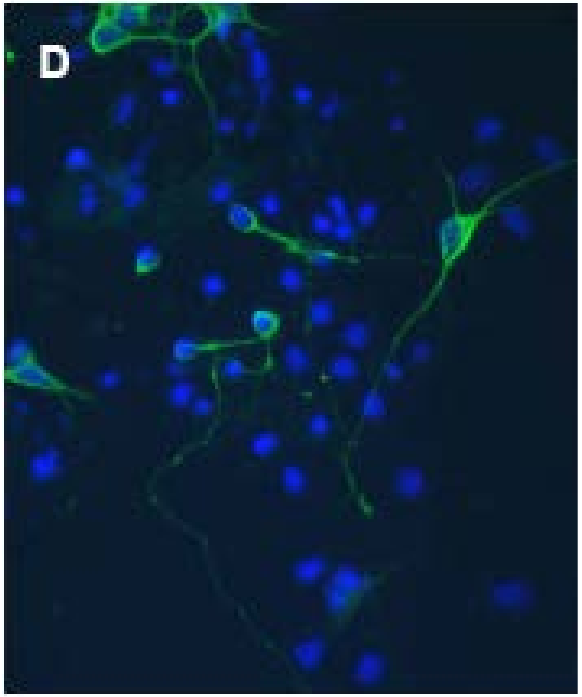
Neuronal integrity



Neuronal damage Produced by ATV



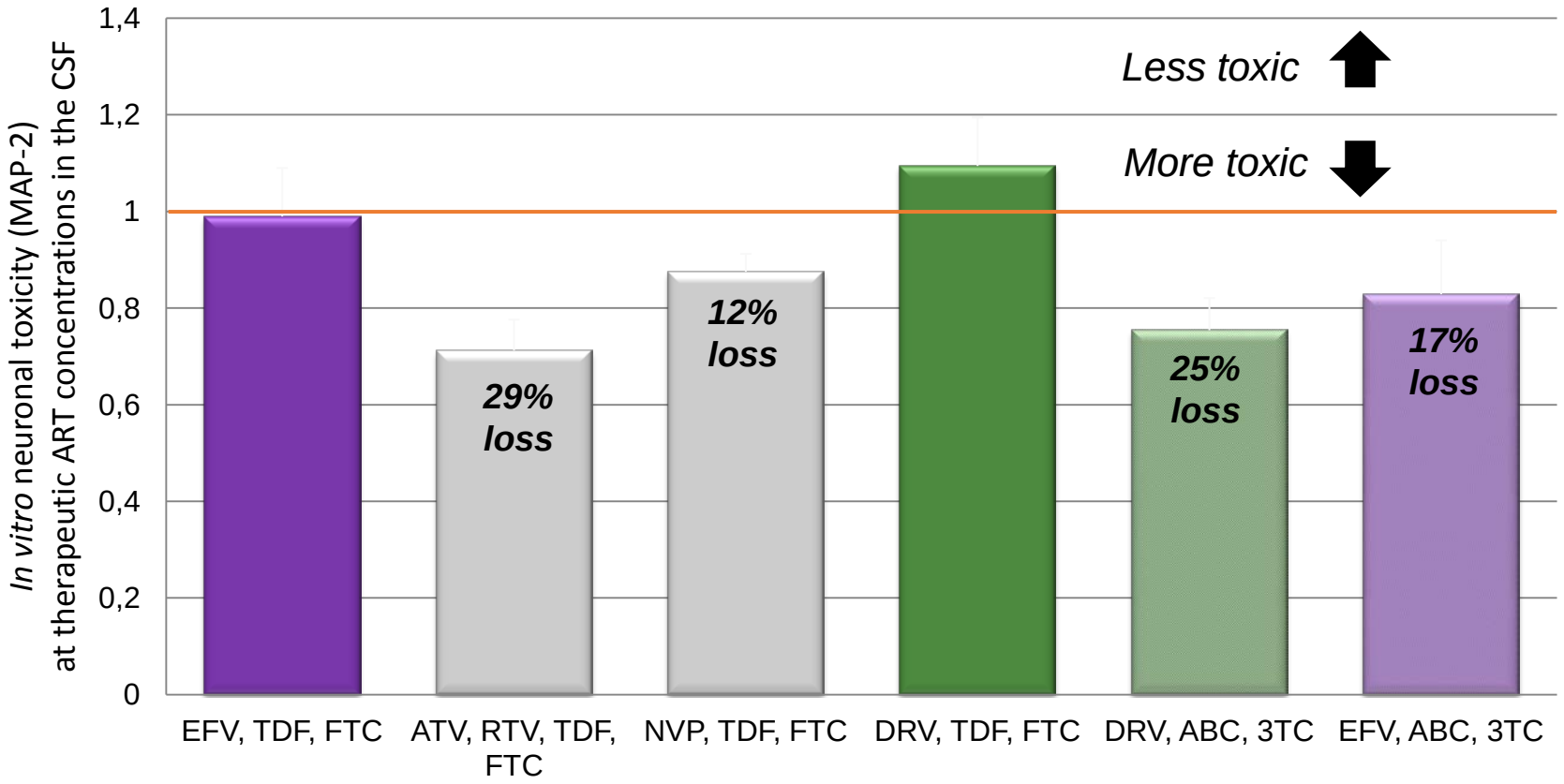
Neuronal damage Produced by EFV



CNS toxicity impairs normal functioning of the brain

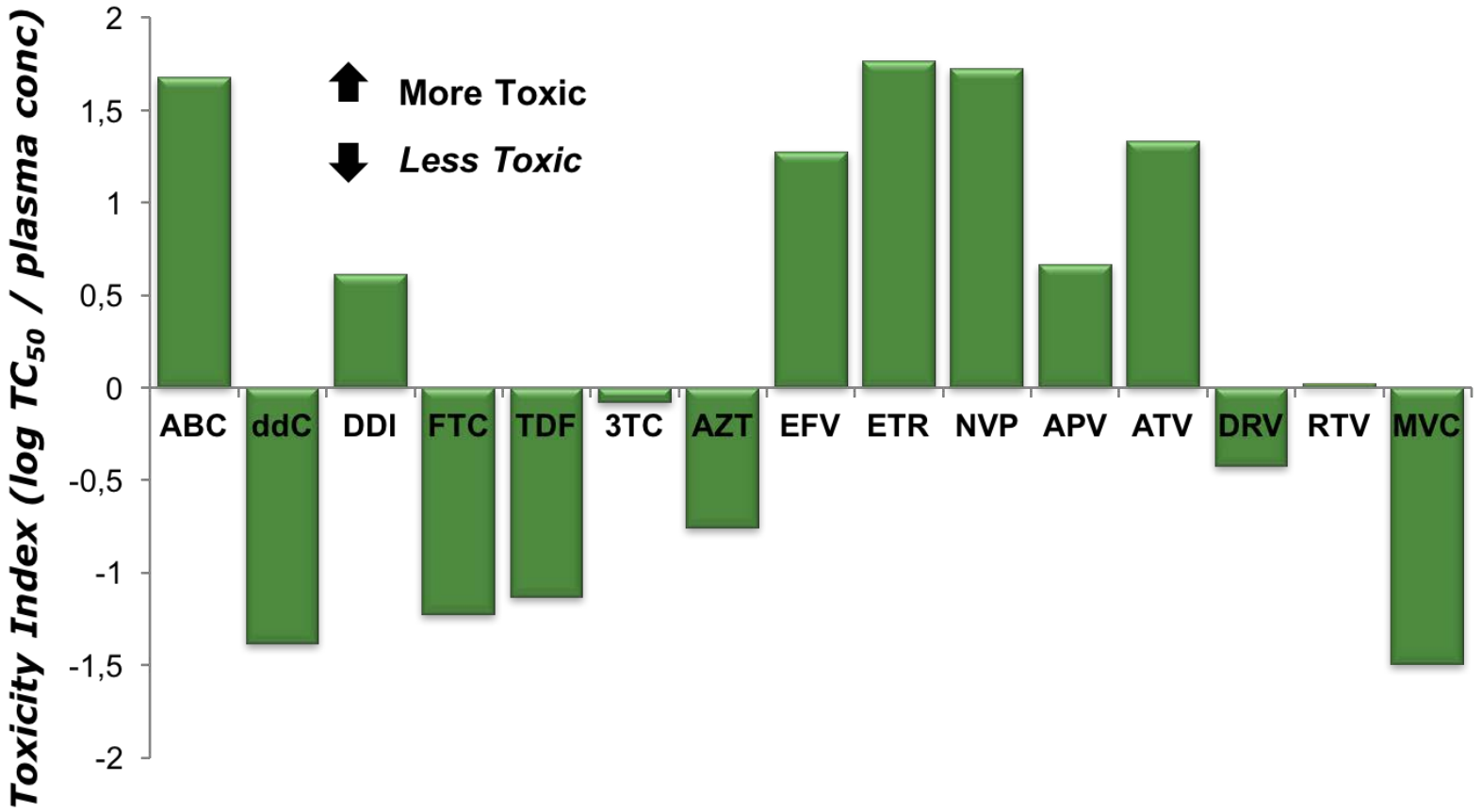
Liner et al. CROI 2010. Abst 435.

In-vitro neurotoxicity is different by ART regimens



Adapted from: Robertson K et al. J Neurovirol 2012;18:388–399

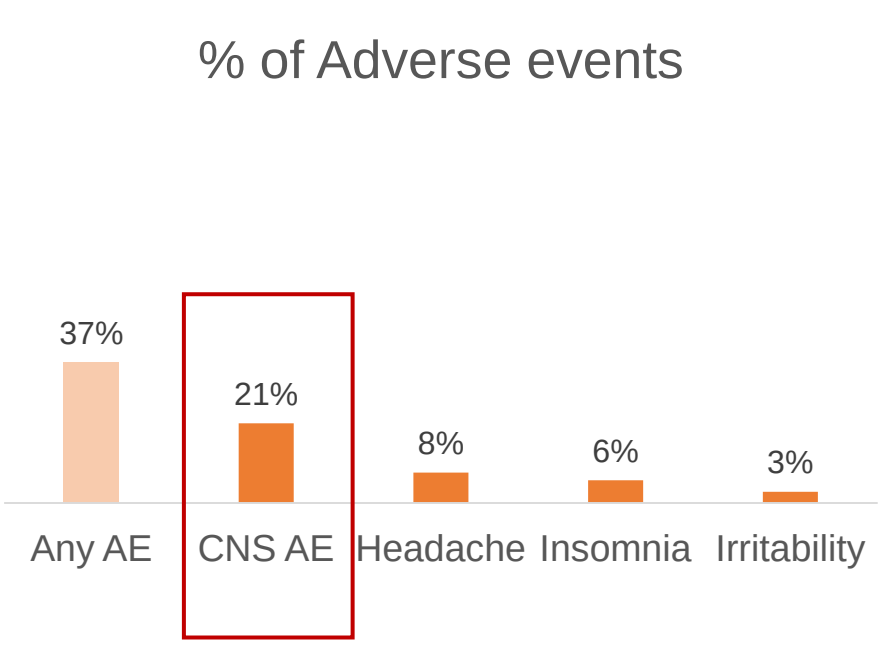
In-vitro neurotoxicity is associated to drug levels

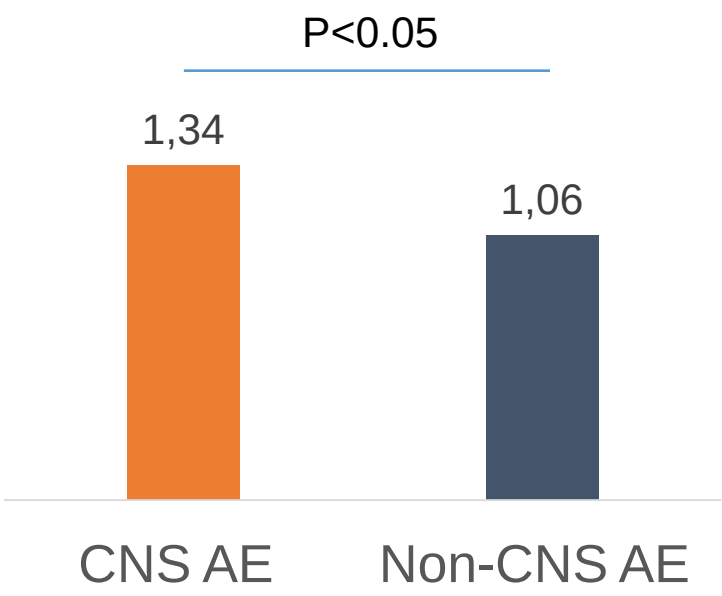


Robertson K et al. J Neurovirol 2012;18(5):388-99.

In-vivo, neurotoxicity is also related to drug levels?

101 Japanese HIV-infected patients taking DTG (2014-2016)





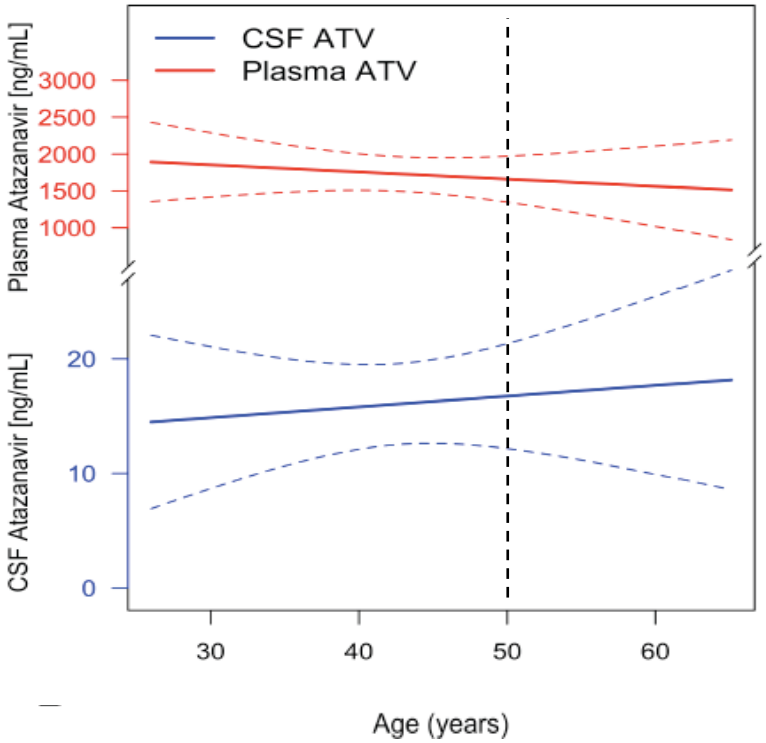
Correlations between [DTG] and UGT1A1 Genetic polymorphisms were not observed

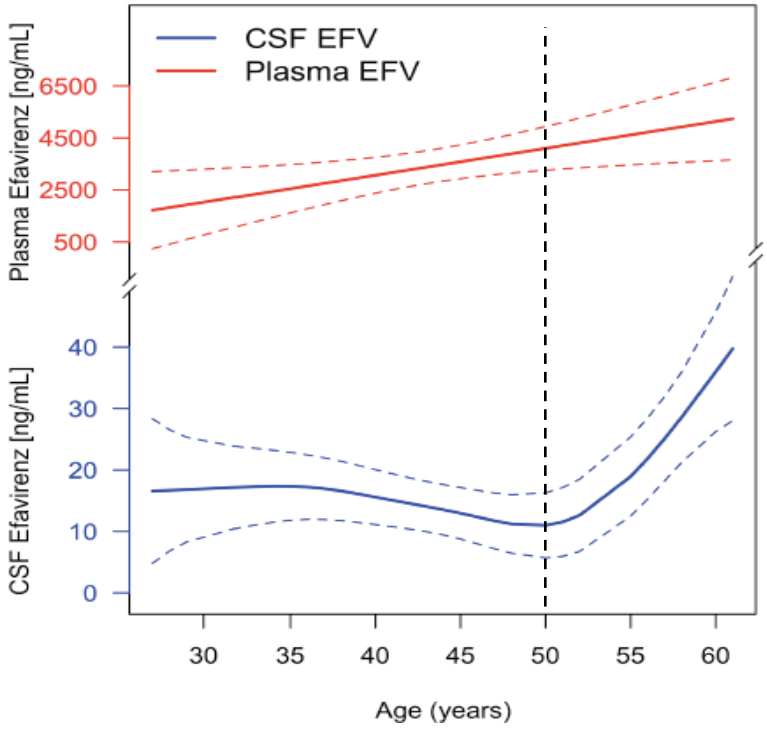
* DTG concentrations in mcg/mL

Yagura H et al. HIV Glasgow 2016. P312

CSF drug levels may change over time

- 71 patients/samples on EFV and 98 on ATV-based ART
- Patients had similar characteristics and similar overall neurocognitive performance





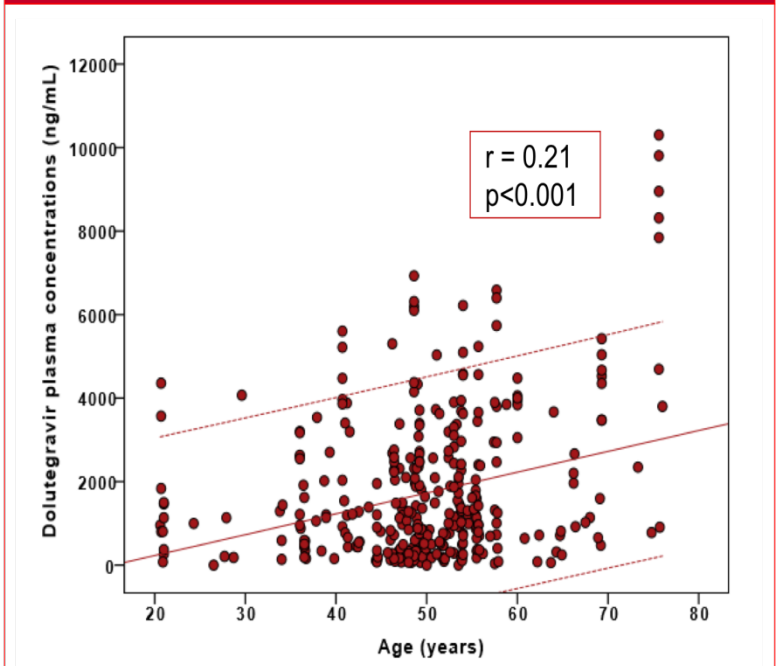
Aging affects efavirenz concentrations but not protease inhibitor concentrations in CSF

Croteau D. et al. CROI 2012, abstract 592.

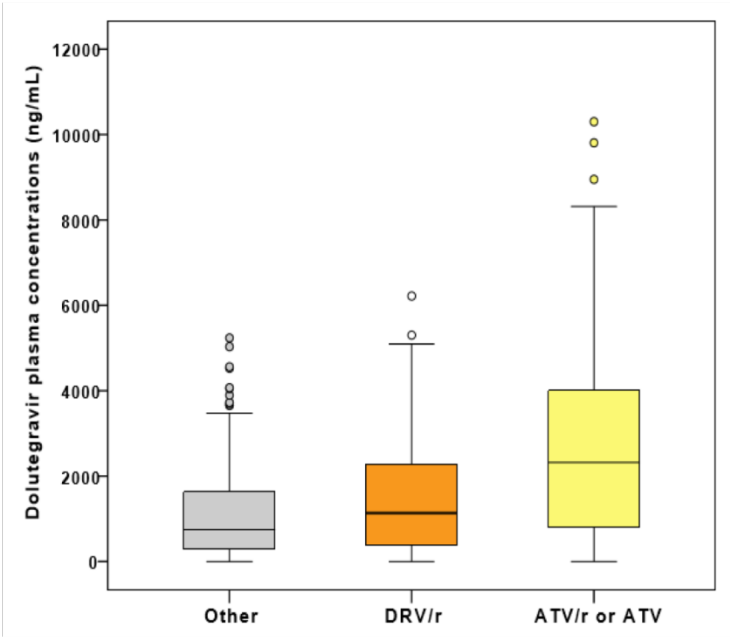
CSF drug levels may change over time

- PK Study. 363 samples were available from 149 patients

Association between dolutegravir concentrations and age



Dolutegravir concentrations with Protease Inhibitors



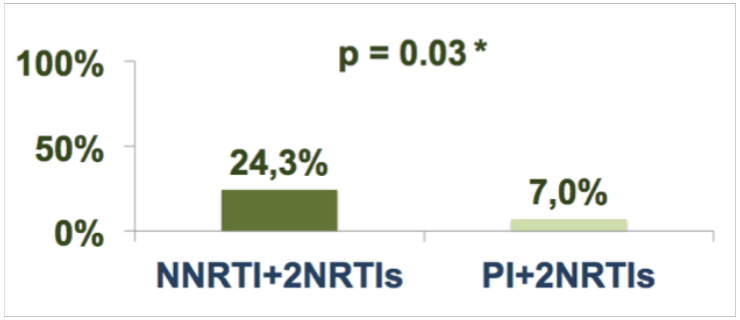
Calcagno A et al. HIV Glasgow 2016. P304

In-vivo evidence of neurotoxicity is limited - EFV

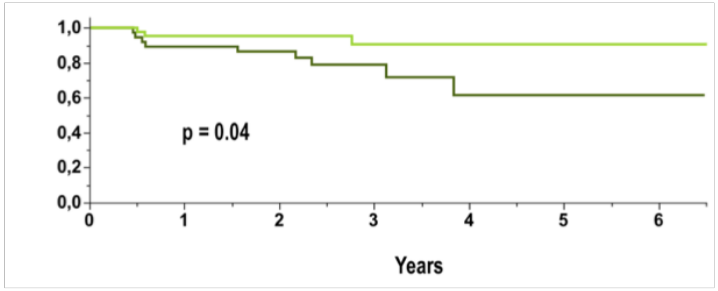
Baseline characteristics

	NNRTI + 2 NRTI (N=37)	PI + 2 NRTI (N=43)	
Edad, media (DS)	46.4 (8.8)	47 (8.3)	p 0 0.76
Educación, media (DS)	12.9 (2.2)	13 (2.3)	p = 0.87
Género: Masculino, N (%)	30 (81.1)	34 (79)	p = 0.83
Raza: Caucasico, N (%)	20 (54.1)	21 (48.8)	p = 0.83
Hepatitis C: HCV Ab+, N (%)	11 (29.7)	16 (37.2)	p = 0.48
SIDA: CDC, N (%)	25 (67.6)	35 (81.4)	p = 0.15
Años de infección VIH+ conocida, mediana (RIC)	8.7 (4.4-15.1)	13.8 (7.8-17.4)	p = 0.02
Sangre			
Nadir CD4, mediana (RIC)	180 (76-285)	93 (10-206)	p = 0.04
CD4 actuales, mediana (RIC)	512 (391-716)	428 (358-652)	p = 0.17
Carga viral de VIH >50 cop/mL en LCR, N (%)	0 (0)	2 (4.9)	p = 0.19
Deterioro neurocognitivo, N (%)	20 (54.1)	18 (41.9)	p = 0.28
Comorbilidades			p = 0.12
Incidentales, N (%)	17 (46)	29 (67.4)	
Contribuyentes, N (%)	15 (40.5)	12 (27.9)	
Confusoras, N (%)	5 (13.5)	2 (4.7)	
TAR			
CPE Vs. 2.0 (2010), mediana (RIC)	8 (7-9)	7 (6-8)	p = 0.04
Años de TAR, mediana (RIC)	4.7 (1.9-8.6)	6.3 (3.3-8.3)	p =0.27
ABC/3TC, N (%)	8 (21.6)	12 (27.9)	p = 0.43
TDF/FTC, N (%)	22 (59.5)	23 (53.5)	p = 0.71
AZT/3TC, N (%)	7 (18.9)	8 (18.6)	p = 0.55

Neurocognitive decline on NNRTI vs. PI ART



Time to decline on NNRTI vs. PI ART



Relative risk of declining on NNRTI vs. PI

NNRTI + 2 NRTIs: (PI + 2 NRTIs como referencia)	3.41 (95% CI: 1.02 – 11.93)

CONCLUSIONS

- **Patients on NNRTI (mainly efavirenz) decline faster than patients on PI-based ART**
- **Patients on NNRTI were more likely to decline than patients on PI-based ART**

Perez-Valero I. CROI 2014; Abstract 478.

In-vivo evidence of neurotoxicity is limited - DTG

HIV Neuropsychiatry

abstract 948

CROI

Unexpectedly High Rate of Intolerance for Dolutegravir in Real Life Setting

Guido van den Berk, Josephine Oryszczyn, Willem Blok, Narda van der Meche, Rosa Regez, Daoud Ait Moha, **Kees Brinkman**

dept internal medicin OLVG, Amsterdam, The Netherlands – k.brinkman@olvg.nl

	total (N=387)		naives(N=65)		non-naives (N=322)	
median age (IQR)	48		46	(22)	48	(13)
female	44	11,4%	8	12,3%	36	11,2%
dutch origin	136	35,1%	28	43,1%	108	33,5%
median CD4/mm3 (IQR)	650		530	(395)	655	(345)
median DGV days (IQR)	220		196	(147)	221	(148)
DGV separate..	156		15		141	
DGV in STR..	231		50		181	
DGV stopped	62	16,0%	13	20,0%	49	15,2%
median DGV days (IQR)	78		81	(71)	75	(99)
female	5	11,4%	3	37,5%	2	5,6%
DGV separate	24	15,4%	1	6,7%	23	16,3%
DGV in STR	38	16,6%	12	24,0%	26	14,4%

p

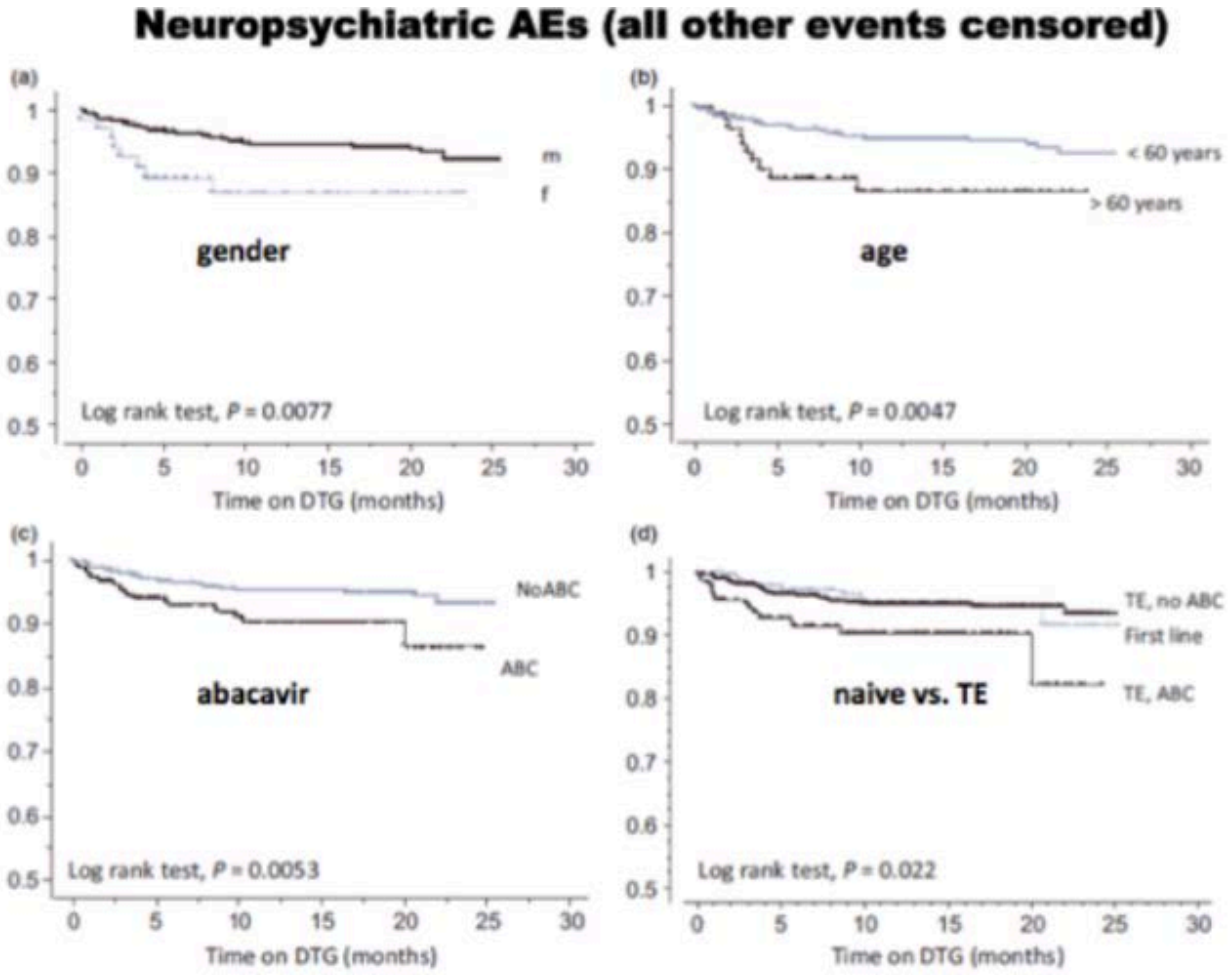
reason for interruption

other than toxicity*	6	9,7%	1	7,7%	5	10,2%
toxicity	56	90,3%	12	92,3%	44	89,8%
sleeping..	19	31,3%	5	38,5%	14	28,6%
gastro-intestinal..	18	29,5%	4	30,8%	14	28,6%
neuro-psychiatric..	12	19,7%	3	23,1%	9	18,4%
paresthesia..	6	9,7%	0	0,0%	6	12,2%
headache..	8	12,9%	0	0,0%	8	16,3%
fatigue..	9	14,6%	1	7,7%	8	16,3%
allergy..	1	1,7%	1	7,7%	0	0,0%
other..	5	8,2%	1	7,7%	4	8,2%

*LTFU, HBV protection, insurance, induction, patient request, interaction

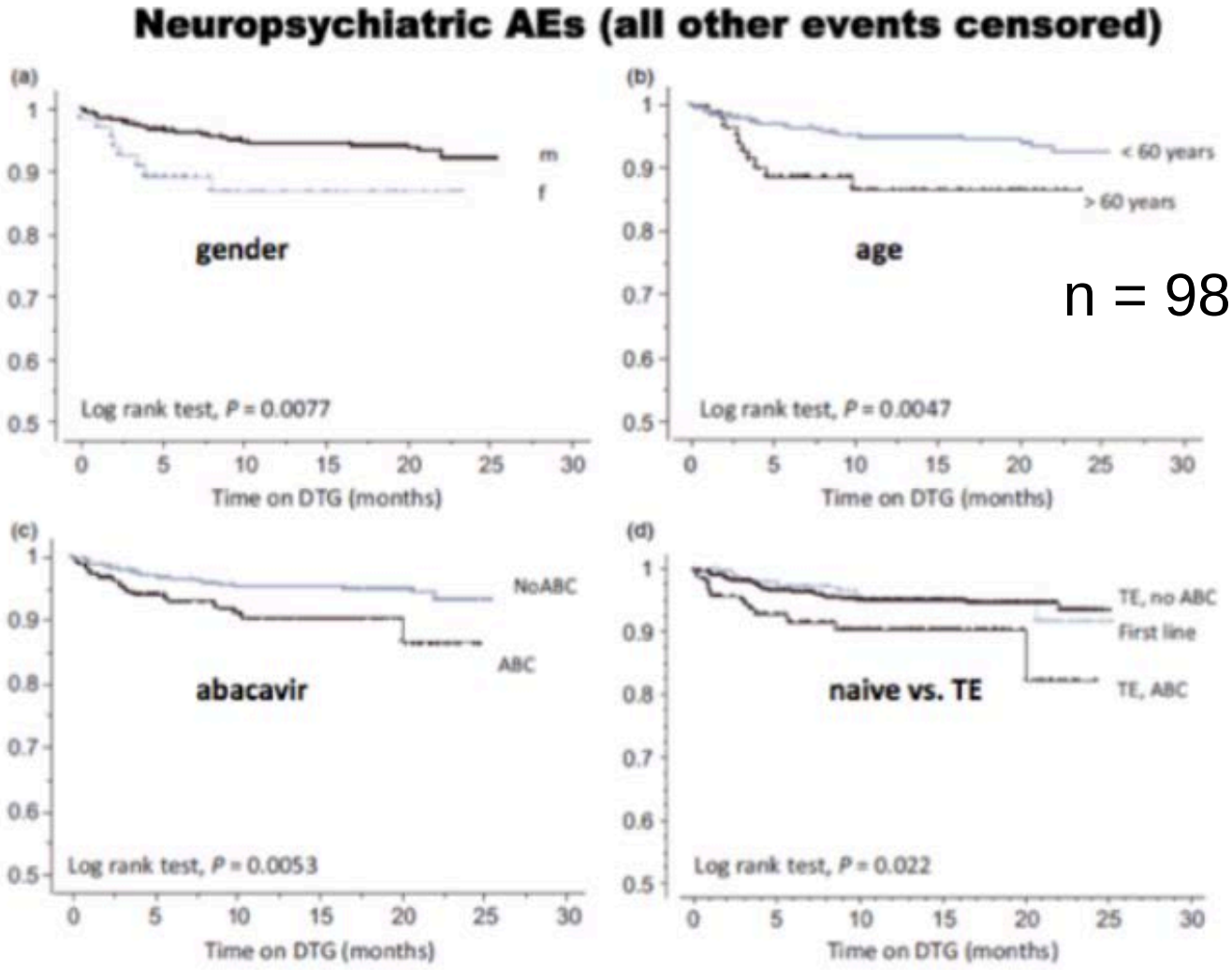
Van der Berk G et al. CROI 2016. Abstract 948

Probably because host predisposition is needed



Sabrinski M et al. HIV Glasgow 2016

High Rates of CNS AE leading to DTG discontinuation in Women and older patients



n = 985

Sabrinski M et al. HIV Glasgow 2016

But its consequences may be important

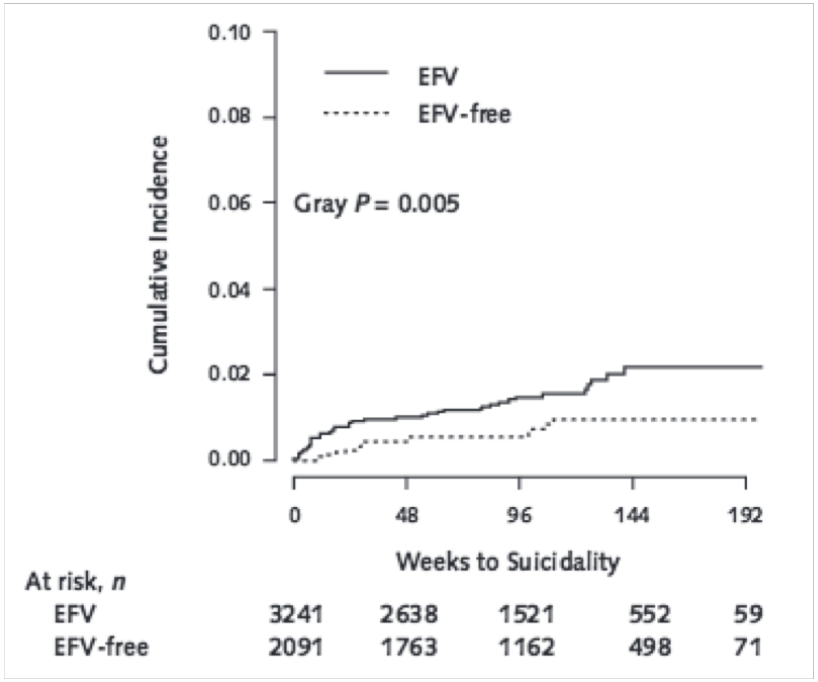
Annals of Internal Medicine | ORIGINAL RESEARCH

Association Between Efavirenz as Initial Therapy for HIV-1 Infection and Increased Risk for Suicidal Ideation or Attempted or Completed Suicide

An Analysis of Trial Data

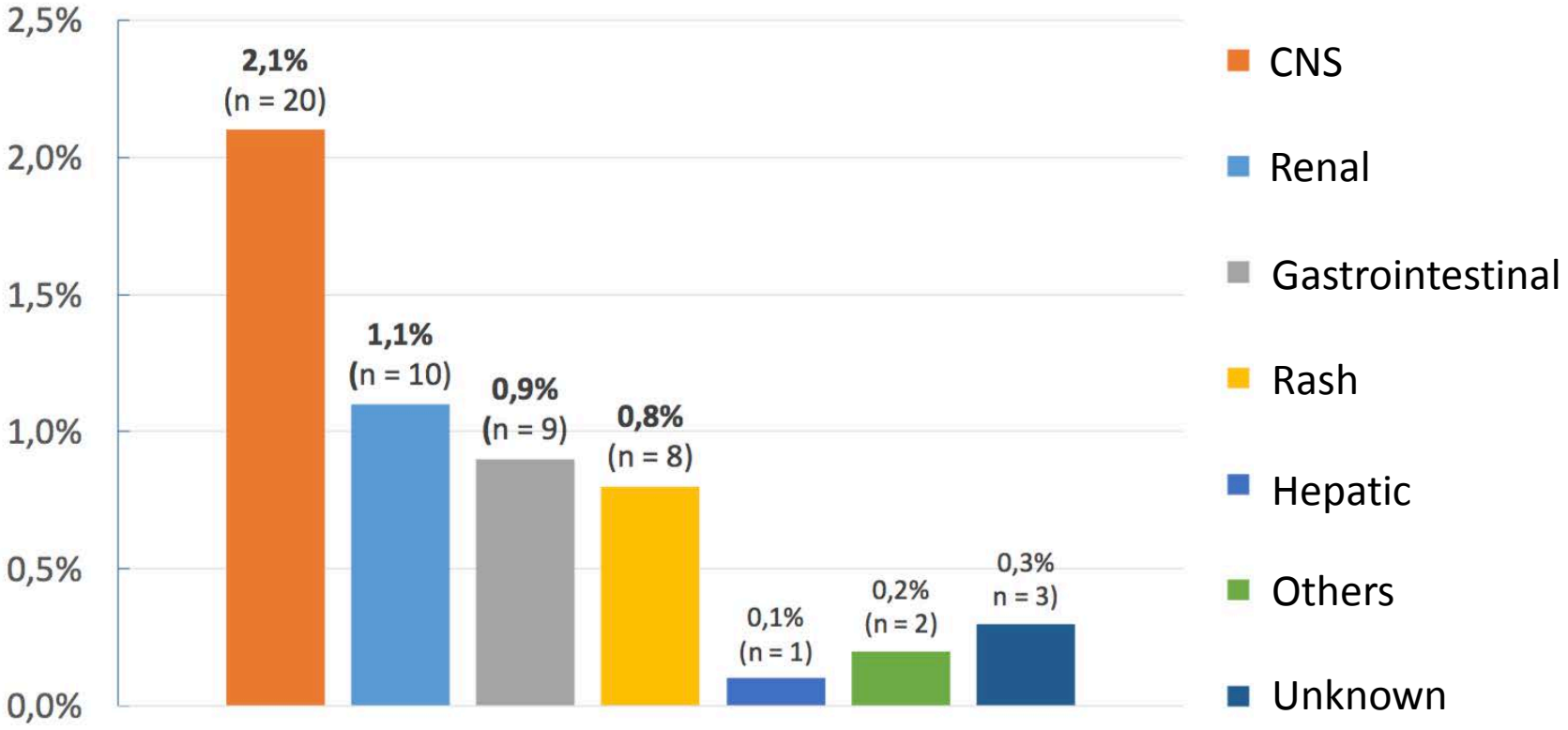
Table 1. Summary of Included Studies*

Study	Participants Receiving EFV-Containing Regimen, *n*
A5095	Total: 765 EFV + ZDV/3TC/ABC: 383 EFV + ZDV/3TC: 382
A5142	Total: 502 EFV + 3TC + NRTI§: 250 EFV + LPV/r: 252
A5175	Total: 1045 EFV + 3TC/ZDV: 519 EFV + FTC/TDF: 526
A5202	Total: 929 EFV + FTC/TDF: 464 EFV + 3TC/ABC: 465
Total	3241



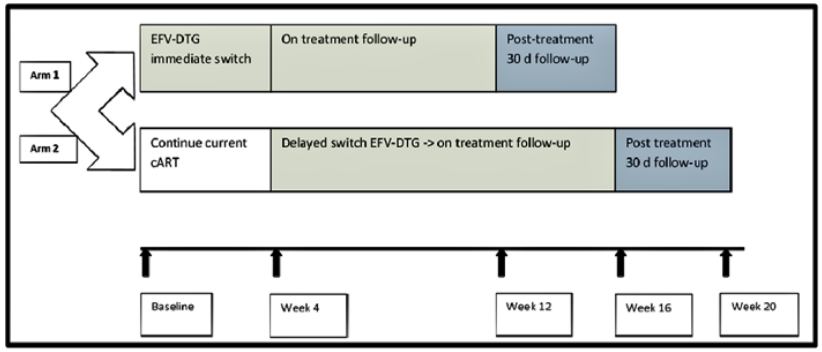
And a main reason for ART Switch

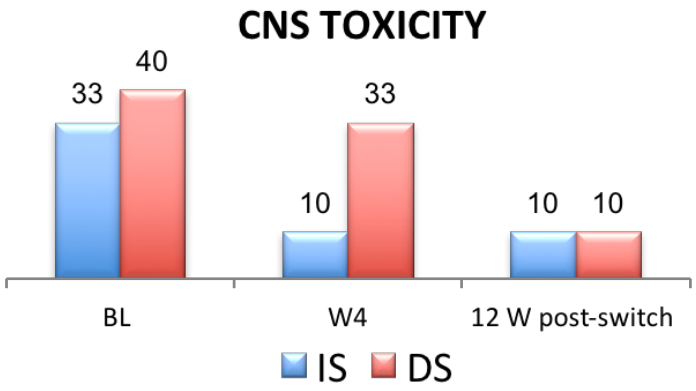
Reasons for first-line ART discontinuation due to AE in CORIS (2014–2015)

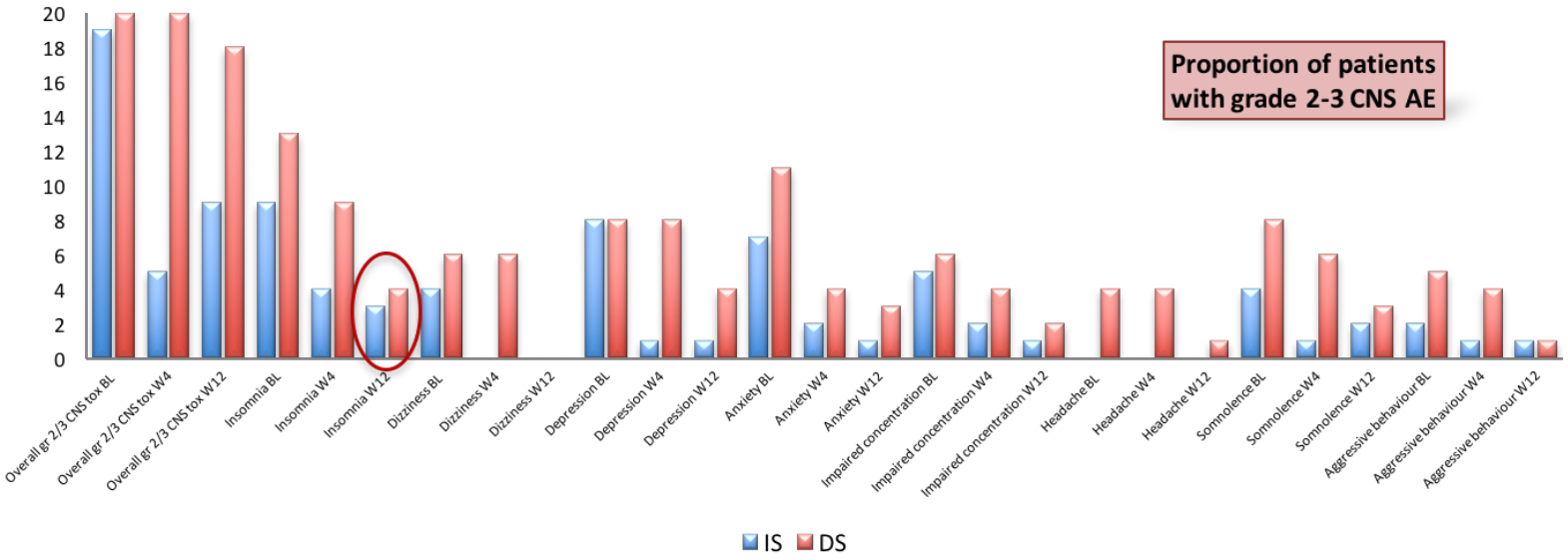


Jarrin I, et al. GESIDA 2016; CO-09

The problem is we unknown about reversibility

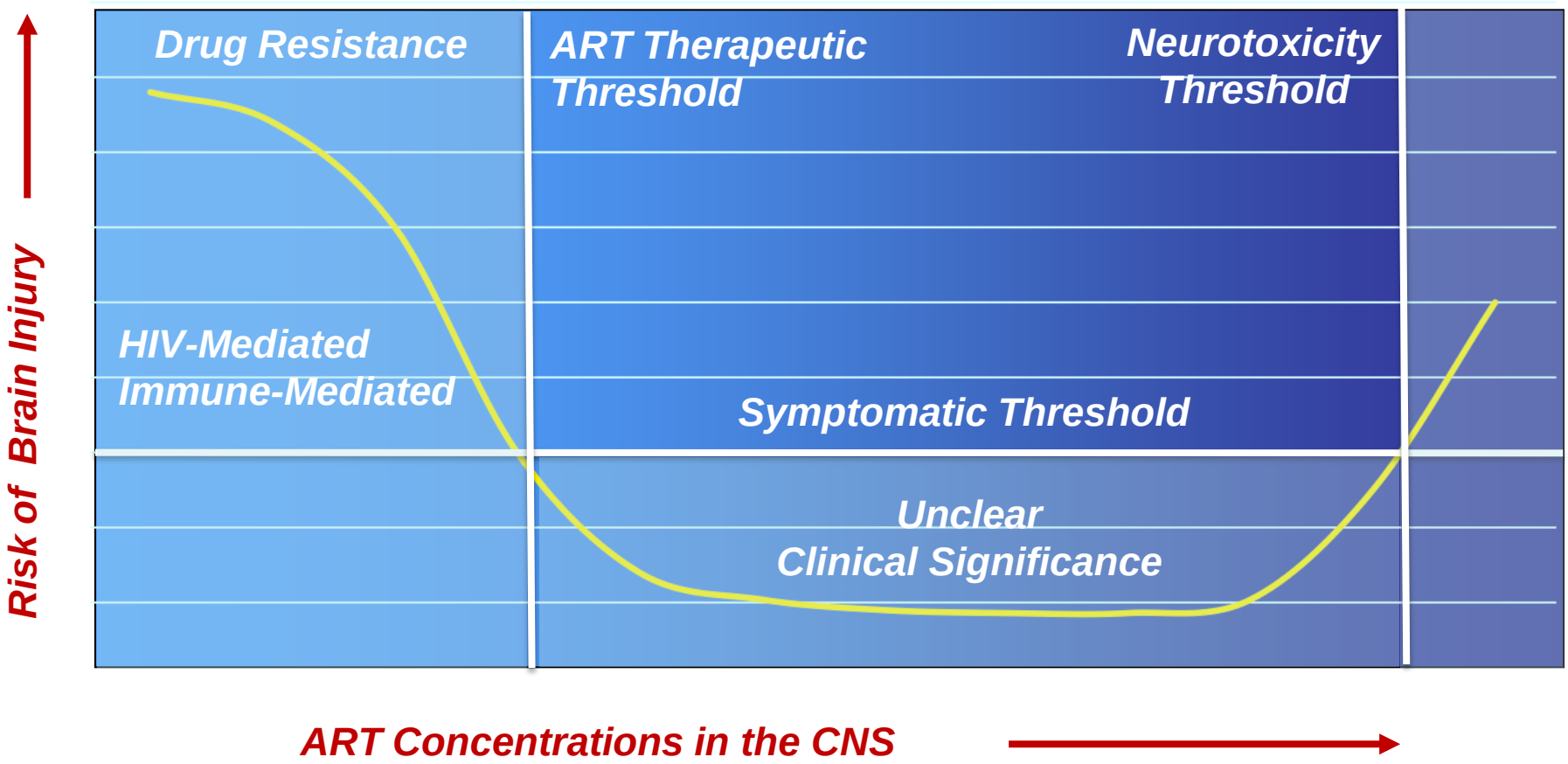






AE, adverse event; BL, baseline; DS, Delayed switch; IS, inmediate switch.
Bracchi M et al. HIV Glasgow 2016. P209

We need ART to be balanced



Personal Slide Courtesy of S. Letendre

Take Home Messages

HIV Neuropsychiatry

- Be on ART (early) is important to protect the CNS.
- ART is not able to control and reverse all brain damage produced during the HIV infection.
- In addition, other comorbidities may produce CNS damage in patients on ART.
- And, diagnostic methods used to evaluate the effect of ART on the CNS are inaccurate.
- High intensity CSF suppression doesn't seem to be important for all patients (but is important for some)
- CNS benefits of ART may diminish in presence of ART-related neurotoxicity.