

ARROW MEETING

CSF HIV ESCAPE

Myth or Reality

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Disclosures

Honoraria for advisory boards or lectures from:

- Gilead Sciences
- VIIV Healthcare
- Merck & Co
- Bristol-Myers Squibb
- Janssen Cilag

What is CSF Viral Escape?

- **Most common definition:**

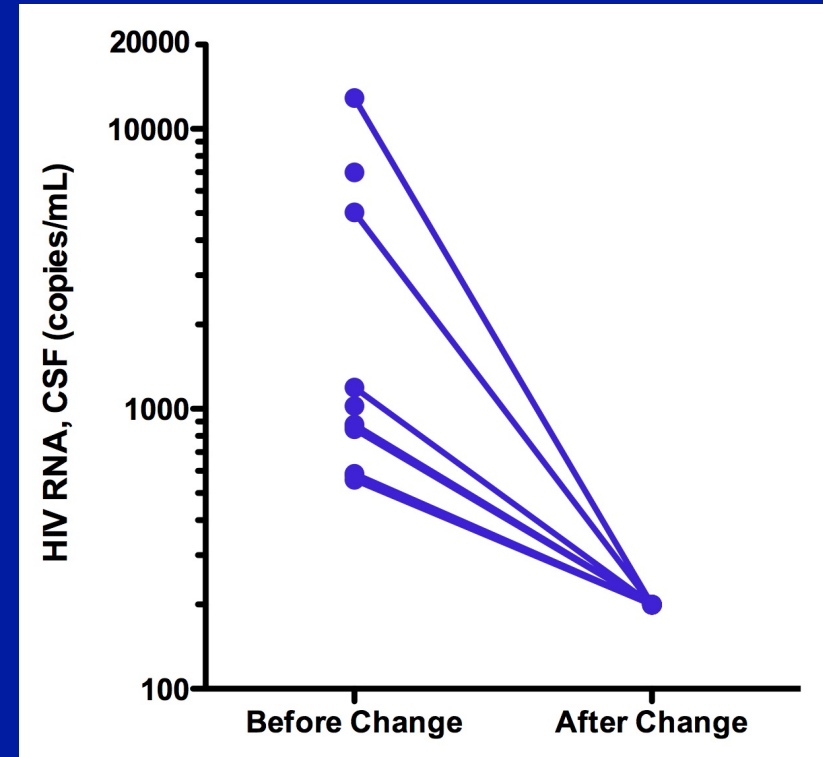
HIV RNA $>$ LLQ in CSF when \leq LLQ in blood on ART for more than 6 months

- **Composite definitions are sometimes used:**

HIV RNA in CSF more than 0.5 or 1.0 \log_{10} above levels in blood when HIV RNA in blood are $>$ LLQ on ART

Case Series from Paris Raised Awareness of CSF Viral Escape

- 11 patients with **new neurological symptoms** and CSF viral 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 log₁₀ c/mL greater than plasma HIV RNA

CSF HIV Escape was also observed in asymptomatic HIV patients

69 patients included between 2002-2010

Characteristic	CSF viremic (<i>n</i> = 7)	CSF aviremic (<i>n</i> = 62)	<i>P</i>
Age, years	46 (36–64)	45 (22–71)	NS
Male sex, no. (%) of patients	4 (57)	45 (73)	NS
CD4 cell count, × 10 ⁶ cells/L	620 (400–810)	525 (390–642)	NS
CD4 nadir, × 10 ⁶ cells/L	133 (40–200)	150 (68–213)	NS
CSF HIV-1 RNA level, copies/mL	121 (54–213)	<50	
CPE rank	1.6 ± 0.5	1.7 ± 0.6	NS
CPE-2010 rank	7.3 ± 0.76	7.4 ± 1.23	NS
CSF neopterin level, nmol/L	9.2 (6.6–16.2)	5.1 (4.4–8.4)	.03
Plasma neopterin level, nmol/L	7.2 (6.1–8.0)	7.6 (5.1–10.3)	NS
WBC count, × 10 ⁶ cells/L	1 (1–6)	1 (1–3)	NS
Time on ART, months	77 (67–101)	35 (17–59)	.002

What is the significance of CSF Viral Escape?

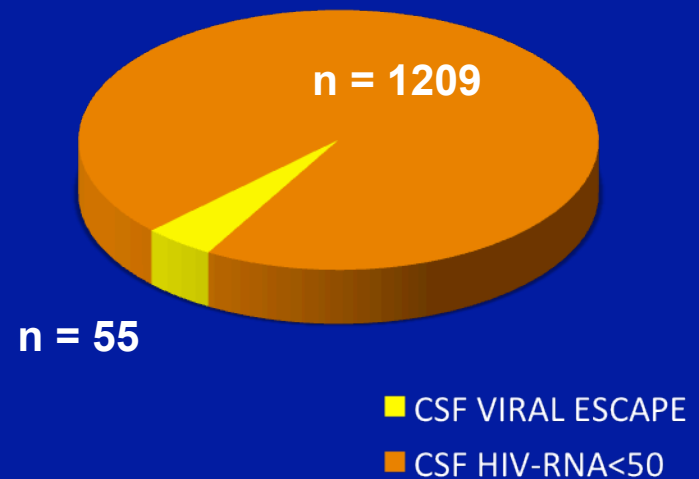
- Is CSF HIV Escape a prevalent condition?
- May I identify factor associated with CSF HIV Escape?
- Is it associated with worse neurocognitive performance?

Prevalence of CSF HIV Escape in CHARTER

1264 volunteers included: CHARTER (675) & HNRP (589)

Characteristics	Total (n=1264)
Age (years), $X \pm SD$	46 \pm 9
Gender (Male), n (%)	1021 (82)
Race (Caucasian), n (%)	615 (49)
Years of education, $X \pm SD$	13 \pm 3
Years since HIV diagnosis, $X \pm SD$	13 \pm 7
CD4 nadir, median (IQR)	129 (26-240)
AIDS diagnosis, n (%)	816 (70)
HCV Ab+, n (%)	793 (22)
Years on ART, median (IQR)	6 (3-10)
Adherence >95% (4 days), n (%)	1044 (91)
Neurocognitive impairment, n (%)	468 (38)

Prevalence of CVE
4.4% (3.4-5.6%)*



* 95% CI

Prevalence of CSF HIV Escape

First Author	Sample Size	Design	% CNS VE
Rawson ¹	69	C-S	13%
Cusini ²	60	C-S	6.7%
Edén ³	69	C-S	10%
Perez-Valero ⁴	1,264	C-S	4.4%
Pinnetti ⁵	303	C-S	10.6%
Nightingale ⁶	145	C-S	13%
Weighted Median	1910		6.5%

¹Rawson et al, Journal of Infection (2012) 65, 239e245; ²Cusini et al, J Acquir Immune Defic Syndr 2013,62:28–35; ³Eden et al, J Infect Dis 2010, 202(12):1819–1825; ⁴Perez-Valero et al, J Intl AIDS Soc 2012, 15(Suppl 4):18189; CROI 2014; ⁵Pinnetti et al, No. 443; ⁶Nightingale et al, No. 1023

Case series/reports: Canestri et al, CID 2010; Peluso et al, AIDS 2012; Khoury et al, J Neurovirol 2013

Factors associated with CSF HIV Escape in CHARTER

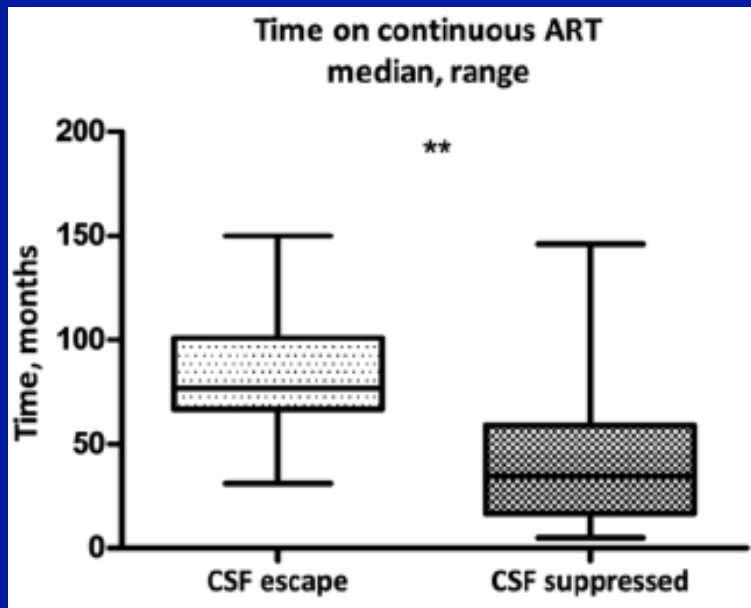
Results of the multivariable logistic regression model*

Variable	Risk direction	p Value
Duration of HIV infection	Longer	0.01
Platelets level	Higher	0.01
Protein level in serum	Higher	0.04
CSF pleocytosis (<i>WBC</i> ≥ 5 cells)	Present	< 0.01
Regimen type	PI/r Use	0.01
	ATV Use	< 0.01

* Non-significant variables included in the model were CSF proteins, ALT, NNRTI use, AIDS, and CD4 nadir.

Factors associated with CSF HIV Escape in other Cohorts

	CV LCR >50	CV LCR <50	
BLIPS	2,5 (1-4)	0 (0-1)	p=0,001
>1 Interruptions	5 (71%)	8 (15%)	p<0,01
Months on HAART	77 (67-101)	35 (17-59)	p=0,002
Months of ART	100 (80-183)	38 (18-63)	p<0.001



Drug	CSF viral escape, no. (%) of subjects	Total, no. of subjects
Efv	4 (15)	27
Lpv/r	1 (5)	21
Atv/r	2 (10)	21
Tdf	3 (9)	34
Abc	4 (22)	18
Zdv	0 (0)	17
3TC	4 (10)	43
FTC	3 (12)	26

Factors associated with CSF HIV Escape in other Cohorts

Multivariable logistic regression model				
Dependent variable: CSF viral escape				
	Adjusted odds ratios	(95%CI)		P-value
Male gender vs female	0.26	0.07	0.94	0.039
CD4 count at sample, cell/mm ³				
0-200	1.00			
201-350	0.25	0.08	0.83	0.023
>350	0.28	0.07	1.13	0.074
Calendar year of sample				
1999-2003	2.10	0.43	10.29	0.360
2004-2008	1.00			
2009-2013	0.09	0.02	0.41	0.002
Nucleoside analogues in the current regimen				
tdf+ftc	1.00			
tdf+3tc	1.52	0.33	7.11	0.592
abv+3tc	3.52	1.02	12.18	0.047
azt+3tc	1.49	0.16	13.96	0.727
other NRTI combinations	0.94	0.20	4.27	0.931
Third drug in the current regimen				
EFV	1.00			
LPV/r	1.44	0.32	6.47	0.638
ATV/r	12.71	2.33	69.22	0.003
DRV/r	N.E.*	-	-	-
Other	0.79	0.15	4.14	0.782
Months of current cART (per each month more)	1.00	0.97	1.03	0.917

*N.E. due to lack of CVE in pts treated with DRV/r

Factors associated with CSF HIV Escape

First Author	Sample Size	% CNS VE	Factors associated	
Rawson ¹	69	13%	-	↓ CPE*
Cusini ²	60	6.7%	CSF inflammation	↓ CPE
Edén ³	69	10%	CSF inflammation ART duration	---
Perez-Valero ⁴	1,264	4.4%	CSF Inflammation HIV duration	PI/r Use ATV Use
Pinnetti ⁵	303	10.6%	CD4 account	ATV/r Use ABC+3TC Use
Nightingale ⁶	145	13%	-	Lower [DRV]

* Patients with HIV

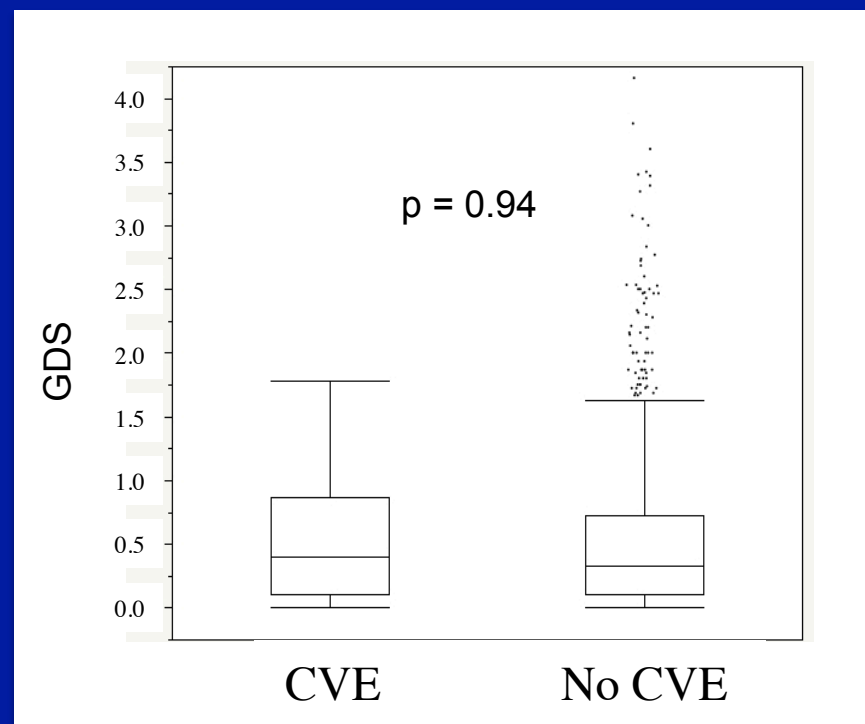
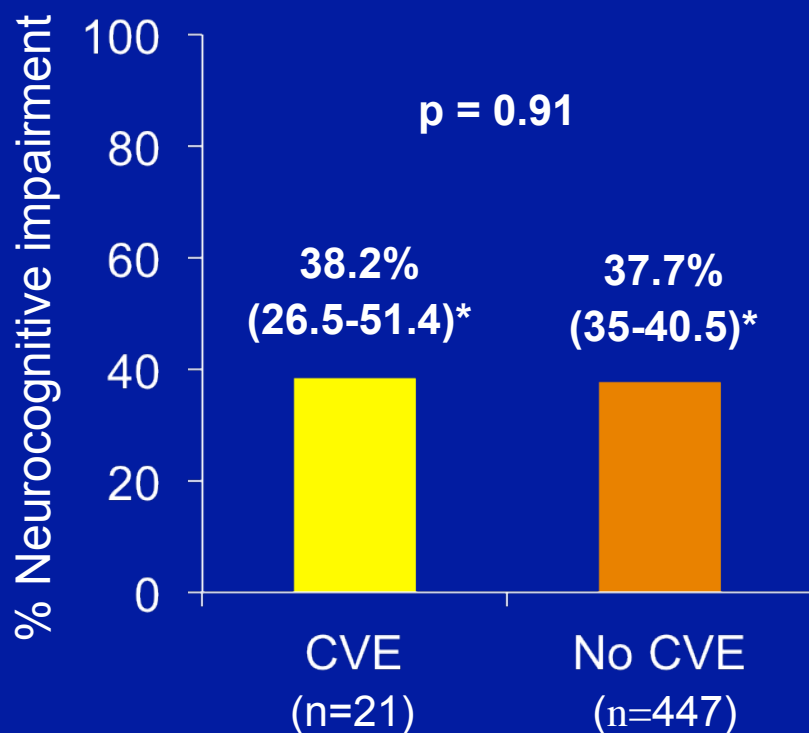
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Case series/reports: Canestri et al, CID 2010; Peluso et al, AIDS 2012; Khoury et al, J Neurovirol 2013

Is CSF HIV Escape associated with Neurocognitive Impairment?

Frascati criteria¹

Global deficit score²



1. Antinori et al. Neurology 2007;69(18):1789-99

2. Carey CL et al. J Clin Exp Neuropsychol. 2004;26(3):307-19.

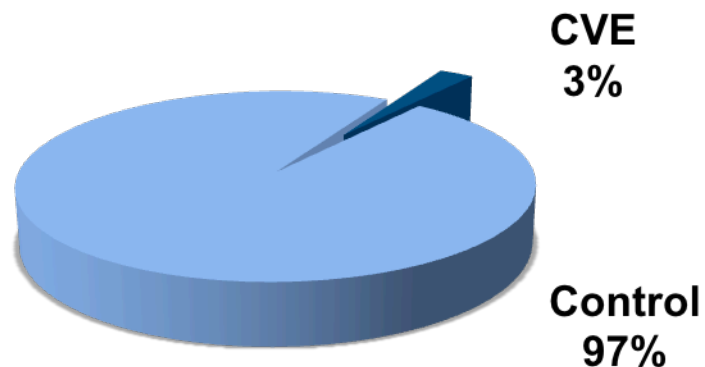
* 95% CI

What is the Significance of CSF Viral Escape?

- Is CSF HIV Escape incidence high?
- Are all patients presenting CSF HIV Escape similar?
- May I predict patients at risk of presenting CSF Escape?
- Is it associated with neurocognitive decline?

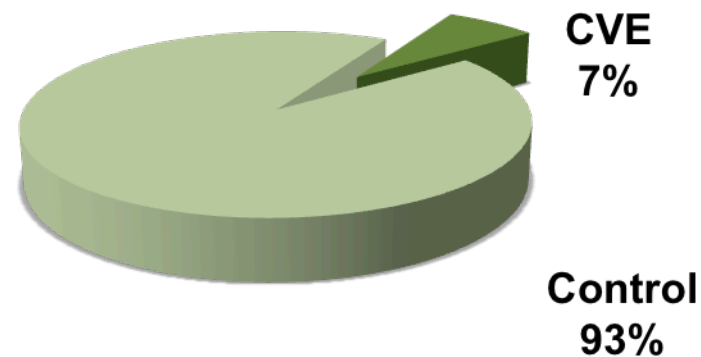
Longitudinal CSF HIV Escape CHARTER Analysis

INDIVIDUALS



N = 849

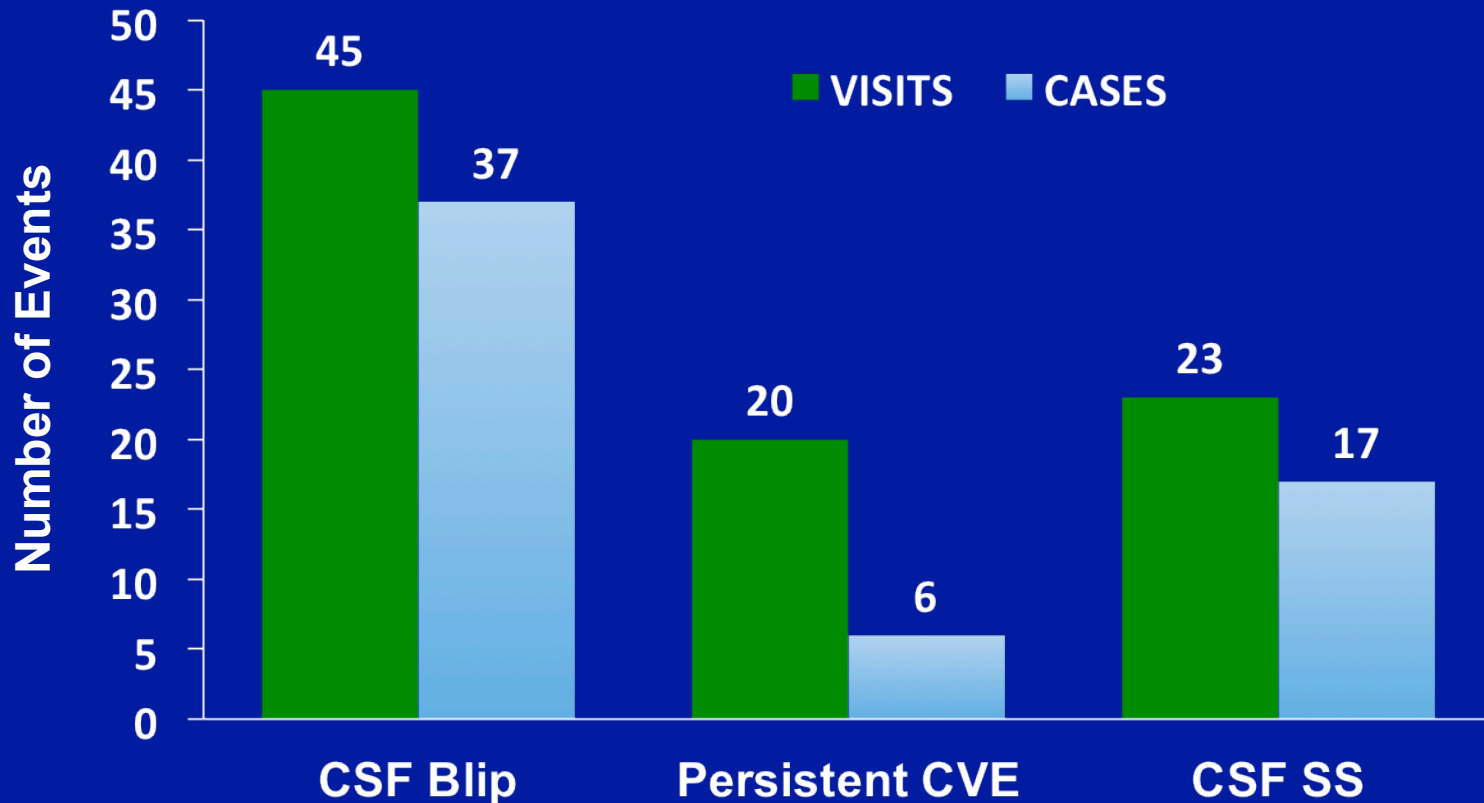
VISITS



N = 3392

Median time of follow up: 2.5 years (IQR 1-4.8)

We observed 3 different forms of CSF HIV Escape

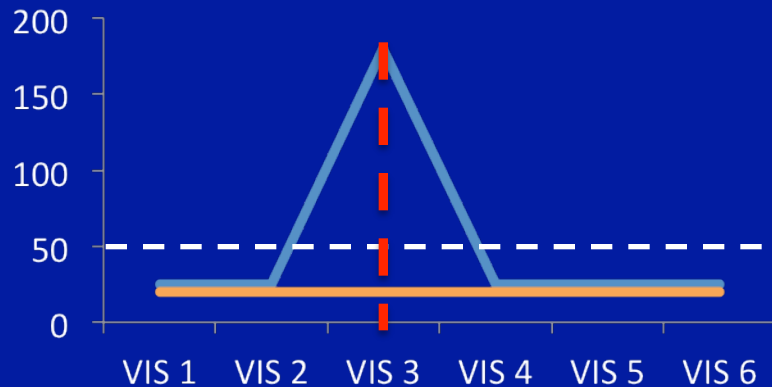


849 adults with 3,392 visits performed over a median of 2.5 years (IQR 1.0-4.8)

Different Forms of CSF Viral Escape

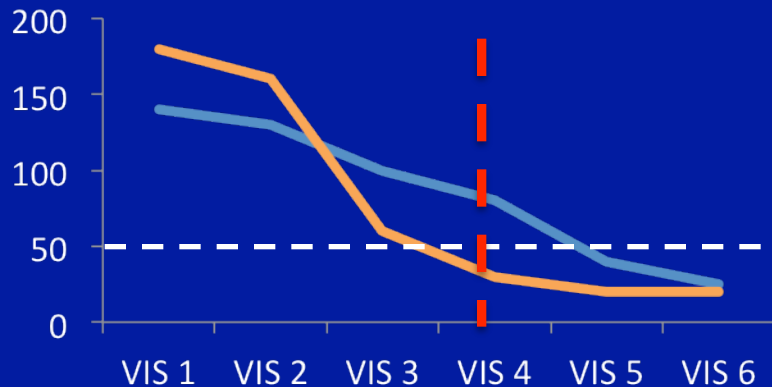
CSF Blip

Single occurrence of CVE while suppressed in plasma



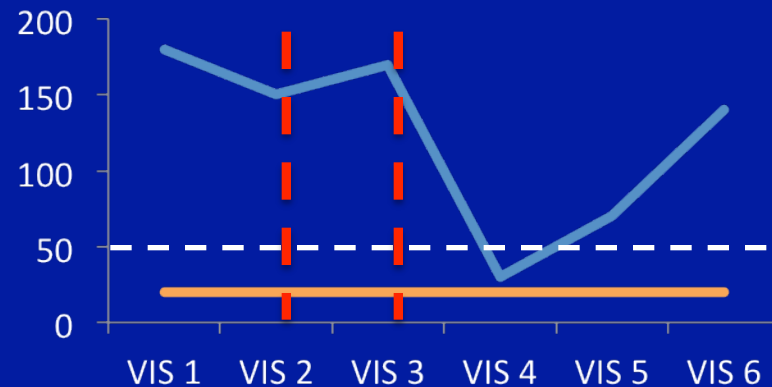
CSF Slow Suppression (SS)

CVE with preceding lack of suppression in plasma



Persistent CSF VE

≥ 2 consecutive CVE while suppressed in plasma



Incidence of CSF HIV Escape types in CHARTER

	Incidence per 1000 person-years
CSF Viral Escape (all types)	37.4
CSF Blips	19.1
CSF Slow Suppression	9.8
Persistent CSF Viral Escape	8.5

Risk factors for CSF HIV Escape in CHARTER

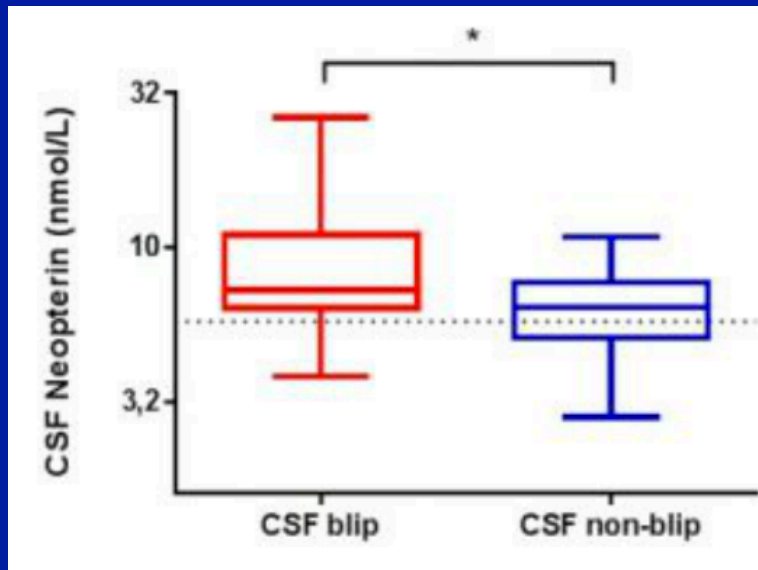
Multivariable mixed models

Variable	Risk direction	p Value
Plasma HIV RNA (0-50 cop/mL)	Higher	0.03
Protease inhibitor based ART	Present	0.02
CSF Pleocytosis (>5 WBC)	Higher	< 0.01

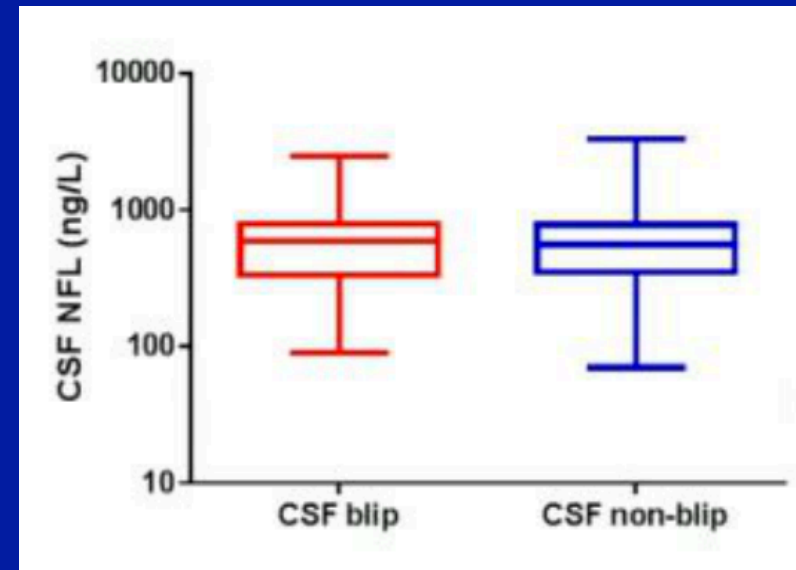
Incidence and risk factors of CSF Viral Escape in other cohorts

- 75 patients on effective ART (> 6 months) with ≥ 2 LP
- 23% CSF Blips
- 3% Persistent CSF Viral Escape

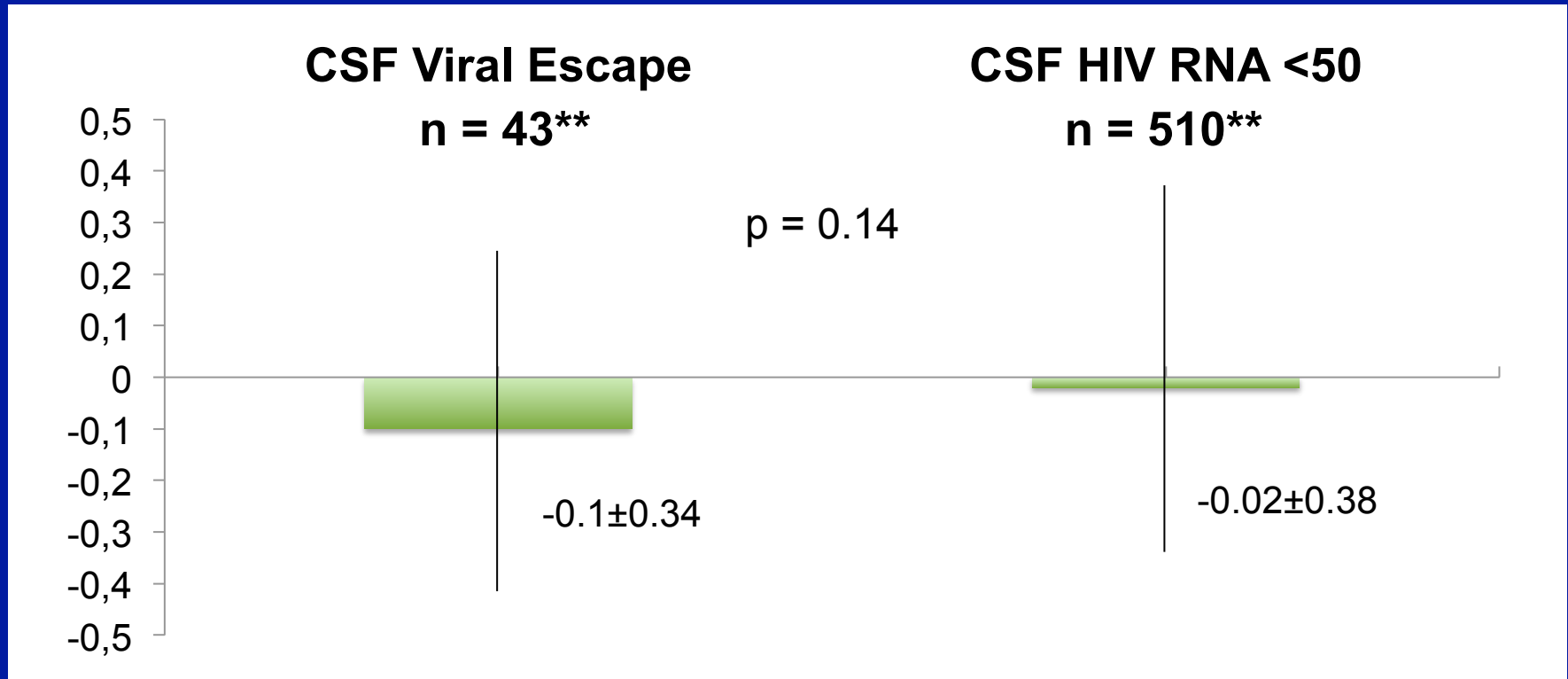
CSF Neopterin



CSF NFL



Neurocognitive evolution (by GDS change)* of patients presenting CSF HIV Escape



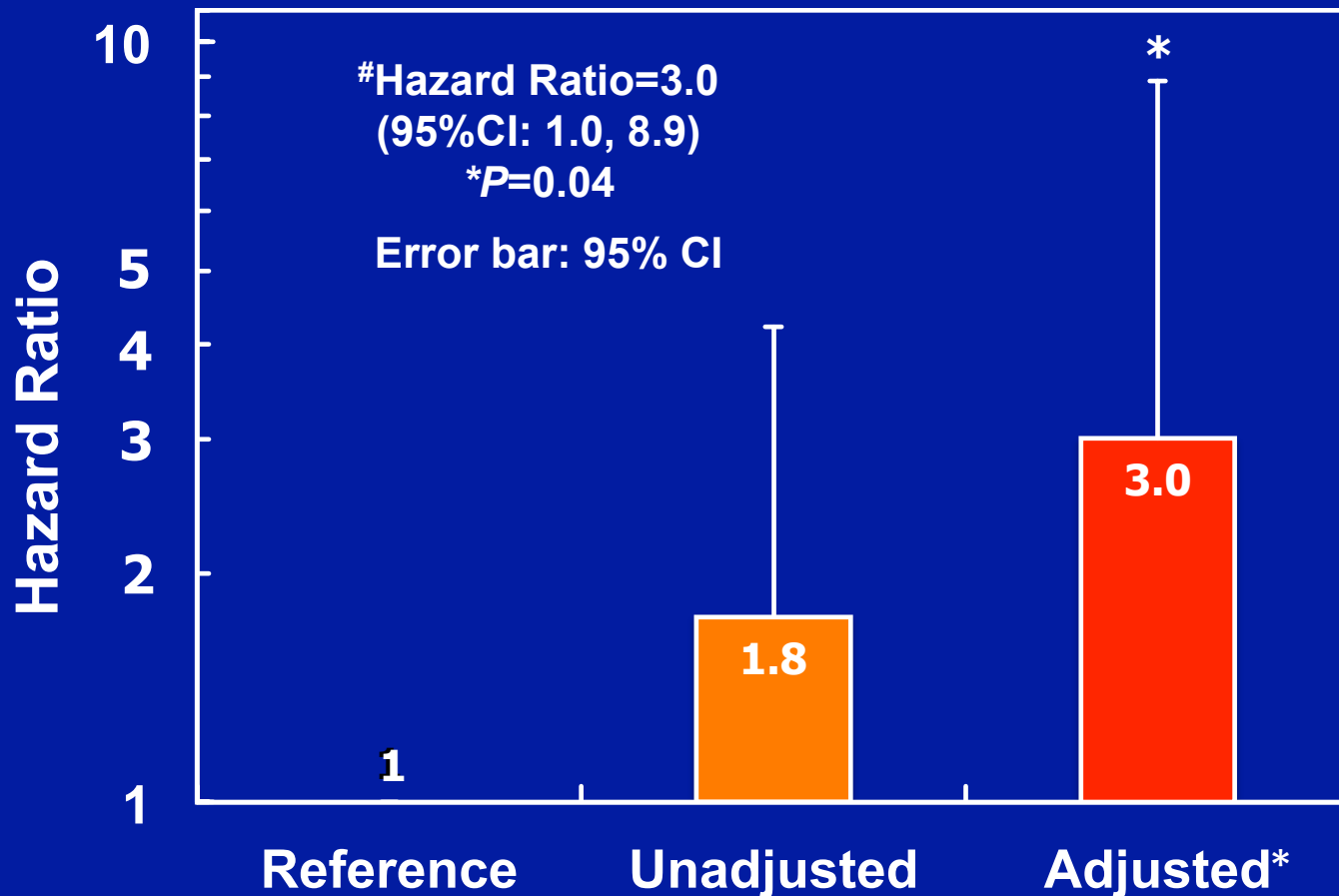
** Individuals with previous neurocognitive assessments were excluded.

* Carey CL et al. J Clin Exp Neuropsychol. 2004;26(3):307-19.

What is the Significance of CSF Viral Escape?

- Is CSF HIV Escape associated with worse clinical outcomes despite neurocognition?

CSF Viral Escape May Be Associated with Depression



*Adjusted for 4-day adherence, lifetime alcohol and substance use disorder, SSRI Use, Type of ART, and CPE

The CNS may be the source of ongoing HIV replication in patients incomplete viral suppression

**PLASMA HIV-RNA
CONTROLLED GROUP
(n=105)**

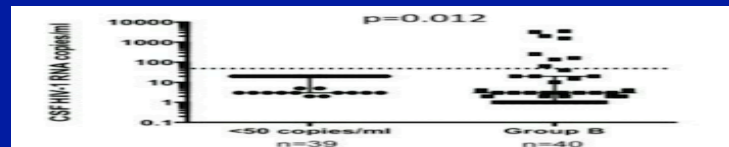
All CNS asymptomatic
with CV<50 c/mL

**PLASMA HIV-RNA
UNCOTROLED GROUP
(n=40)**

83% Blips (CV 66 c/mL)
17% LLV (CV 144 c/mL)

CSF/Plasma discordance > 1 log

0%



18%

Subject	Group	HIV-1 RNA copies/ml		ART at sampling	CSF resistance
		Plasma	CSF		
6	A	<40	422	ATZr/TDF/FTC	M184I
13	B	14	138	DRVr/FTC/TDF	M184I
15	B	48	2,028	DRVr/TDF/RAL	D67N K70R L74V L100I K103N M184V T215Y K219E Y143C
18	B	<40	162	DRVr/FTC/TDF	D67N, M184V, T215Y, K219Q, V108I, V82A

Unsolved questions regarding the significance of CSF Viral Escape?

- Is neuroactive ART important for preventing CSF HIV Escape?

On effective ART, CSF HIV escape ...

Was not associated with the CPE score in CHARTER

	p Value	OR (95% CI)
Protease inhibitors based ART (yes, taking PI)	0.015	21.69 (1.8-261.9)
CSF Pleocytosis (yes, WBC >5 cells/ml)	<0.001	21.6 (6.66-69.93)
Level of plasma HIV RNA within 0-50 cop/mL (per +10 count)	0.032	1.32 (1.02-1.69)

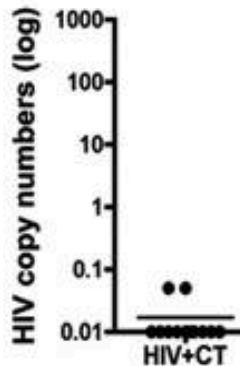
But it was in more selected samples. Why?

TABLE 5. Associations of Detectable HIV-1 VL in CSF With Various Cofactors

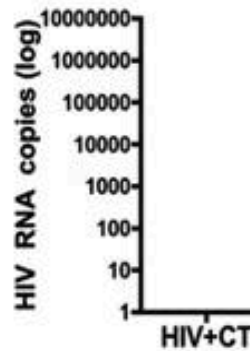
	CSFs With Undetectable VL (n = 83)	CSFs With Detectable VL (n = 4)	OR (95% CI)	P
CPE rank 2008, median (range)	2.3 (1.0–3.5)	1.0 (1.0–1.5)	0.048 (0.005 to 0.50)**	0.011
CPE rank 2010, median (range)	8 (5–12)	6 (6–8)	0.38 (0.17 to 0.87)**	0.022

Brain characteristic of patients without CNS infection

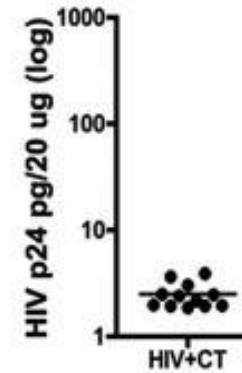
DNA



RNA

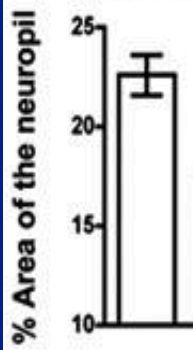


p24

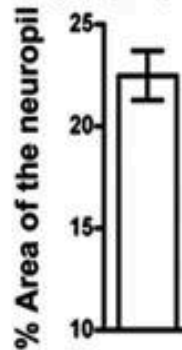


□ HIV+ CT
■ HIV+ Latent
■ HIVE

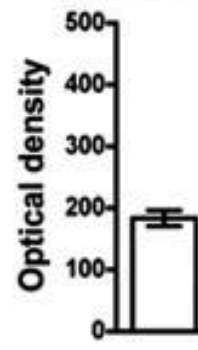
MAP2 (dendrites)



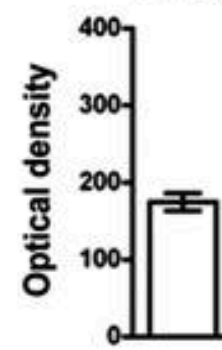
Synaptophysin (synapses)



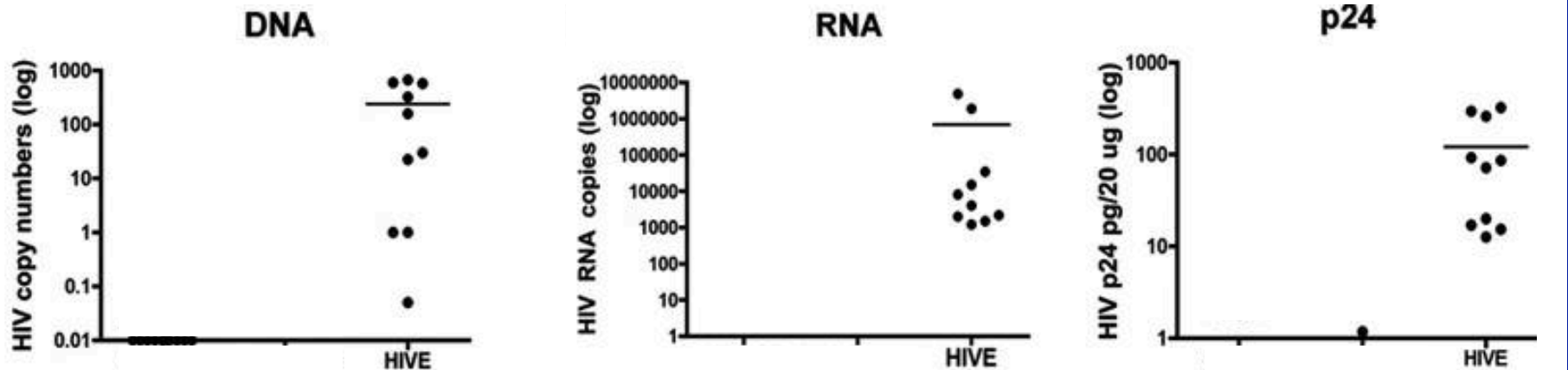
Iba-1 (microglia)



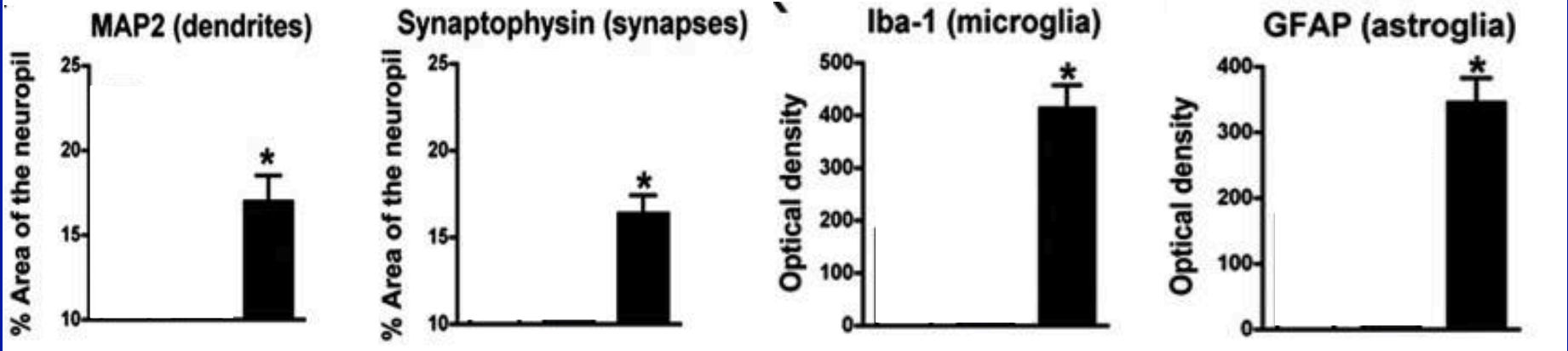
GFAP (astroglia)



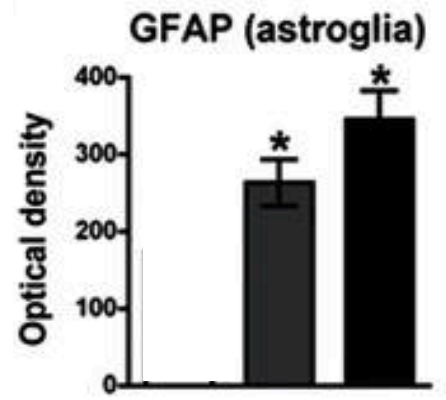
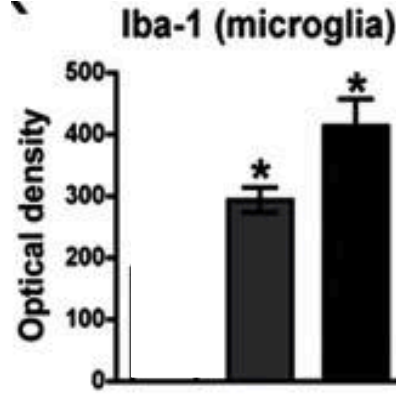
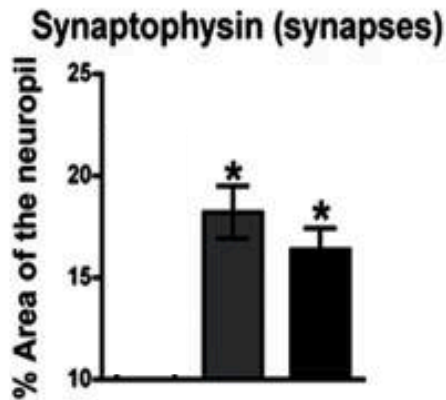
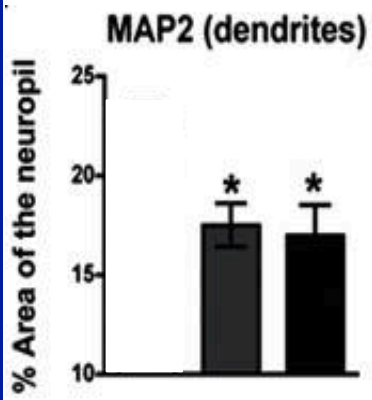
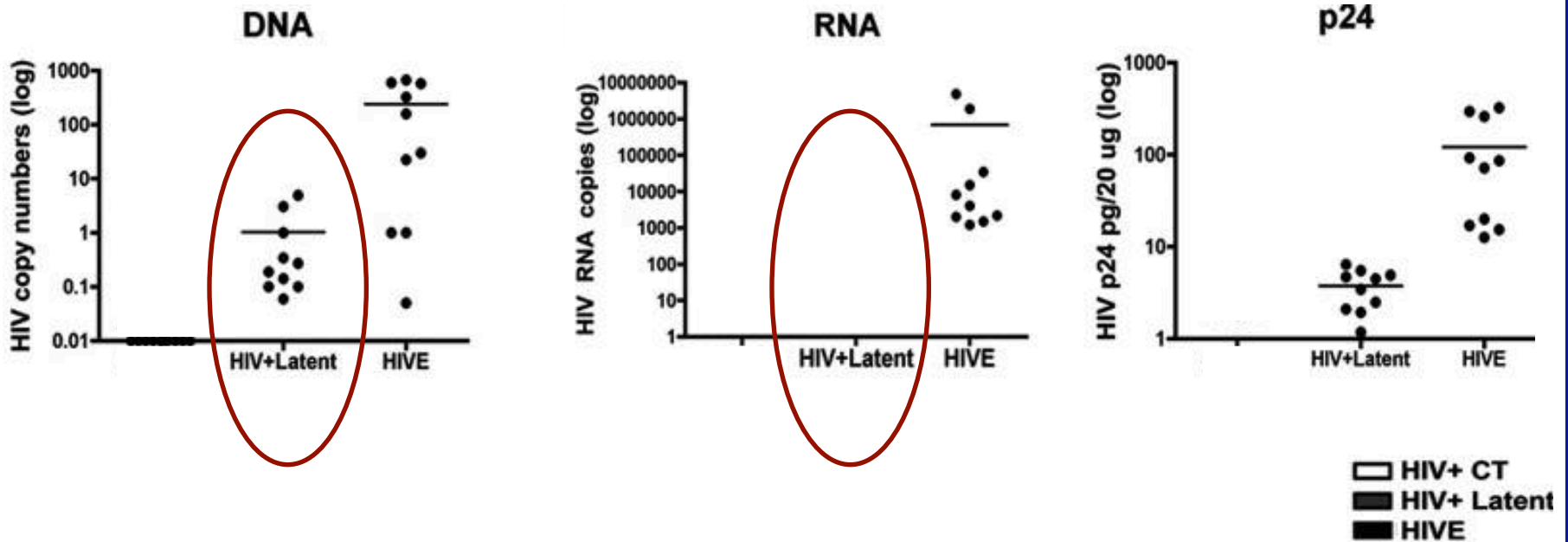
Brain characteristic of patients with CNS infection OFF ART



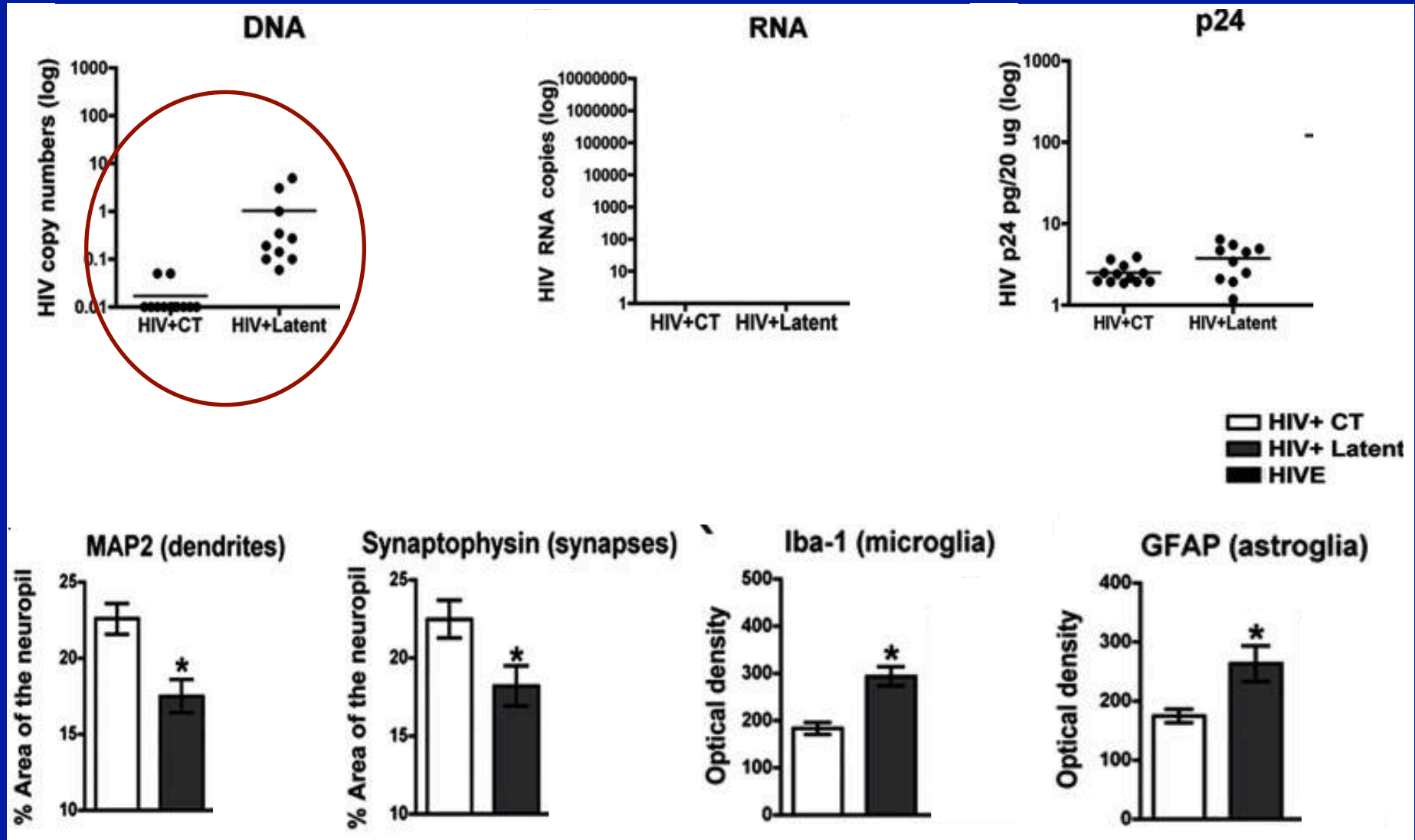
HIV+ CT
 HIV+ Latent
 HIVE



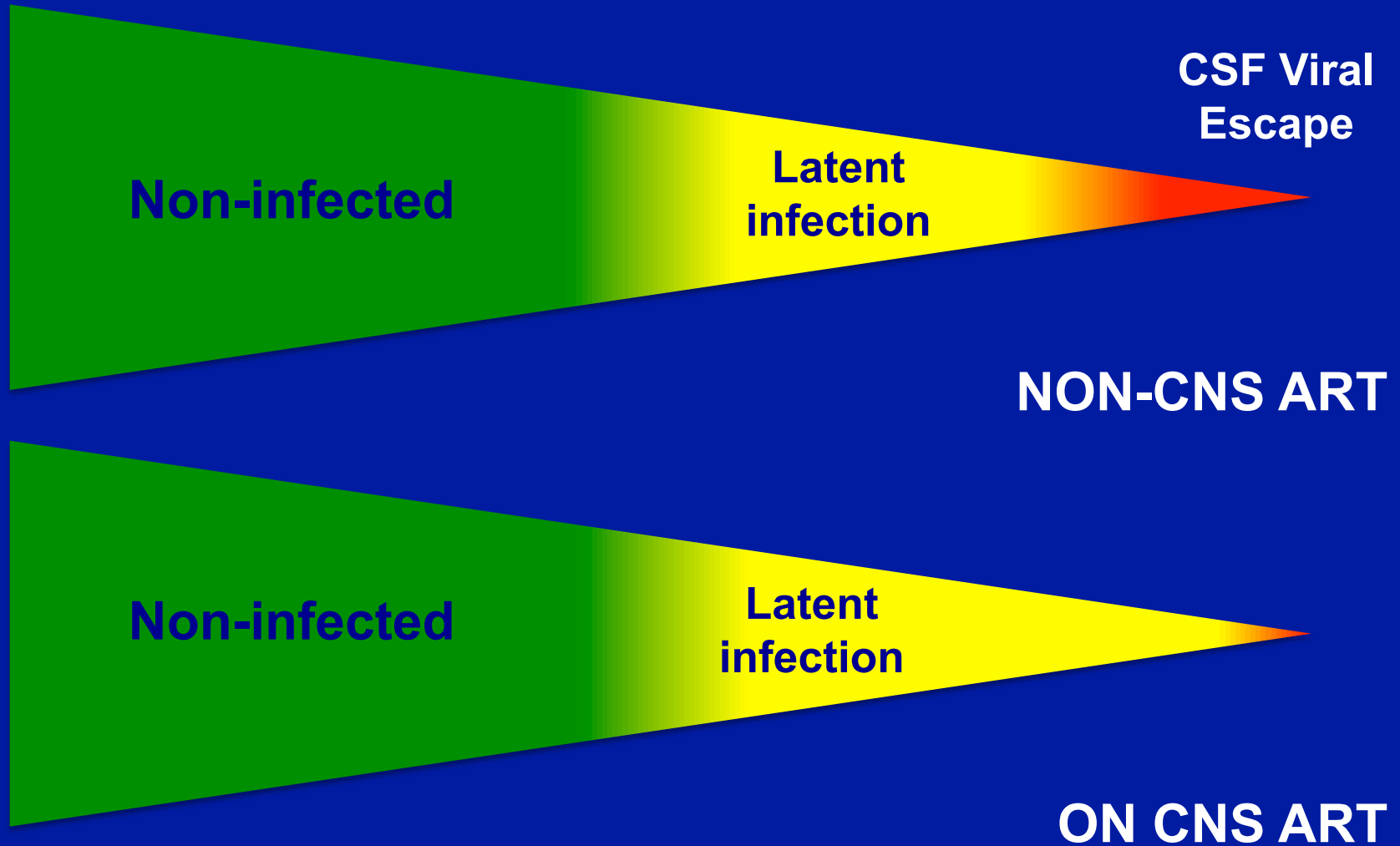
Brain characteristic of patients with CNS infection OFF and ON ART



Differences in brain characteristics of patients with and without CNS infection ON ART



Neuro-effective ART effect over HIV brain infection



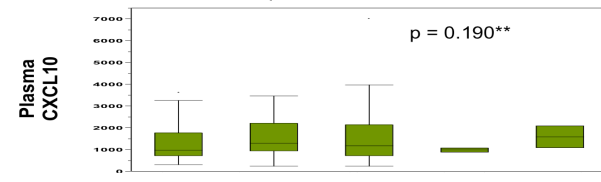
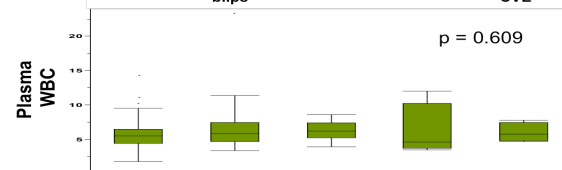
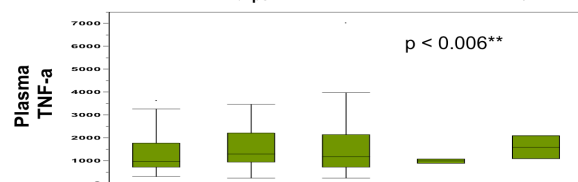
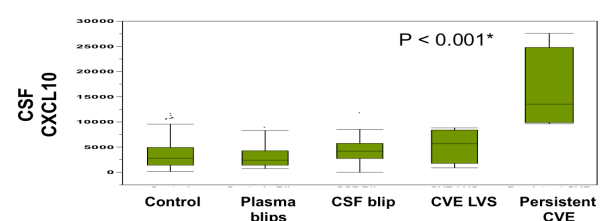
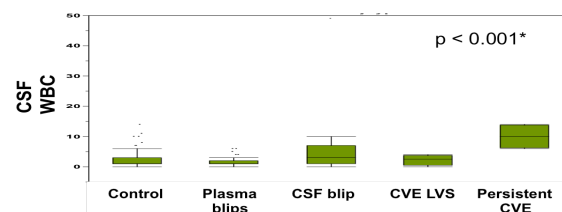
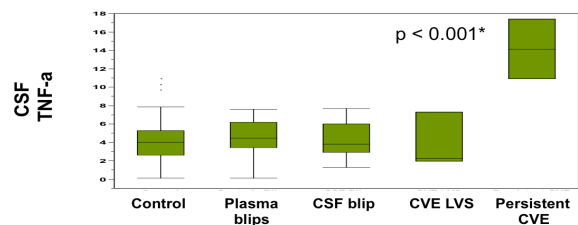
Unsolved questions regarding the significance of CSF Viral Escape?

- Is neuroactive ART important for preventing CSF HIV Escape?
- Have CSF blips and persistent CSF HIV Escape cases different inflammatory profiles?

CSF Biomarker profile in HIV patients with and without CSF Viral Escape

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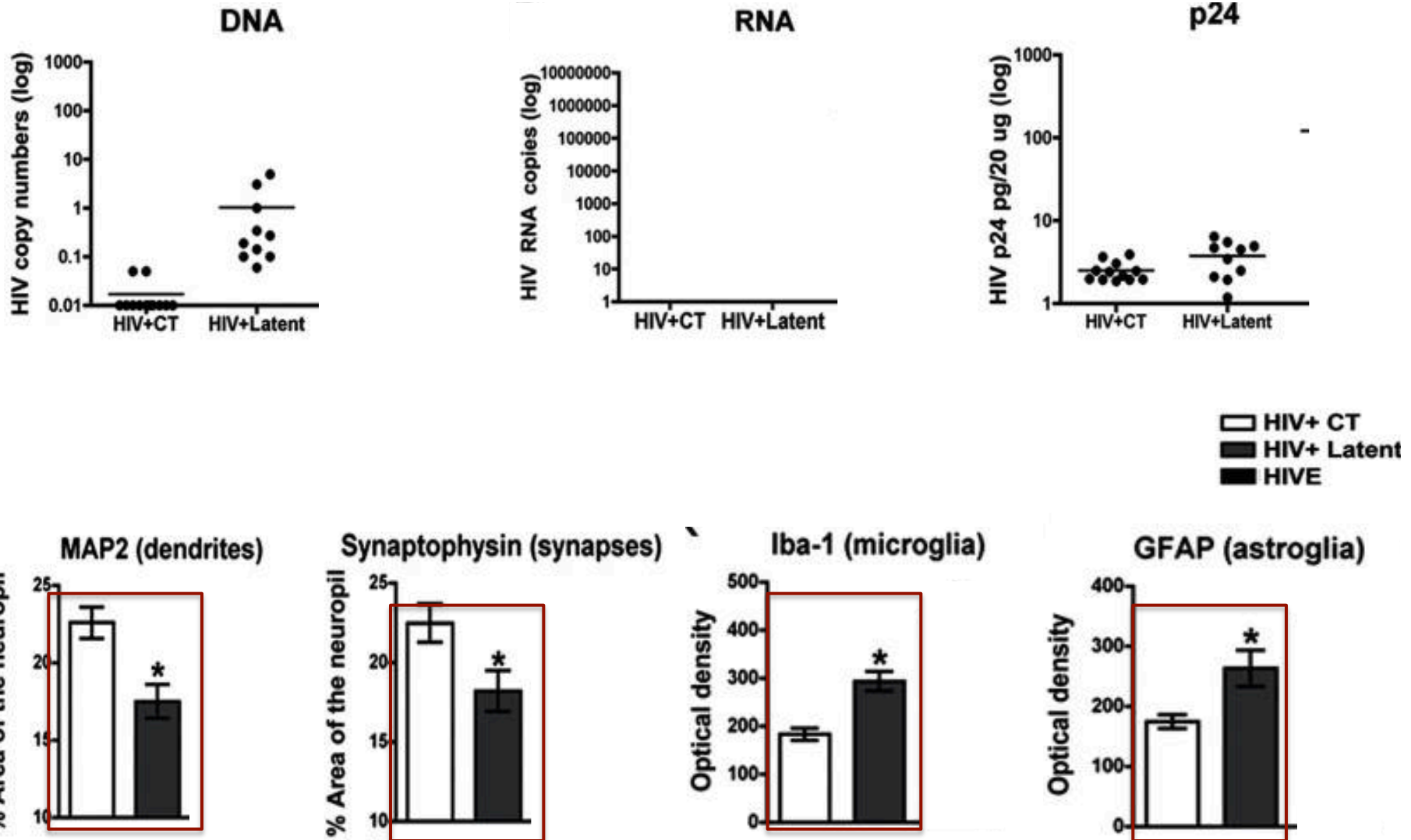


* One to one significant comparisons: Persistent CVE Vs. others
 ** One to one significant comparisons: Control vs. plasma blips

* One to one significant comparisons: Persistent CVE Vs. others
 CSF blip Vs. control & plasma blip
 ** One to one significant comparisons: Control Vs. plasma blip

* One to one significant comparisons: Persistent CVE Vs. others
 ** One to one significant comparisons: Control Vs. Plasma blips

Differences in brain characteristics of patients with and without CNS infection ON ART



Unsolved questions regarding the significance of CSF Viral Escape?

- Is neuroactive ART important for preventing CSF HIV Escape?
- Have CSF blips and persistent CSF HIV Escape cases different inflammatory profiles?
- Considering these data, may be persistent CSF HIV Escape associated with neurocognitive decline?
- Is neuroactive ART effective controlling persistent CSF HIV Escape, reducing inflammation and potentially preventing neurocognitive decline?

Conclusions

- Prevalence and incidence of CSF viral escape are low and the condition is generally transient.
- CSF blips are benign conditions, probably related with poor adherence, transient inflammation and the use of protease inhibitors.
- Persistent CSF HIV Escape is a rare condition, poorly studied, related with CNS damage markers and we cannot ruled out with neurocognitive decline.
- CNS neuroactive ART may have a role in treating and preventing persistent CSF HIV Escape.

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