

How to control HIV in the brain?

Lowering immune activation and
inflammation

Paola Cinque

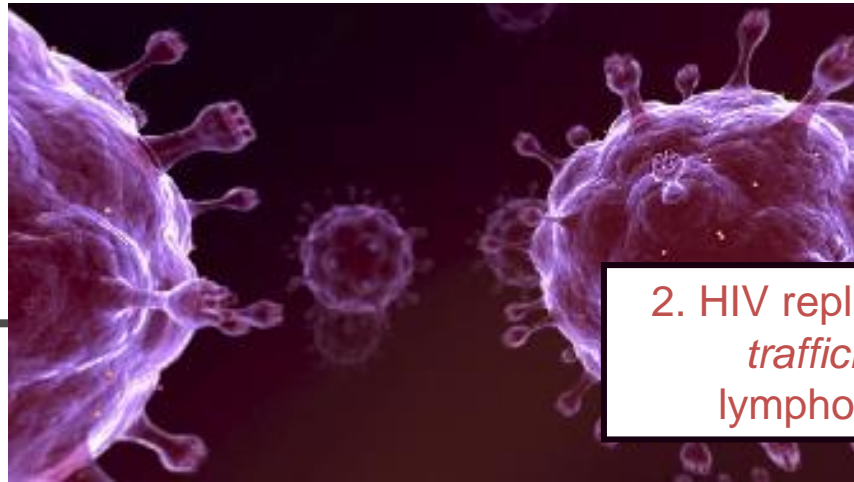
Department of Infectious Diseases

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Lowering immune activation to control HIV brain infection

- Immune activation
 - Untreated infection
 - Treated infection
- Strategies to decrease immune activation

Inflammation in neuropathogenesis of untreated infection



1. Systemic
HIV Replication

2. HIV replication in
trafficking
lymphocytes

BBB

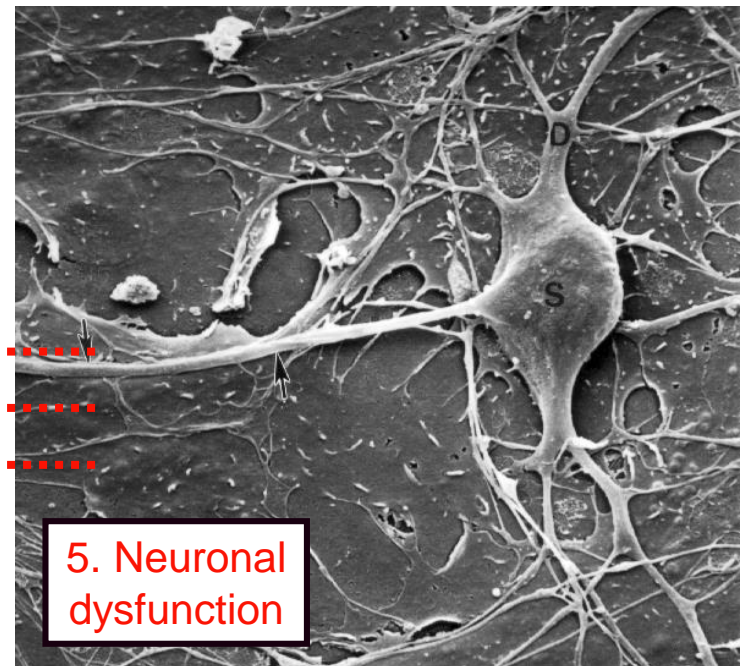
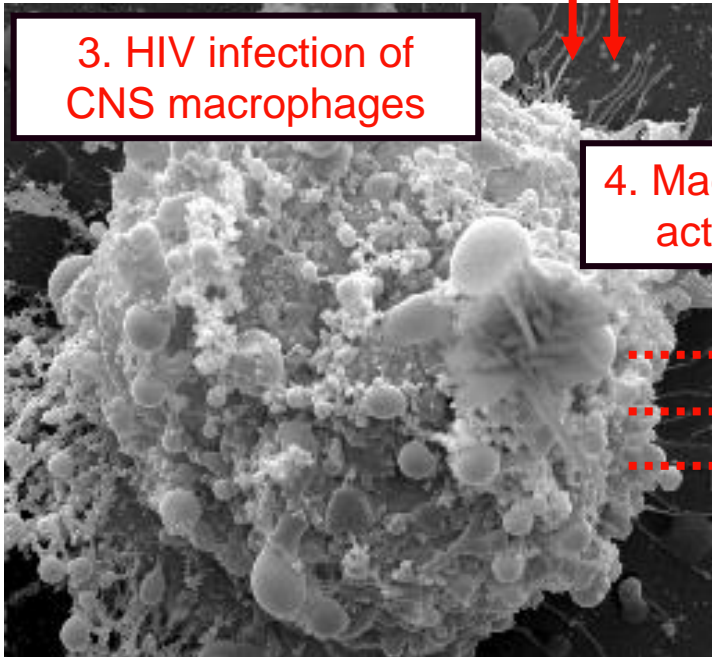


3. HIV infection of
CNS macrophages

4. Macrophage
activation

Soluble
factors

5. Neuronal
dysfunction



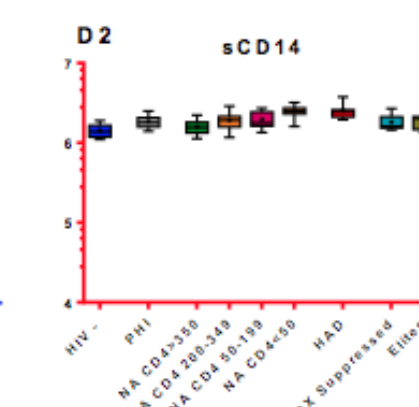
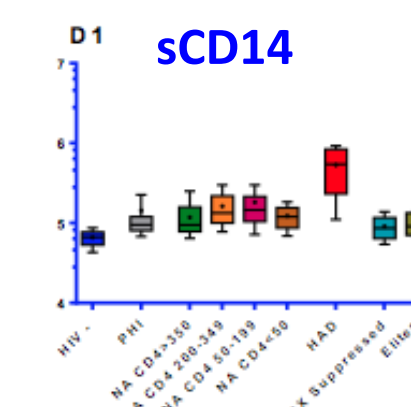
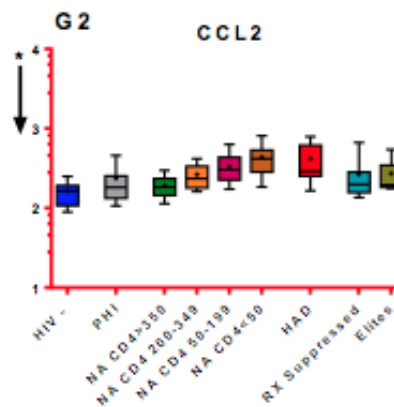
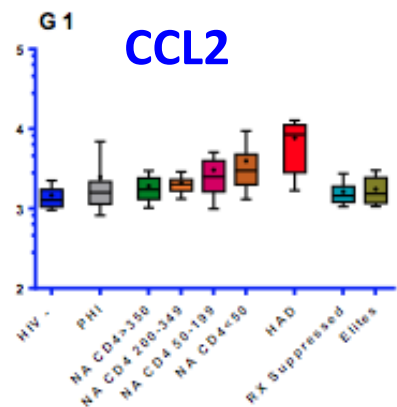
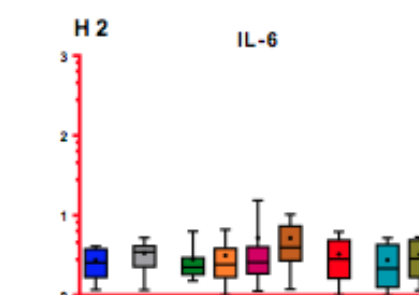
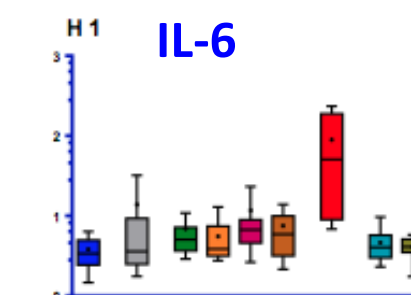
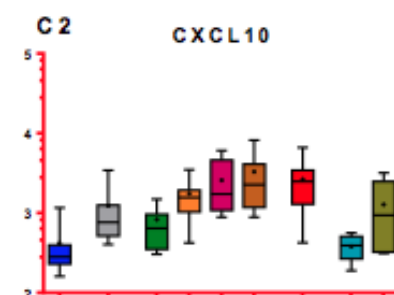
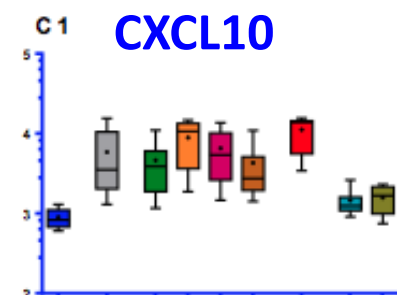
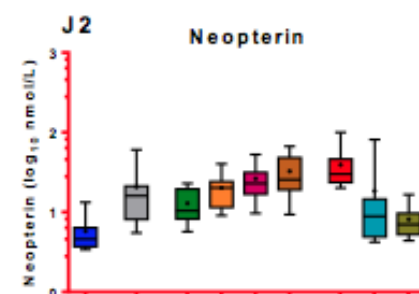
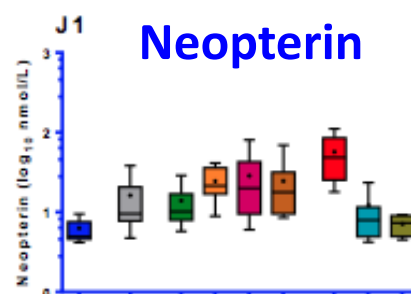
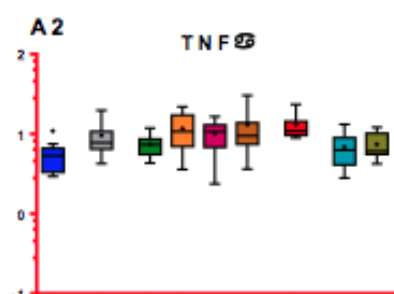
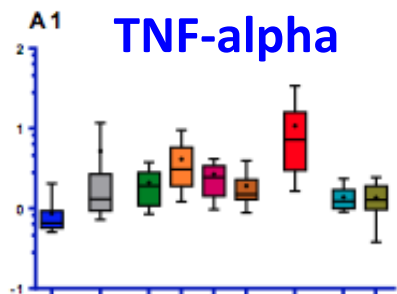
CSF immune activation markers through untreated HIV infection

CSF

Blood

CSF

Blood



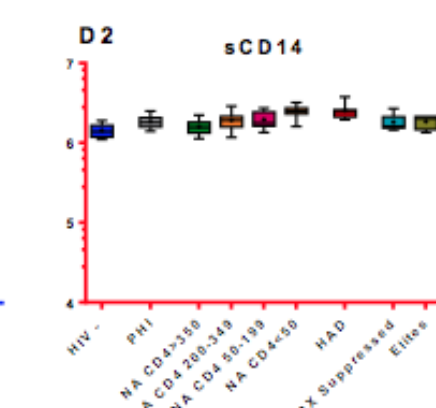
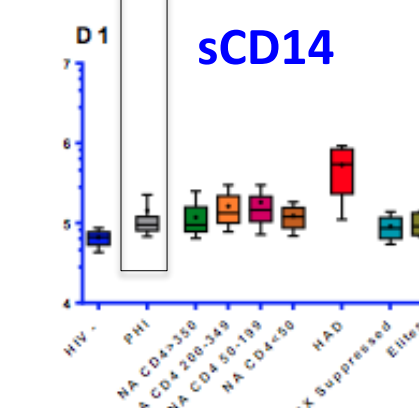
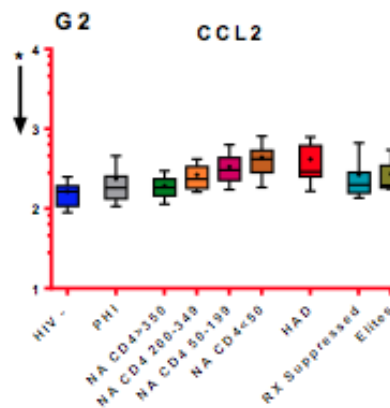
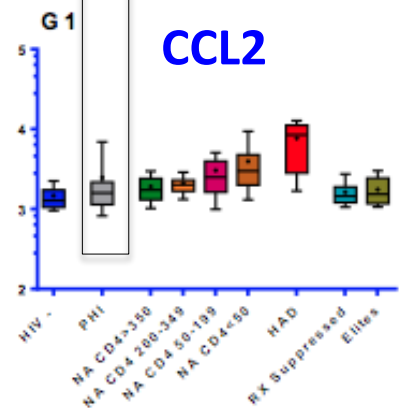
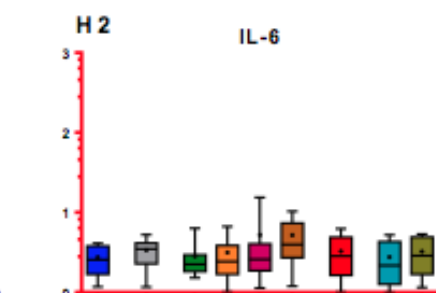
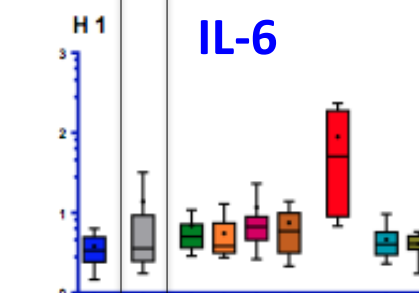
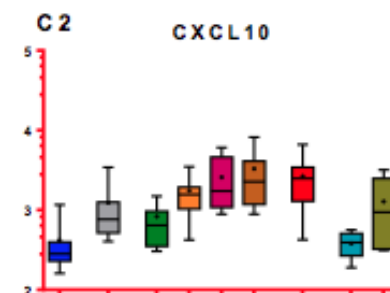
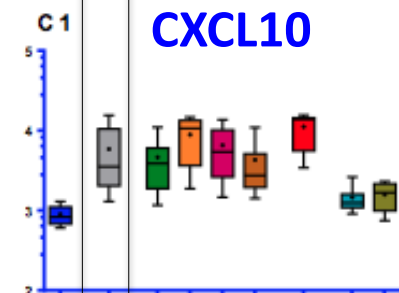
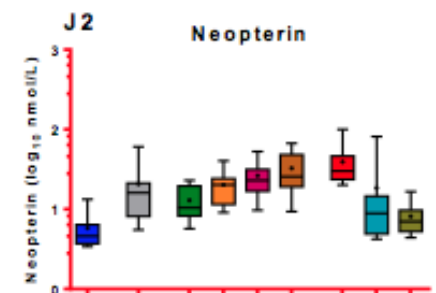
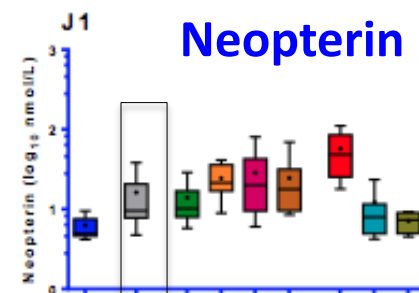
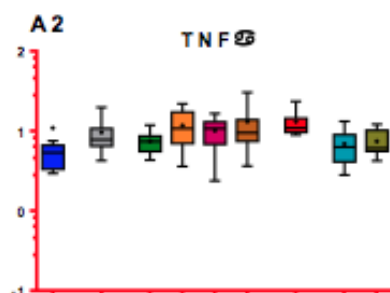
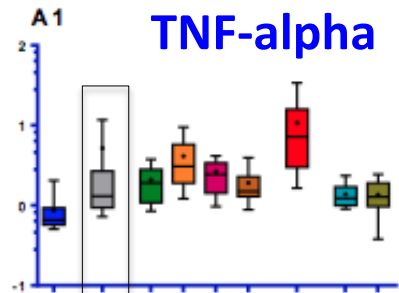
CSF markers through untreated HIV infection: **PHI**

CSF

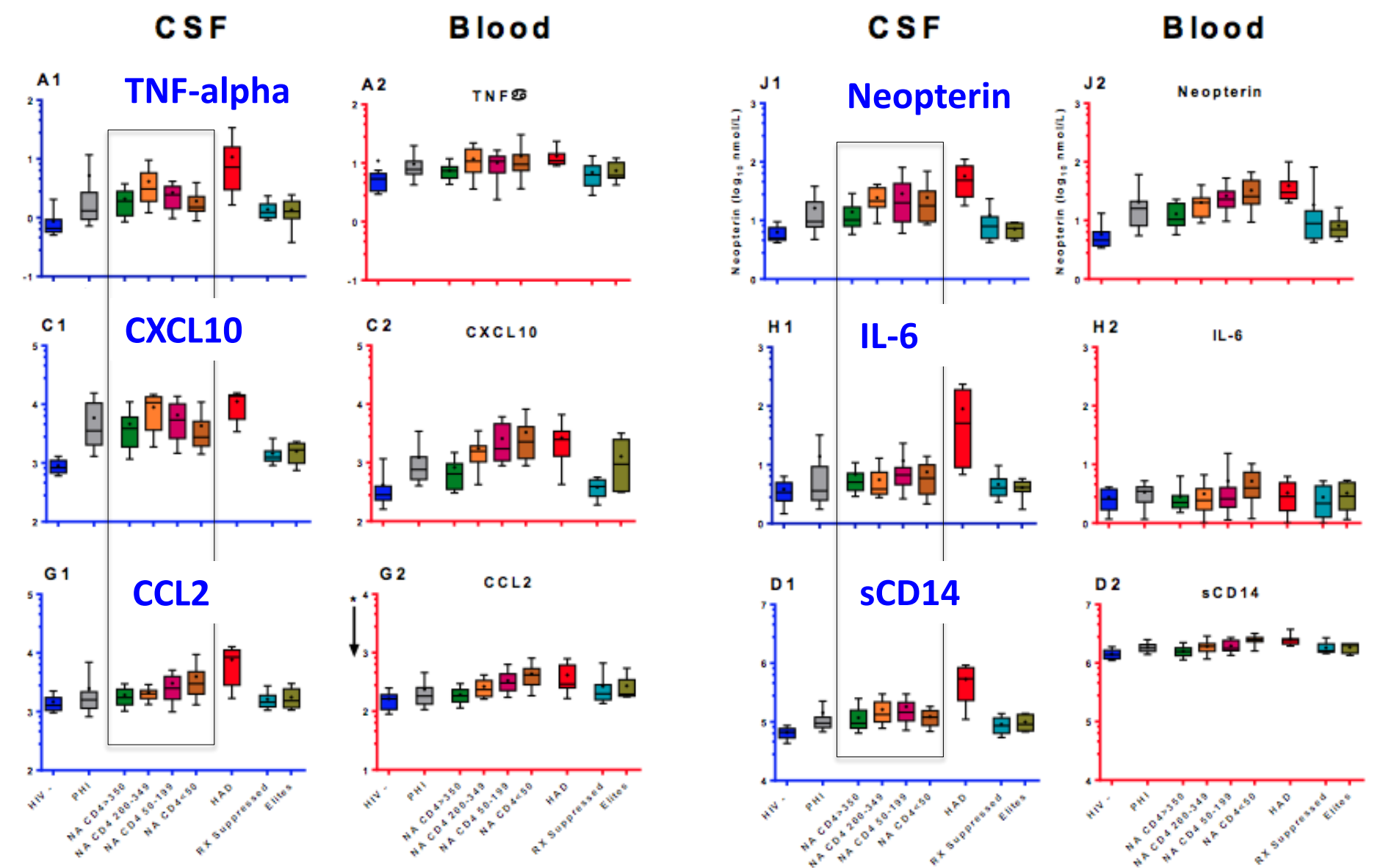
Blood

CSF

Blood



CSF markers through natural HIV infection: neuro-asymptomatic



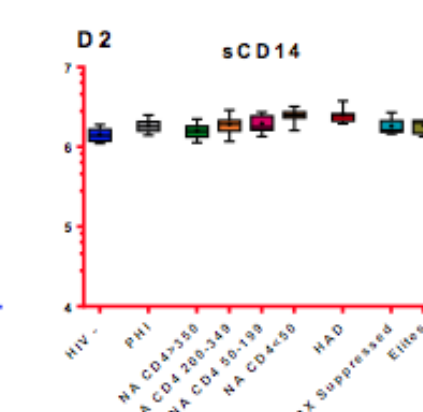
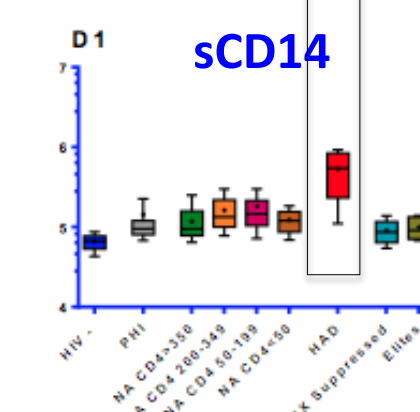
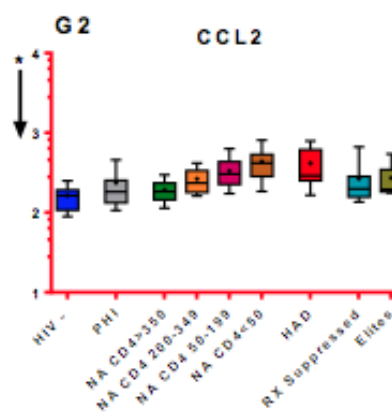
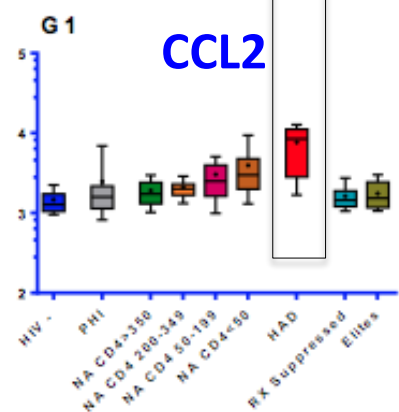
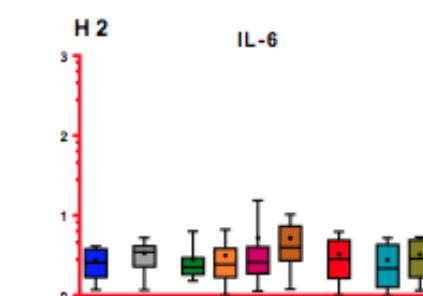
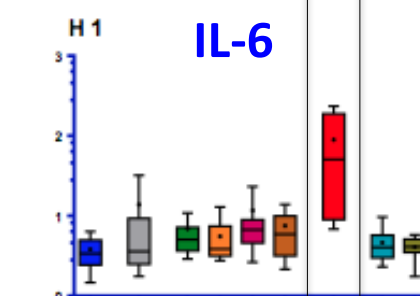
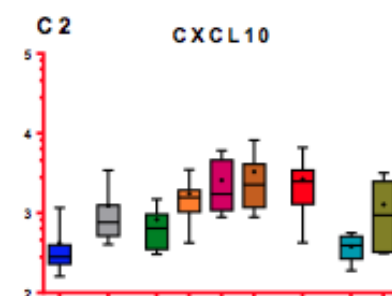
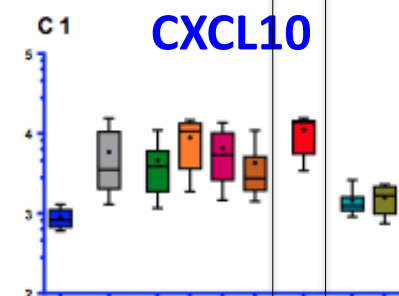
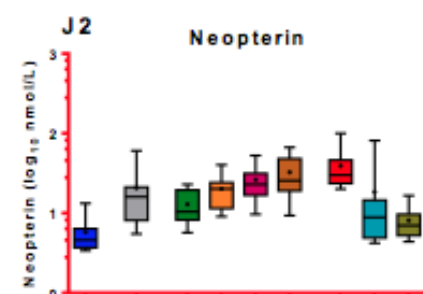
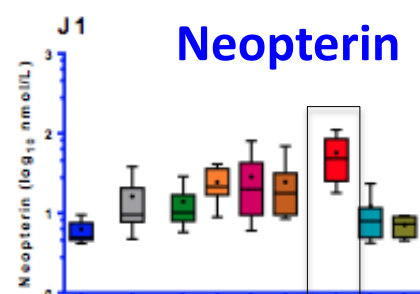
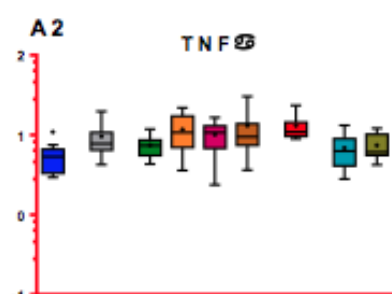
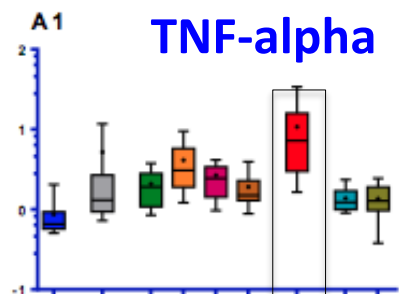
CSF markers through natural HIV infection: ADC

CSF

Blood

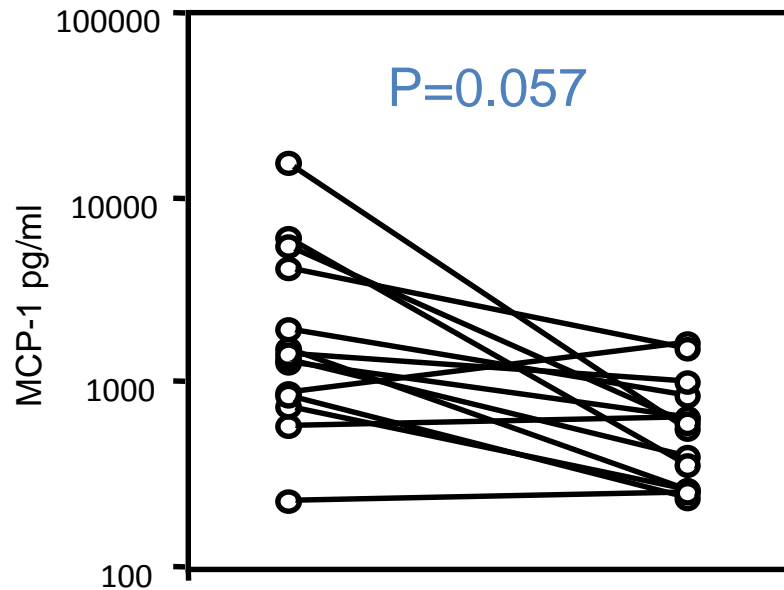
CSF

Blood

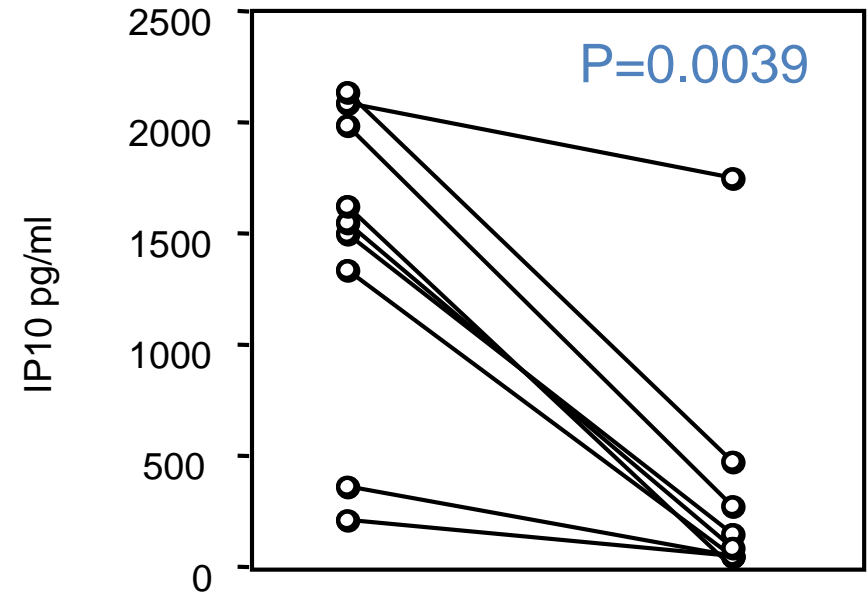


Pre and post-cART CSF immuneactivation markers in HIV-D patients

CCL2

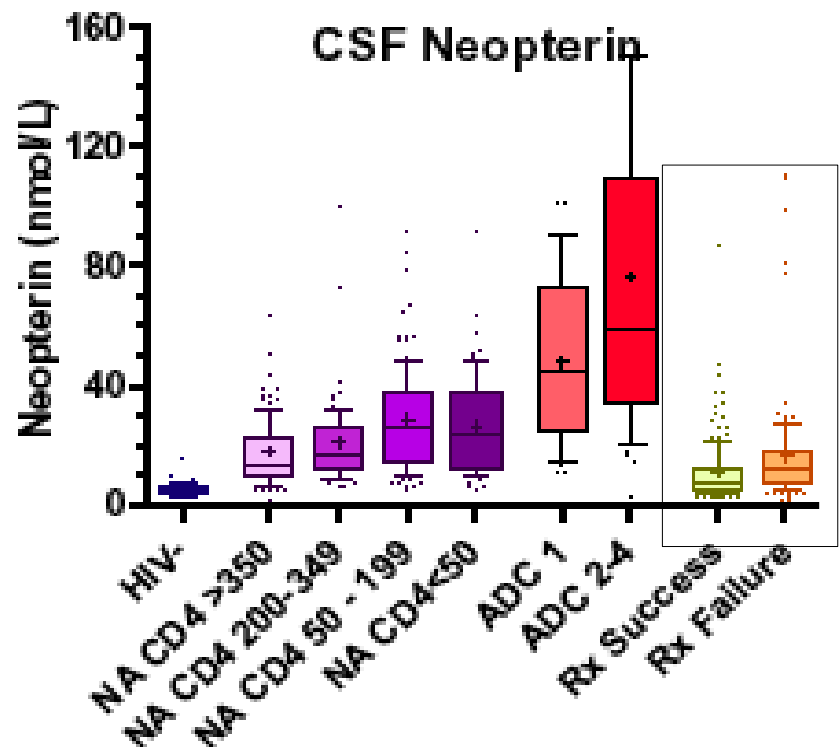
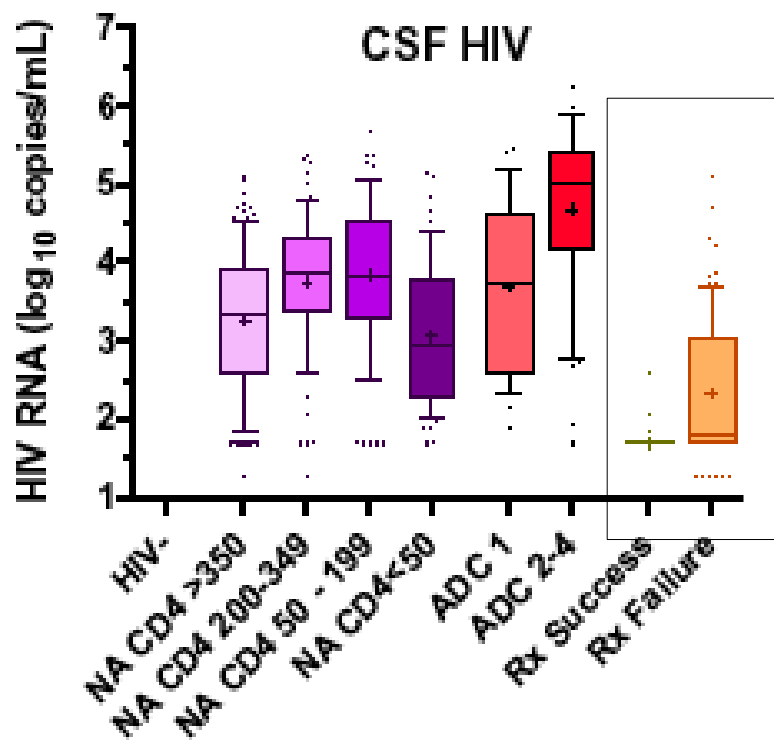


CXCL10

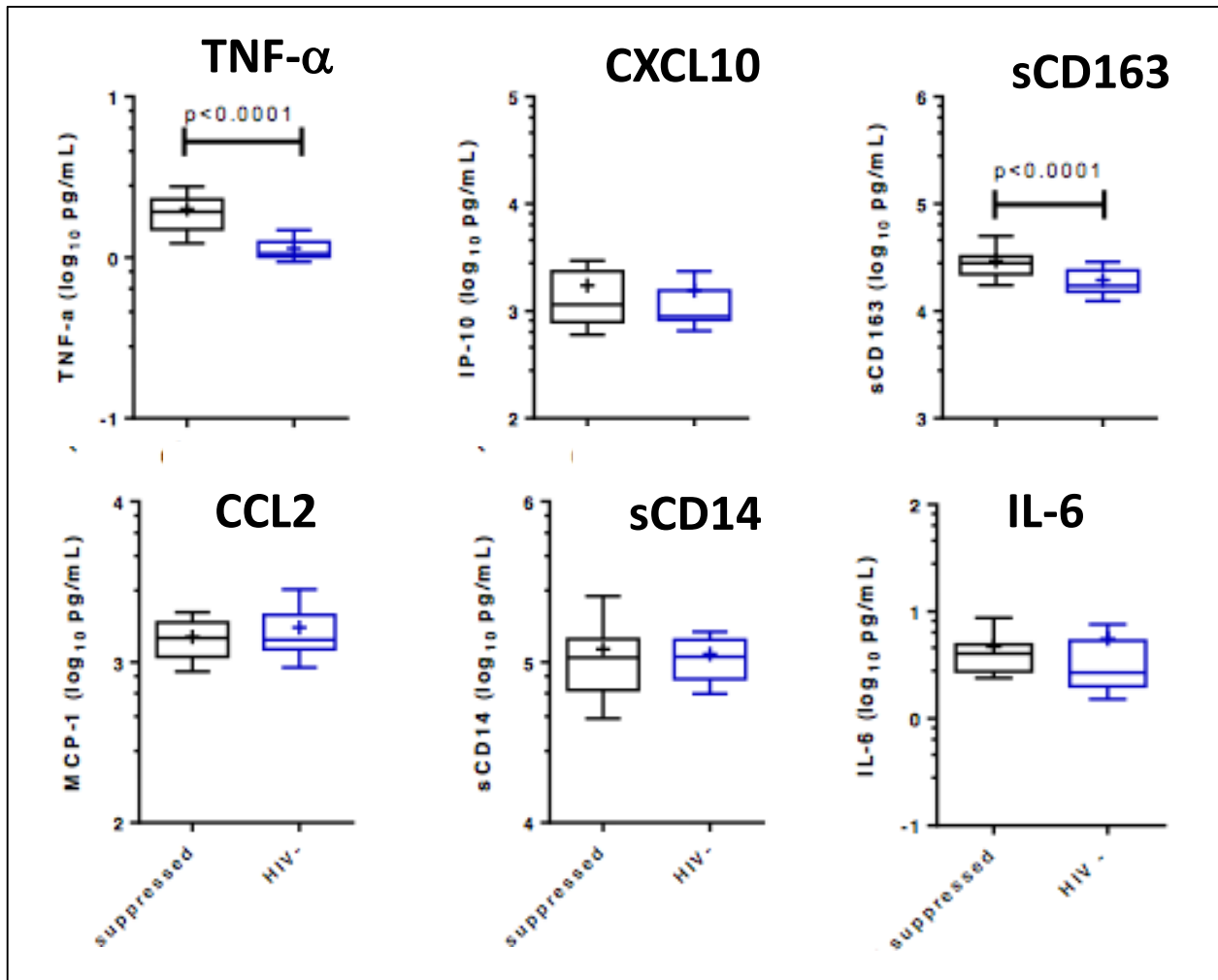


T0-Tx=28-109 days

Persistent elevation of immuneactivation markers in **treated** HIV infection: neopterin



Persistent elevation of immuneactivation markers in treated suppressed HIV infection vs. HIV-negative

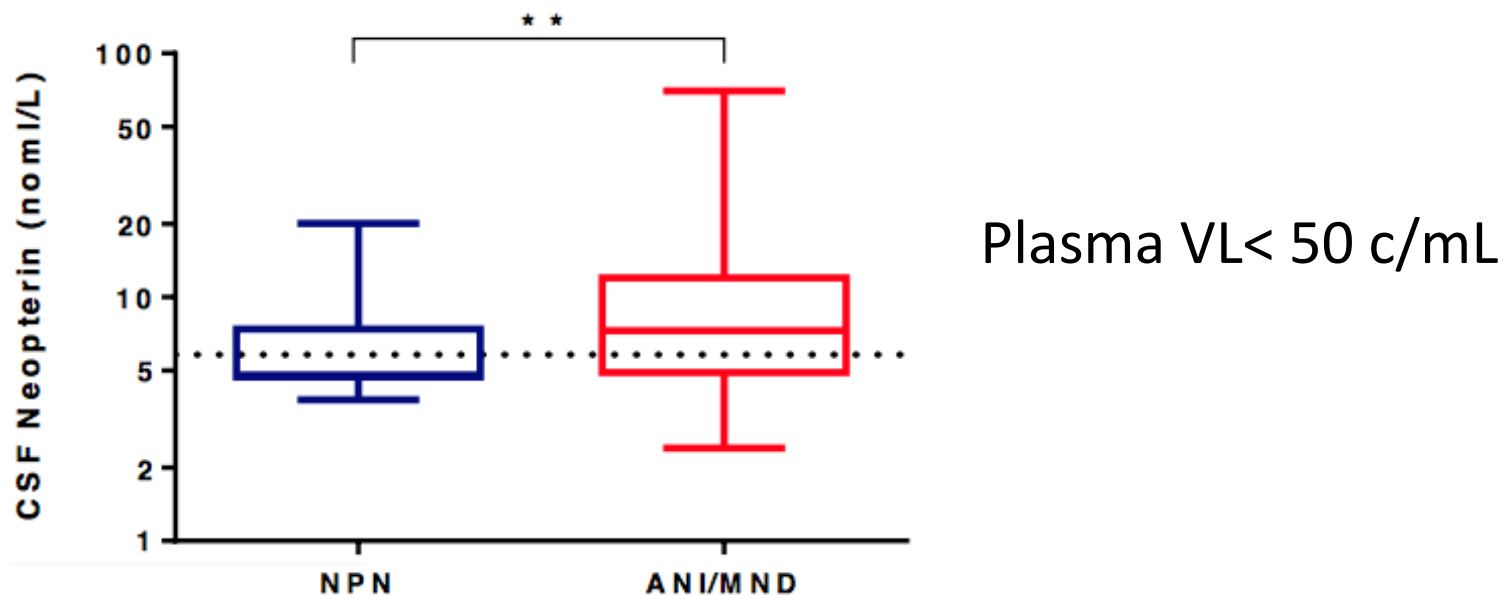


Persistent immuneactivation in treated suppressed HIV infection

- Consequences ?
- Causes ?

Consequences?

Higher CSF neopterin in ART-treated patients with mild neurocognitive impairment



100 subjects: 29 NPN and 71 with ANI/MND (ANI=38; MND=33)

Median (IQR) age: 47 (41-54) years

Current CD4+: 524 (359- 771)

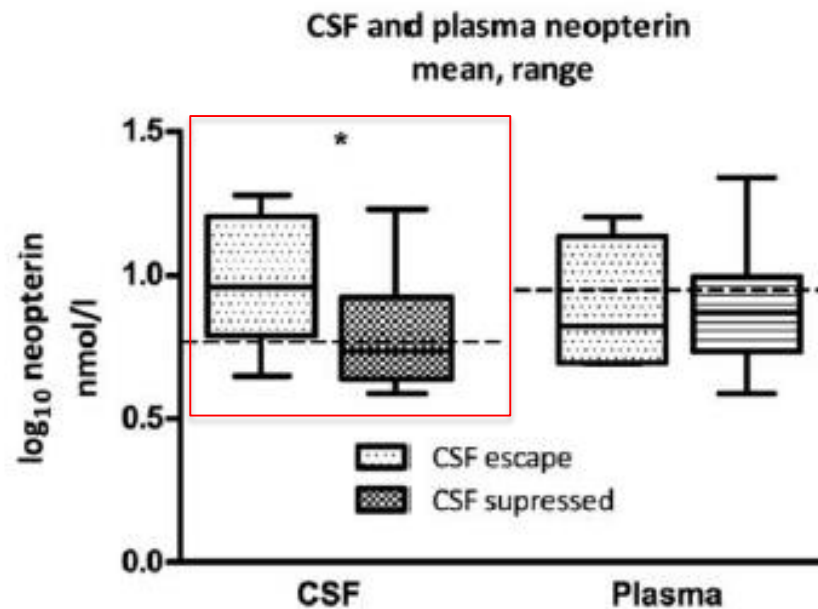
Nadir CD4+: 72 (10-224)

Causes?

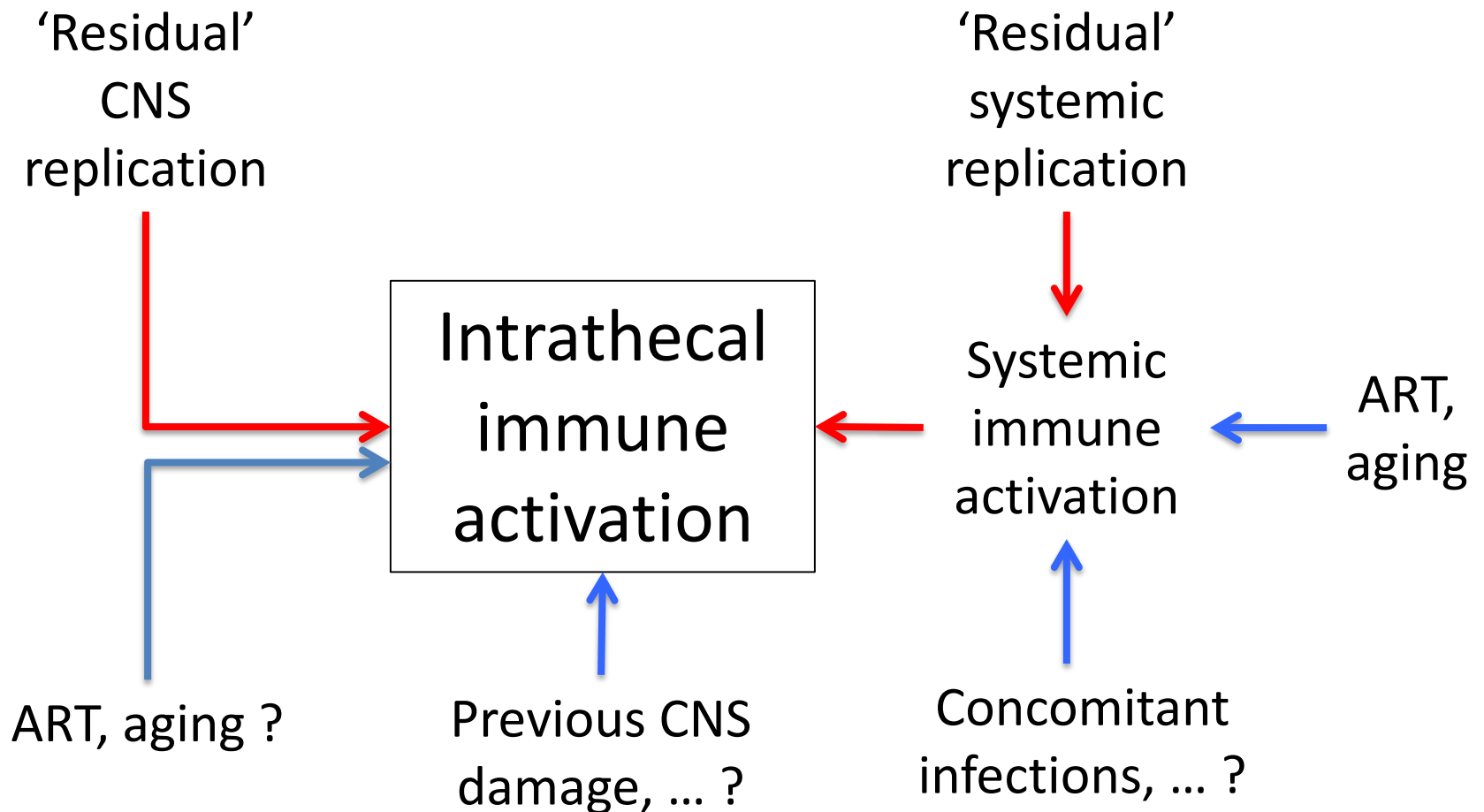
Increased CSF neopterin in ART-treated patients with asymptomatic CSF viral escape

69 neuroasymptomatic patients with plasma HIV RNA < 50 c/mL

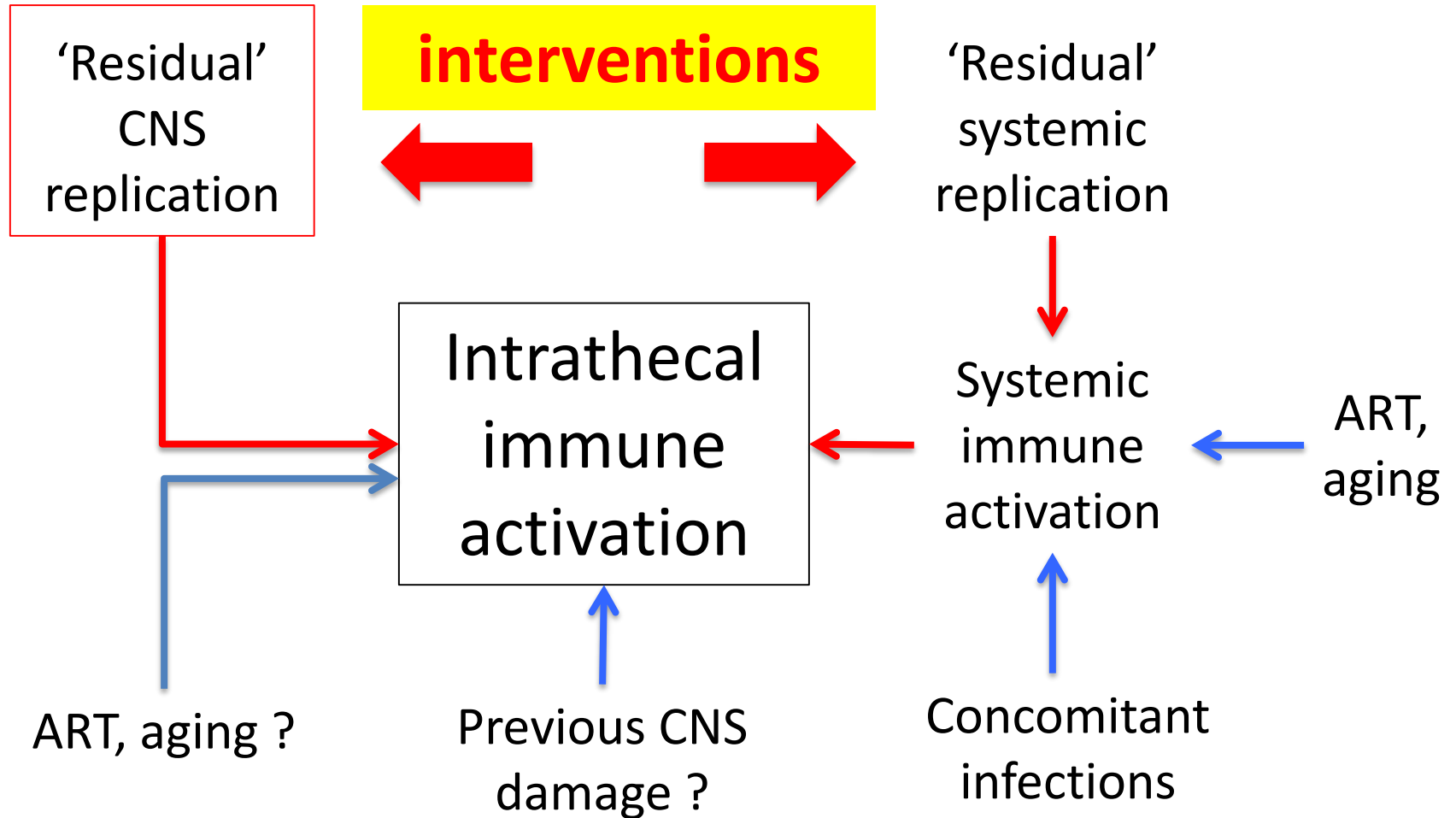
→ CSF escape (>50 c/mL) in 7 (10%), median 121 (range 52-860) c/mL



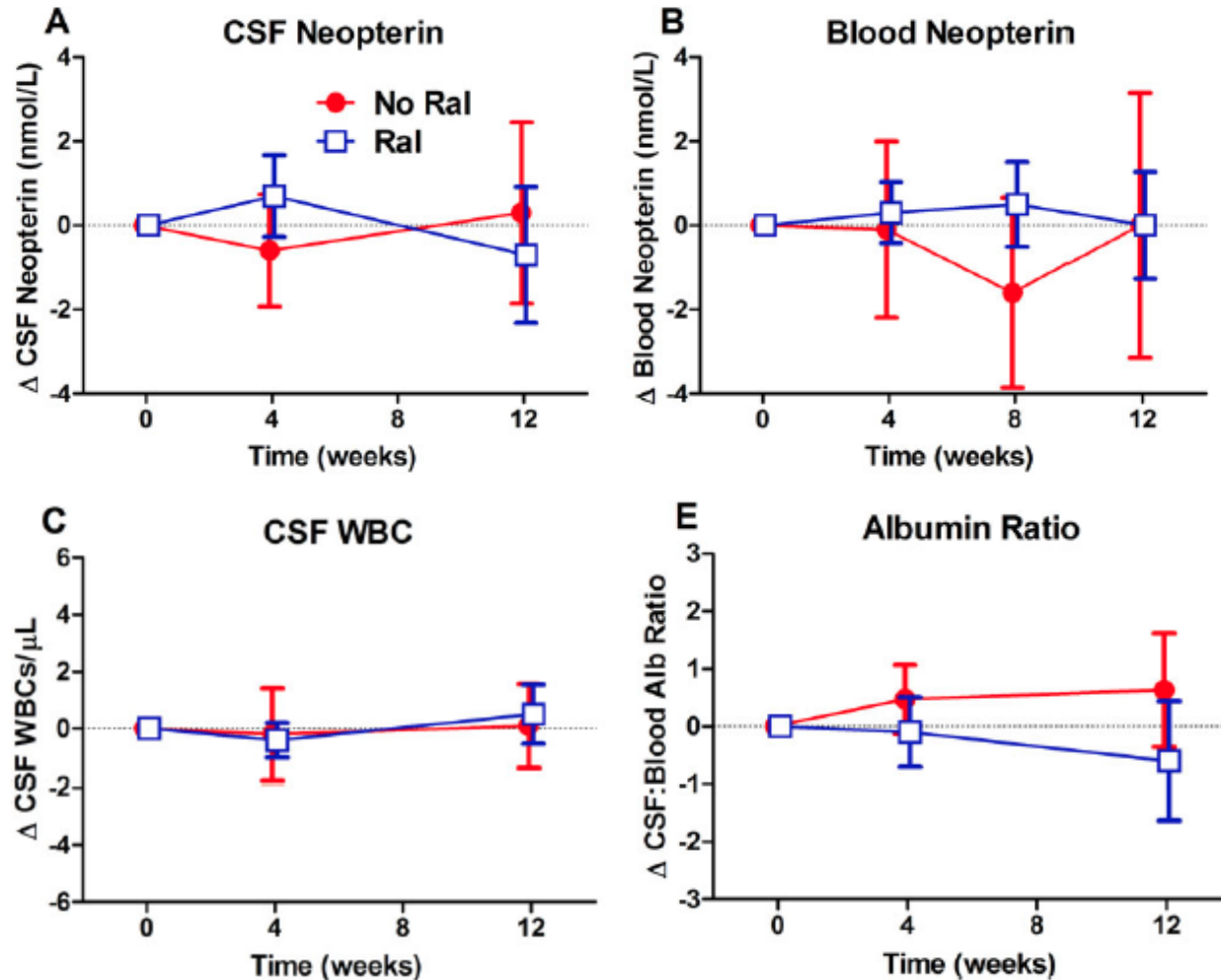
Possible model of persistent intrathecal immuneactivation in treated infection



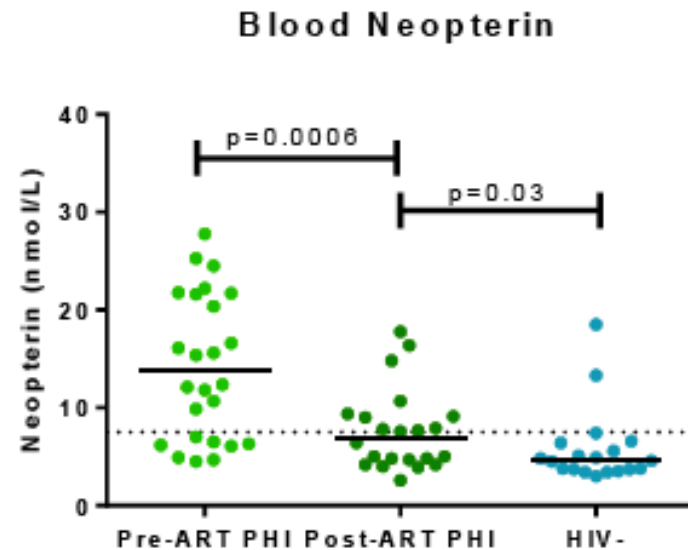
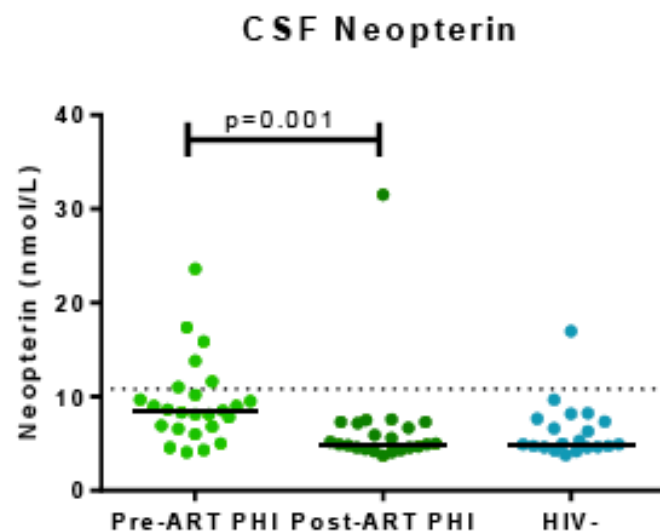
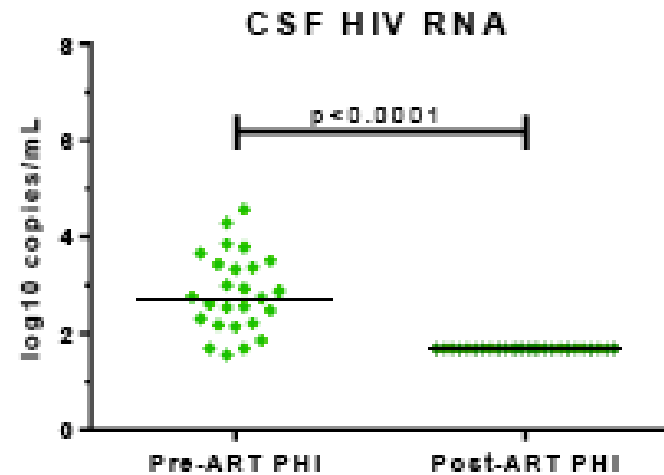
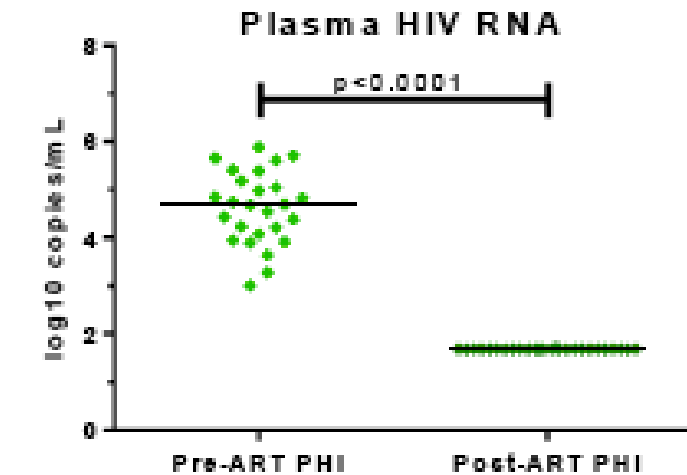
Potential model for persistent intrathecal immuneactivation in treated infection



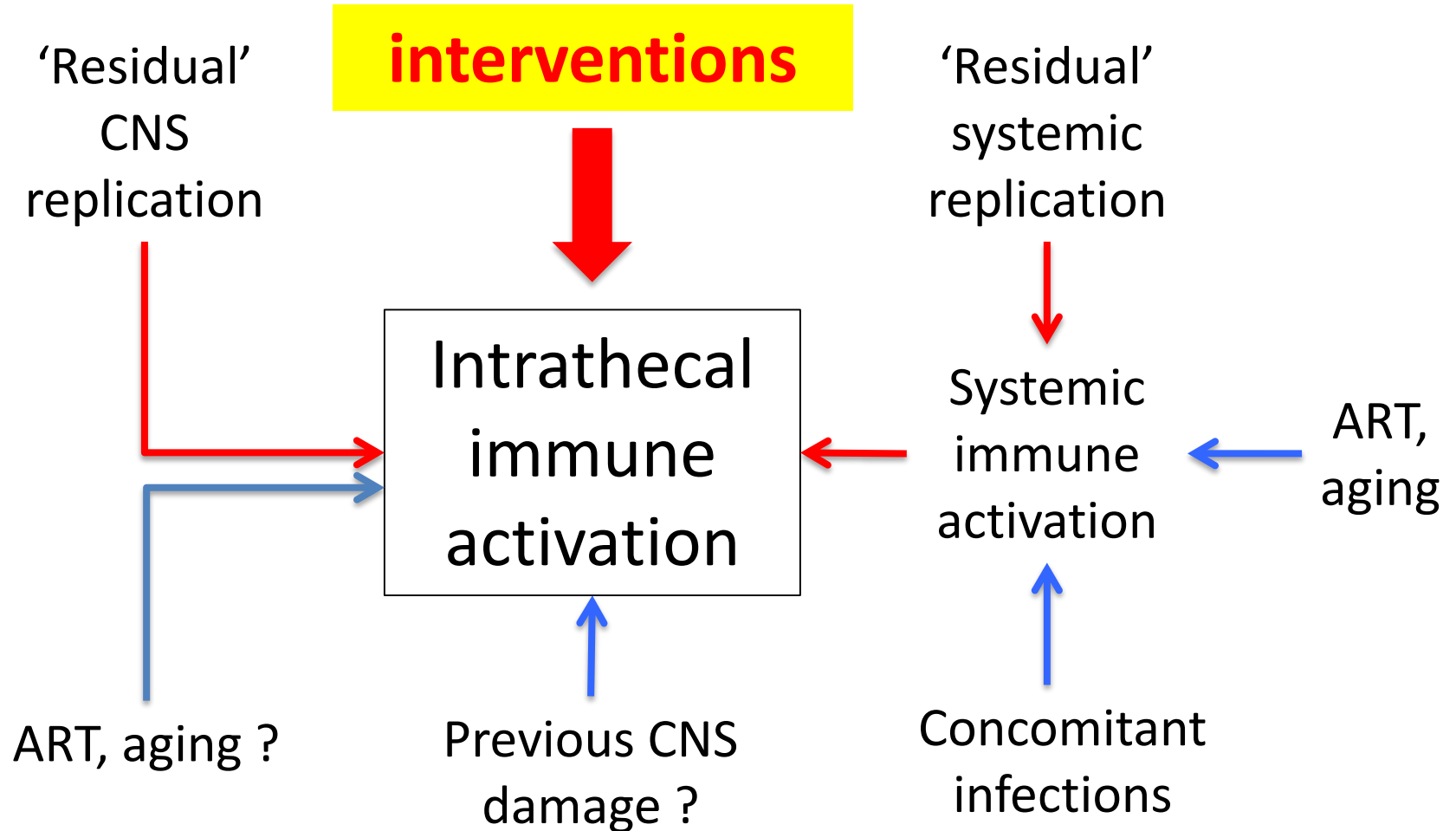
Treatment intensification (RAL) had no effect on CSF immuneactivation in patients on suppressive ART



CSF immuneactivation dropped to normal with Early ART



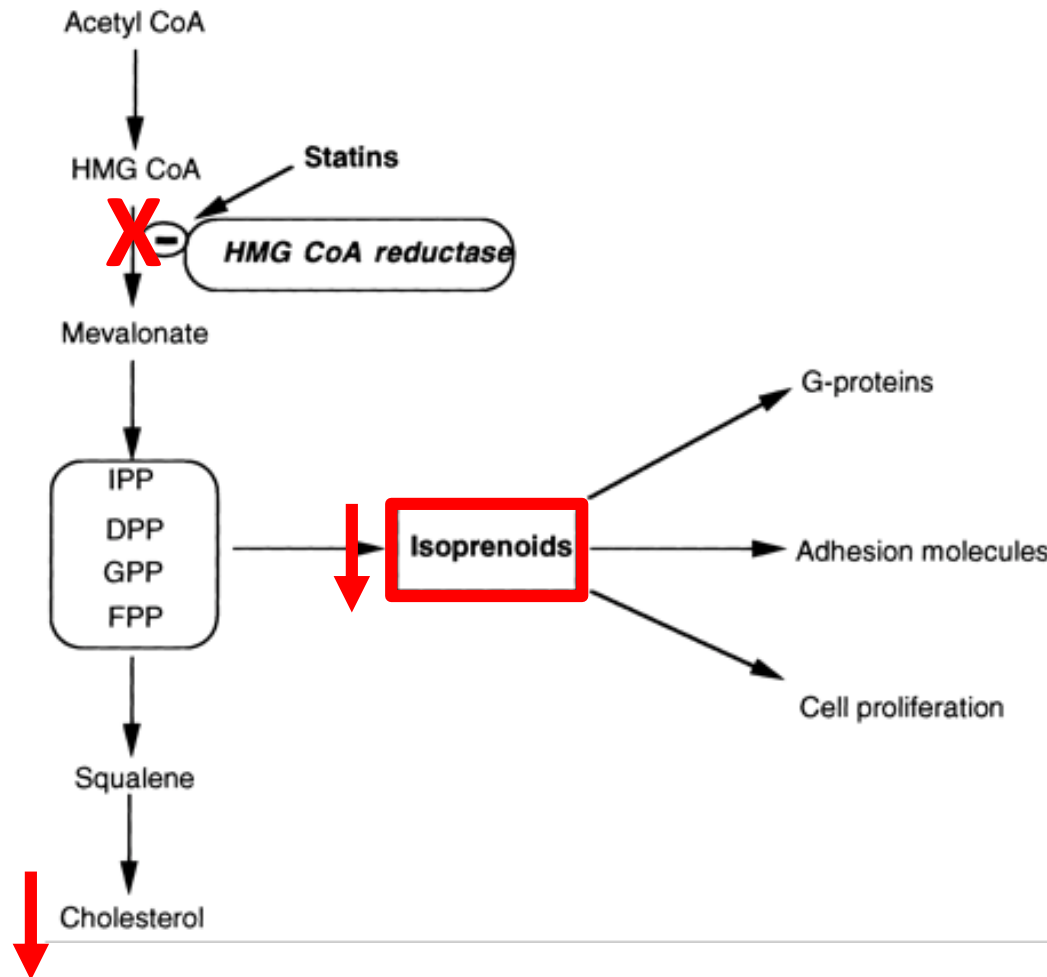
Potential model for persistent intrathecal immuneactivation in treated infection



Drugs with a potential anti-inflammatory effect explored in HIV brain infection

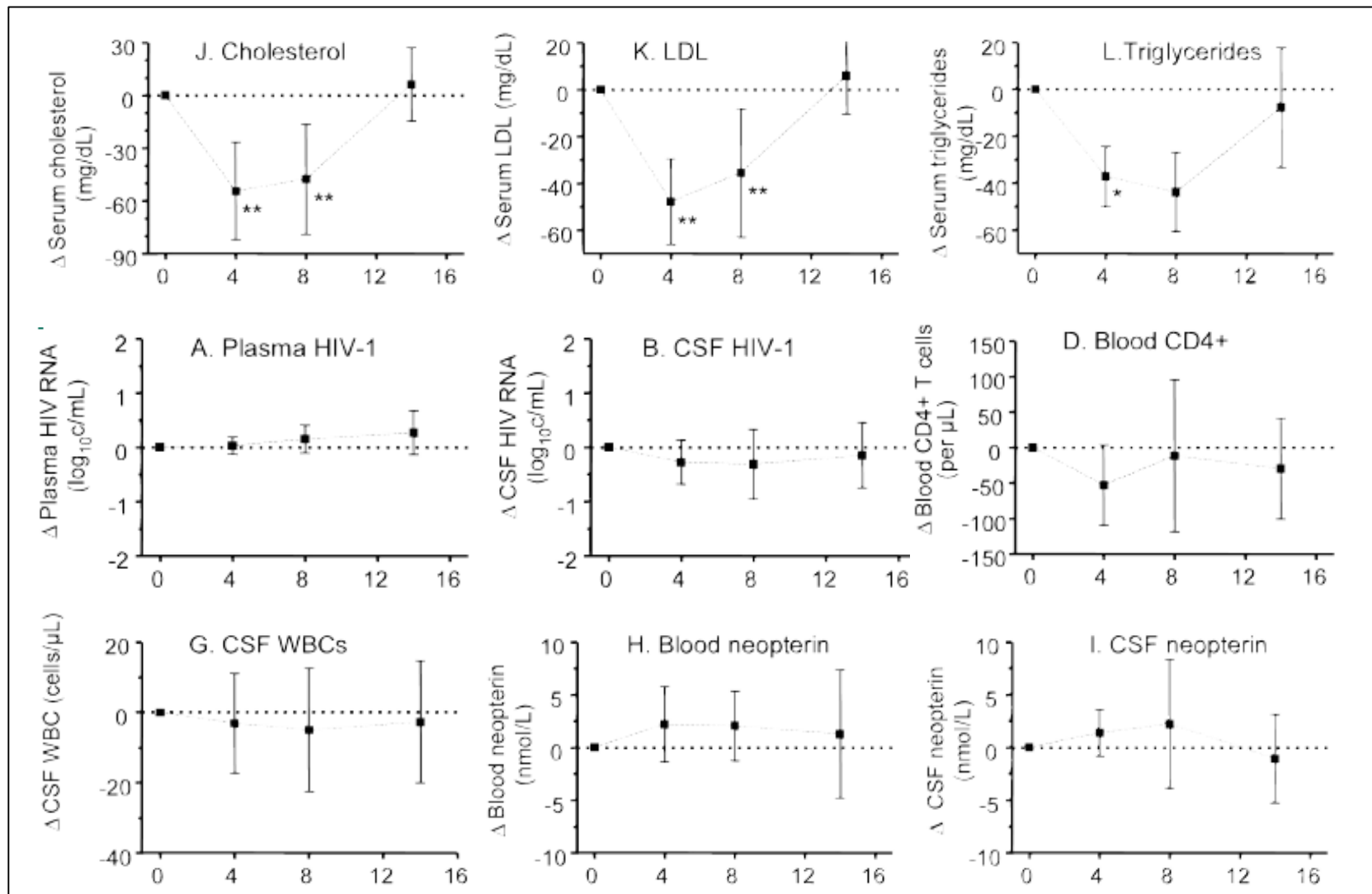
- Statins
 - Minocycline
 - Dimethylfumarate (DMF)
 - Copolymer-1 (Cop-1, Glatiramer acetate)
 - Chloroquine
 - Multilineage kinases (MLKs) inhibitors (e.g., CEP 1347)
 - Indoleamine 2,3-dioxygenase (IDO) inhibitors
 -
-
- Have known immunomodulatory effects
 - Achieve adequate levels in the brain
 - Are effective *in vitro* or in animal models of HIV brain infection
 - **Potential to be used as adjuvants in HIV brain infection**

Statins and anti-inflammatory mechanisms



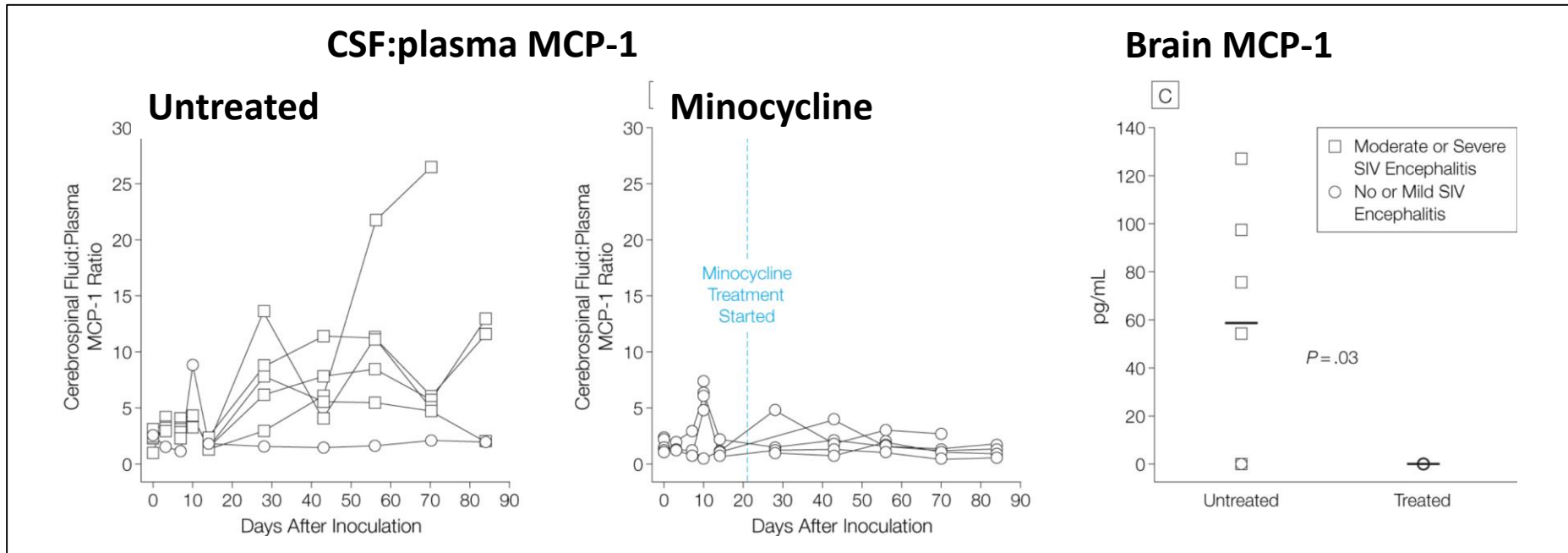
No changes of CSF markers in ART-naïve patients receiving atorvastatin (8 weeks)

Open-label, pilot study, 7 subjects, atorvastatin 80 mg orally/day

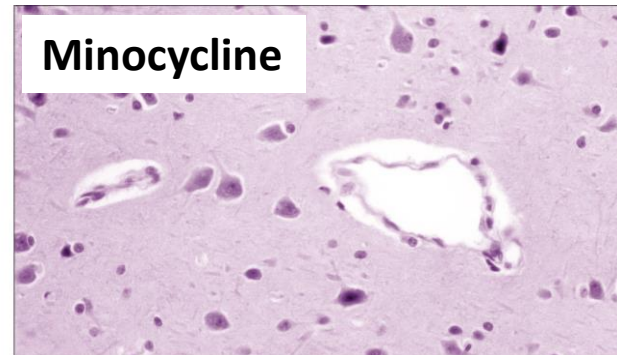
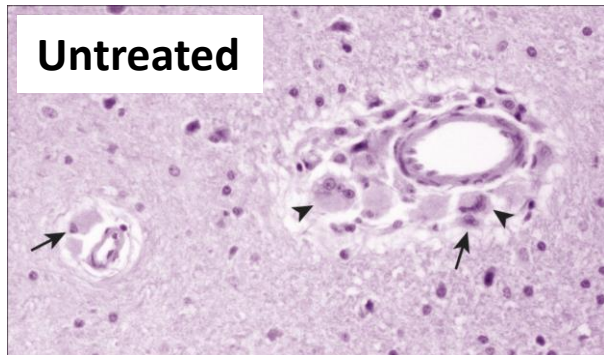


Minocycline

- Potential mechanism: suppression of activation of p38 mitogen-activated PK
- Reduced immuneactivation in the accelerated macaque model of HIV-E (Zink MC, JAMA 2005)

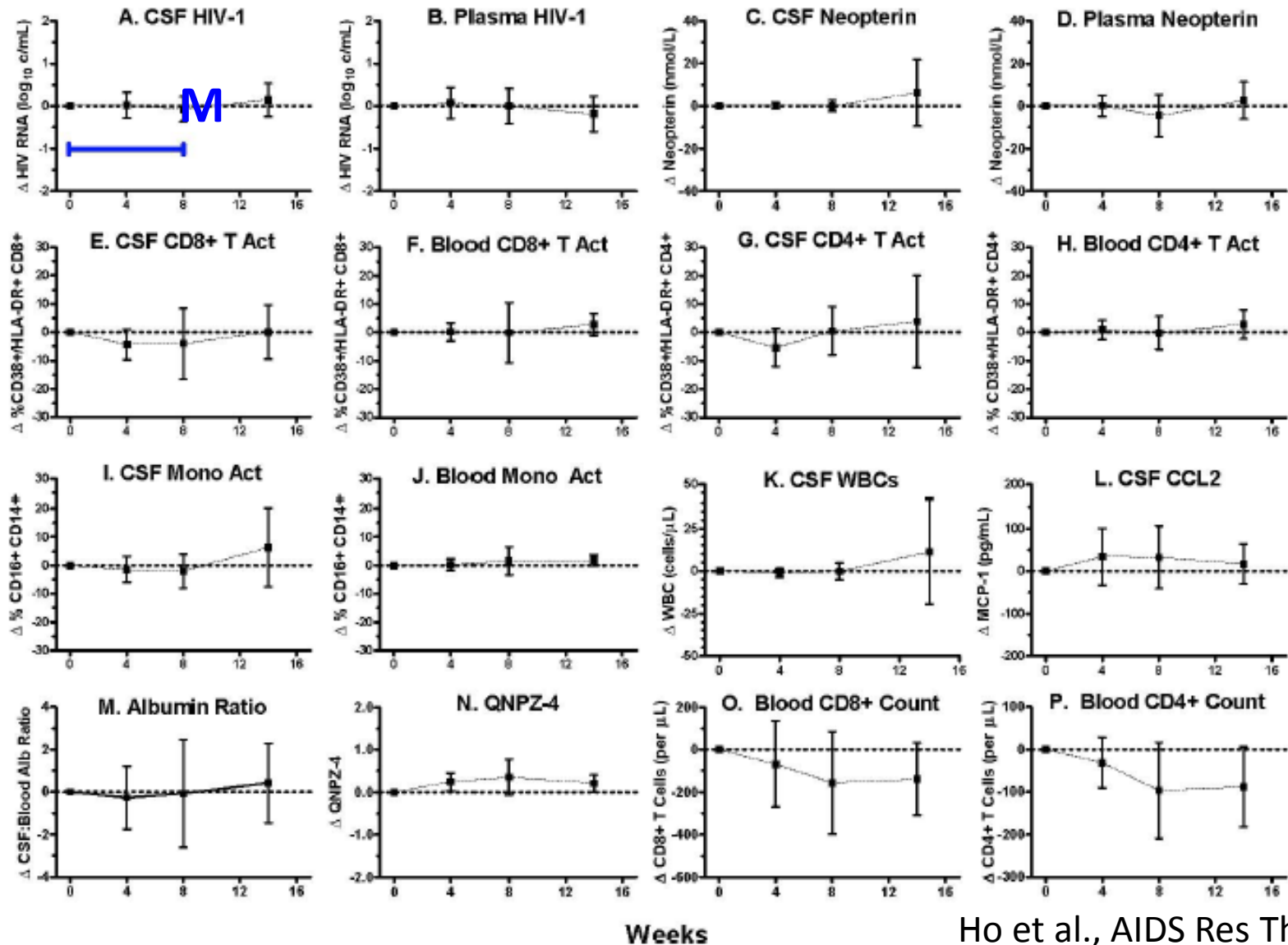


Perivascular
macrophages/
MNGC



No changes of CSF immuneactivation markers in ART-untreated patients receiving minocycline (8 weeks)

Open-label, pilot study, 7 subjects, minocycline 100 mg orally BID



No changes of NP test scores in ART-treated patients receiving minocycline (24 weeks)

	Treatment, mean (SD)			Minocycline effect, 95% confidence interval	p Value
	Placebo (n = 55)	Minocycline (n = 52)	Total (n = 107)		
Timed Gait change	0.08 (2.68)	0.22 (1.61)	0.15 (2.20)	-0.35, 1.36	0.244
Grooved Pegboard Dominant change	0.08 (0.75)	0.46 (1.19)	0.25 (0.99)	0.09, 0.92	0.017
Grooved Pegboard nondominant change	0.03 (0.77)	0.08 (0.76)	0.05 (0.76)	-0.18, 0.44	0.416
Trail Making A change	0.17 (1.12)	0.09 (0.84)	0.13 (1.00)	-0.47, 0.28	0.613
Trail Making B change	0.13 (0.97)	0.06 (0.83)	0.10 (0.91)	-0.40, 0.26	0.679
Symbol Digit change	-0.07 (0.92)	-0.15 (0.76)	-0.11 (0.85)	0.45, 0.28	0.637
Basic Choice Reaction Time change	0.23 (1.66)	0.04 (2.60)	0.14 (2.14)	-0.85, 0.54	0.663
Sequential Reaction Time change	0.18 (1.02)	0.24 (0.95)	0.21 (0.98)	-0.36, 0.39	0.938
NPZ-8 changes	0.17 (0.67)	0.12 (0.71)	0.15 (0.69)	-0.26, 0.39	0.651

Randomized double-blind, placebo-controlled study – minocycline 100 mg orally BID
 107 patients with NCI on stable ART for >16 weeks
 Early study termination for futility after 50% completed the double-blind phase

Lowering immune activation to control HIV brain infection: conclusions

- Immune activation
 - Remains a relevant issue in treated infection
- Strategies to decrease immune activation
 - **Early ART**

Acknowledgements

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Milano

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Treatment intensification had no effect on CSF immuneactivation in patients on suppressive ART

