Reservoirs: Central Nervous System

Turin, January 15-17, 2020

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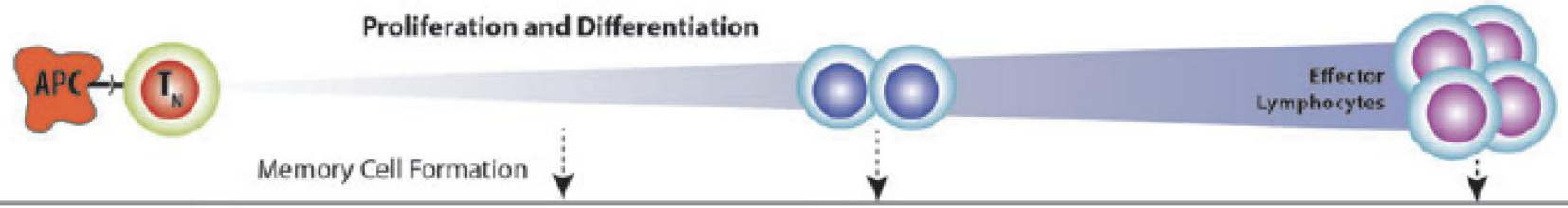
University of California, San Diego

Disclosures

Research awards paid to UC San Diego:

- National Institutes of Health

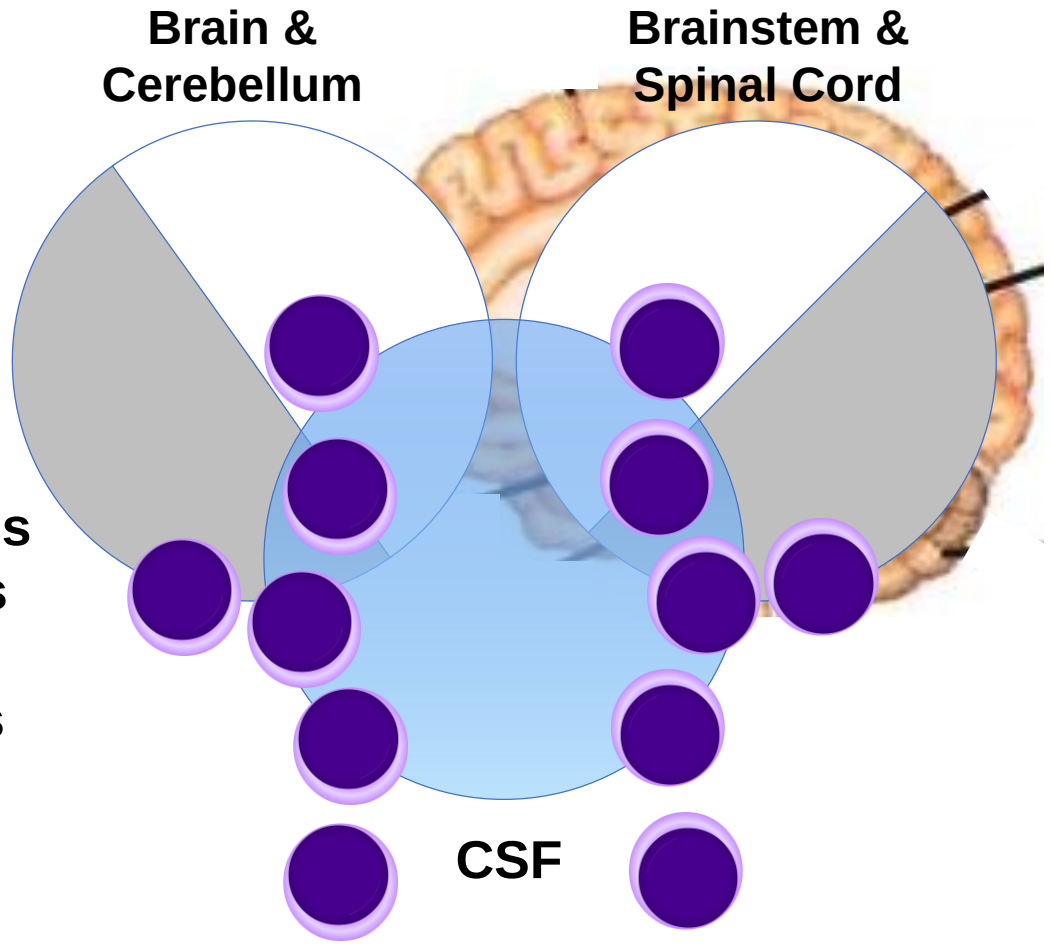


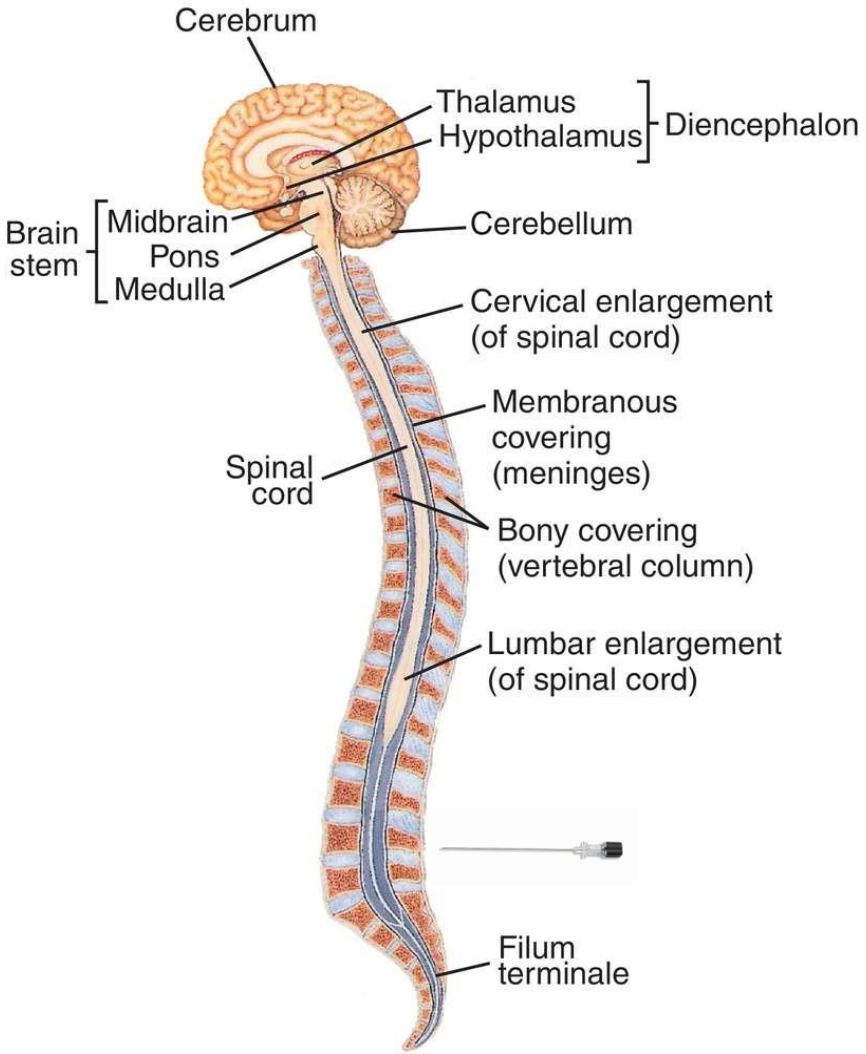
	T_N	T_{SCM}	T_{CM}	T_{TM}	T_{EM}
CD45RA	+	+	-	-	-
CD45RO	-	-	+	+	+
CD27	+	+	+	+	-
CCR7 (lymph/gut homing)	+	+	+	-	-
Prevalence					
Peripheral Blood	+++	*	+++	++	++
Ileum\Rectum	+/-		+	++	+++
Contribution to HIV-1 DNA Reservoir					
Peripheral Blood (High $CD4^+$ T-cell count) [12]			+++	++	+
(Low $CD4^+$ T-cell count) [12]			++	+++	+(?)
Ileum			+**	+	+++
Rectum			+**	++	+++

Henrich & Gandhi, J Infect Dis 2013;208:1189–93

Which Cells Harbor HIV in the CNS?

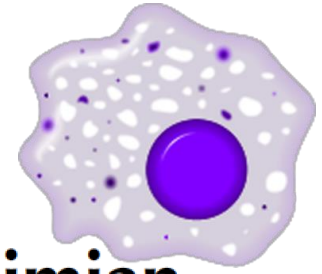
Neurons
Microglia
Macrophages
Astrocytes
Oligodendrocytes
Endothelial Cells
Pericytes
Ependymal Cells
Progenitor Cells
Lymphocytes
Monocytes





How Well Does Lumbar CSF Reflect the Entire CNS?

The HIV Reservoir in Monocytes and Macrophages



AIDS

GLIA

Journal of NeuroVirology

Journal of Neuroimmune Pharmacology

frontiers in Immunology

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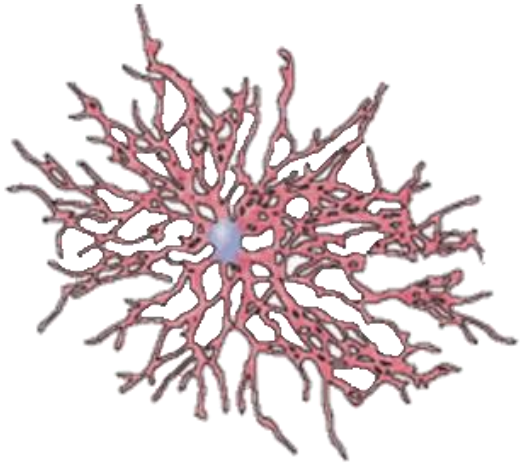
Brain macrophages harbor latent, infectious simian immunodeficiency virus

Microglial Cells: The Main HIV-1 Reservoir in the Brain

Myeloid and CD4 T Cells Comprise the Latent Reservoir in Antiretroviral Therapy-Suppressed SIVmac251-Infected Macaques

Macrophages but not Astrocytes Harbor HIV DNA in the Brains of HIV-1-Infected Aviremic Individuals on Suppressive Antiretroviral Therapy

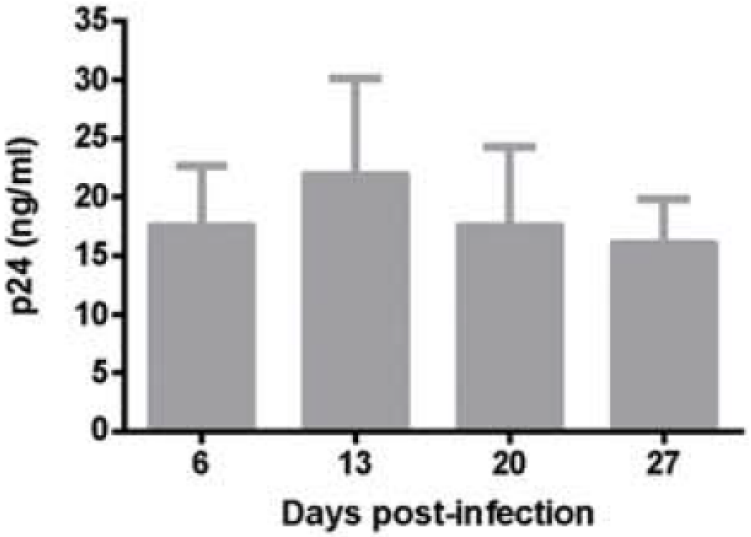


Astrocytes sustain long-term productive HIV-1 infection without establishment of reactivable viral latency

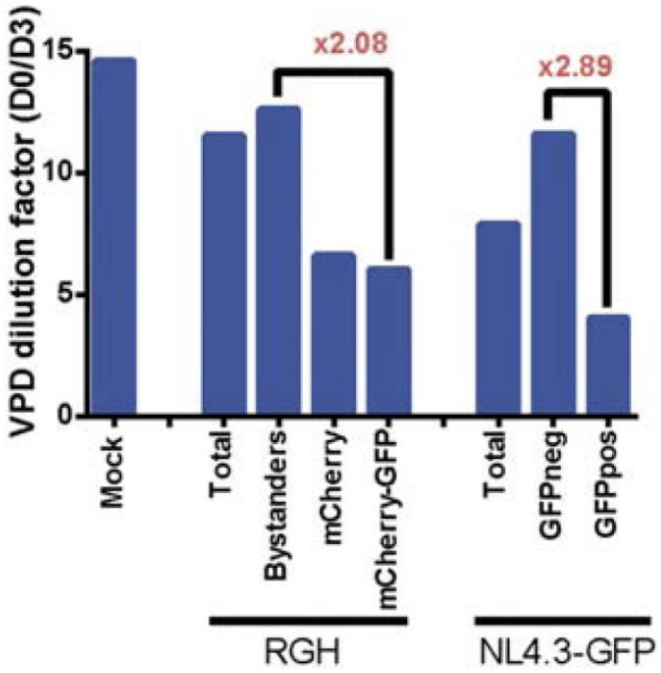
Astrocytes as an HIV CNS reservoir: highlights and reflections of an NIMH-sponsored symposium

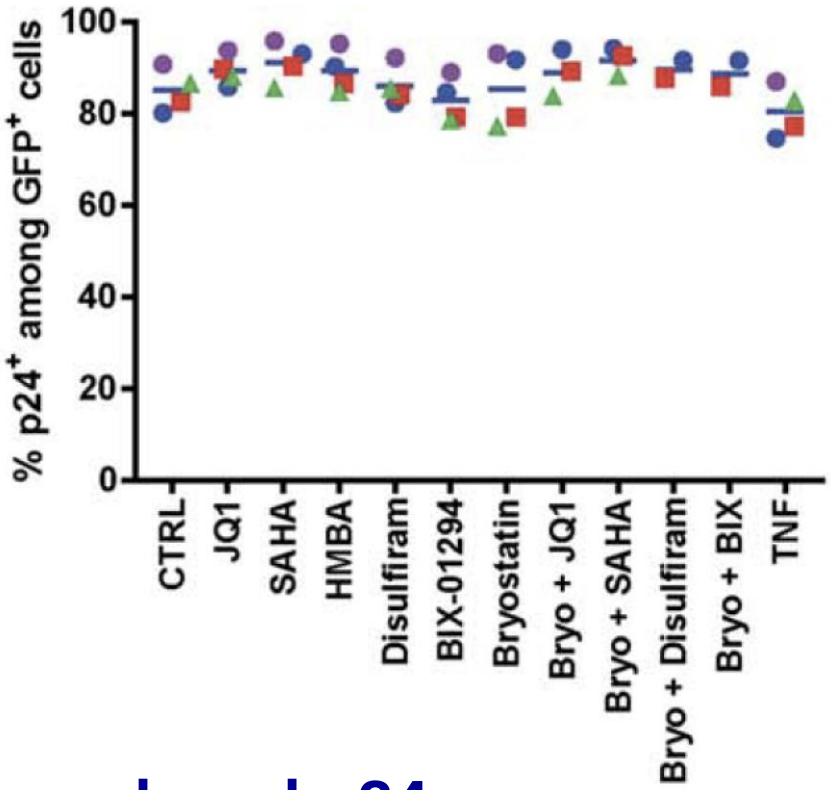
Astrocytes Can Sustain Productive HIV Infection

Non-Proliferating Astrocytes



Proliferating Astrocytes



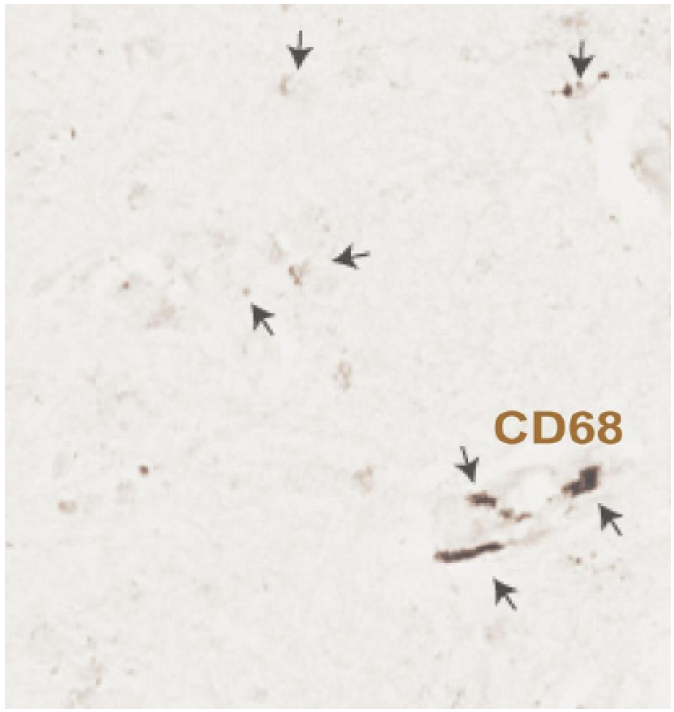


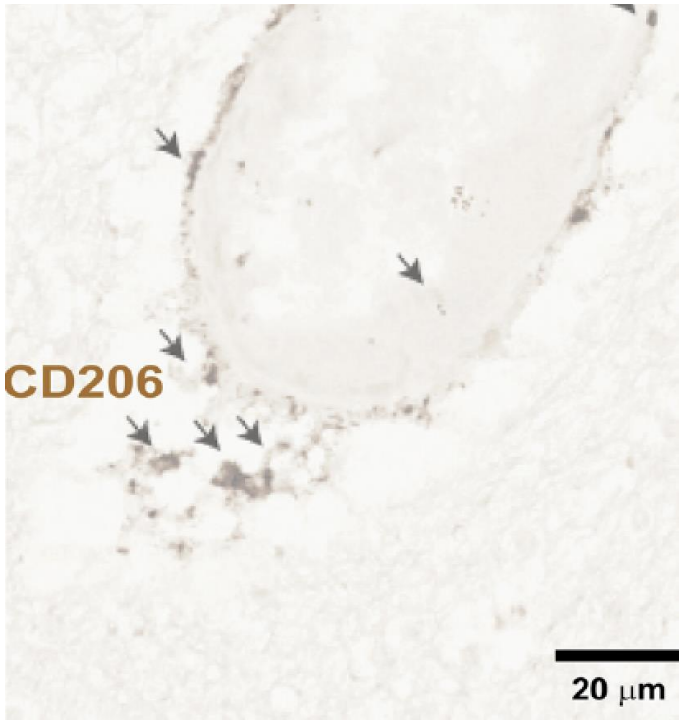
- **HIV-infected non-proliferating astrocytes stably produced p24**
- **HIV infection reduced replicative capacity of proliferating astrocytes**
- **No reactivation with latency reversing agents or strong inducers (TNF-α)**
  - **Proviruses may either not be transcriptionally competent or in a state of deep latency**

Barat et al, Glia 2017, DOI: 10.1002/glia.23310

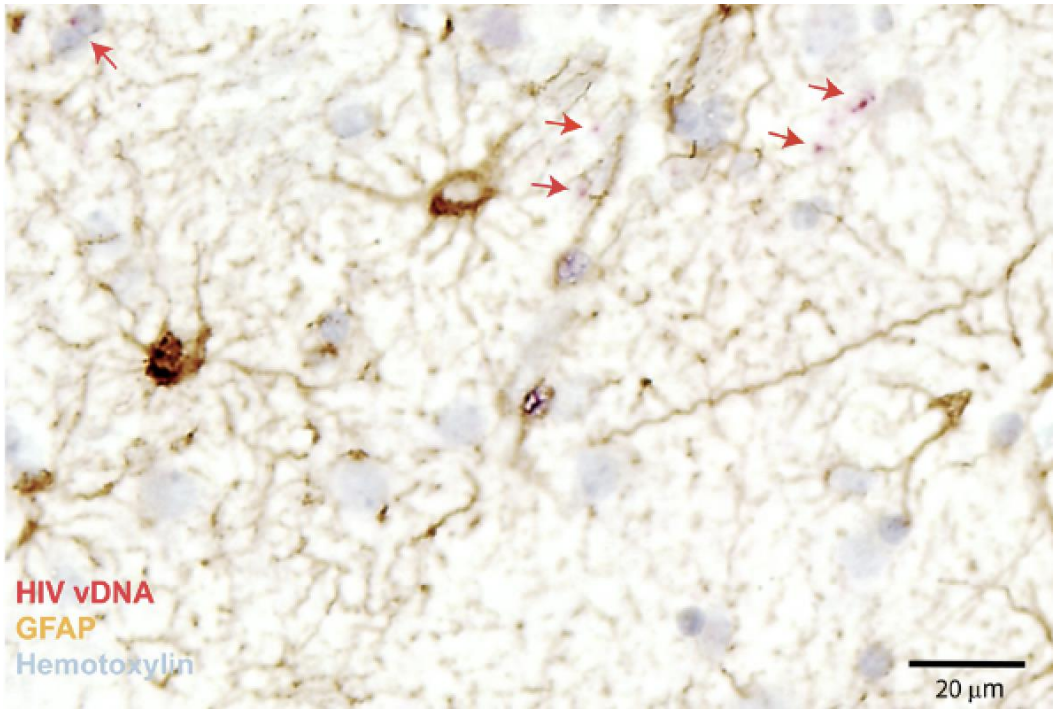
Macrophages but Not Astrocytes Are Infected

Myeloid Cell Markers





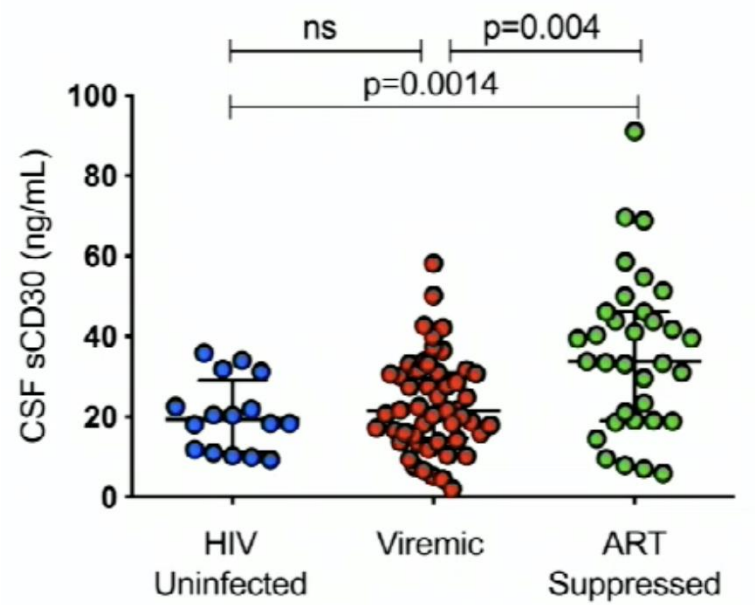
Astrocyte Marker (GFAP)

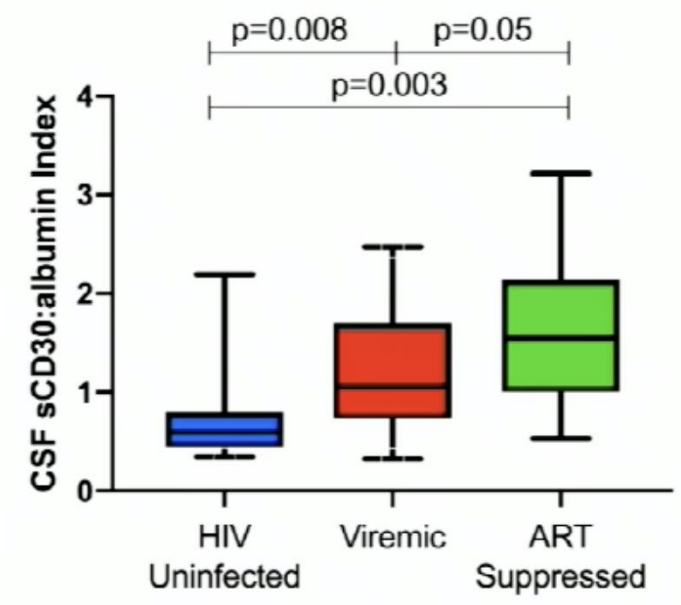


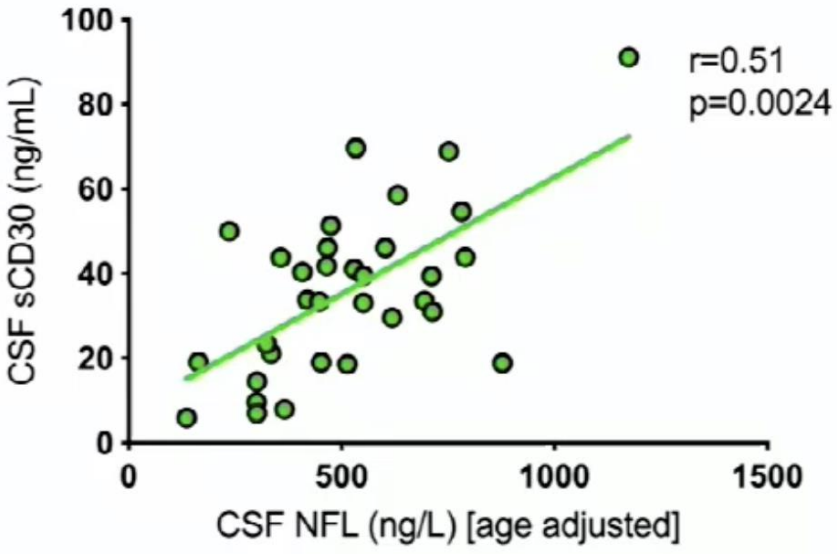
- 29 PWH from the NNTC who died while taking suppressive ART
- HIV DNA and RNA were present in brain tissue from all participants
  - Only present in brain macrophages & microglia, not in astrocytes

Ko et al, J Neuroimm Pharmacol 2019, doi.org/10.1007/s11481-018-9809-2

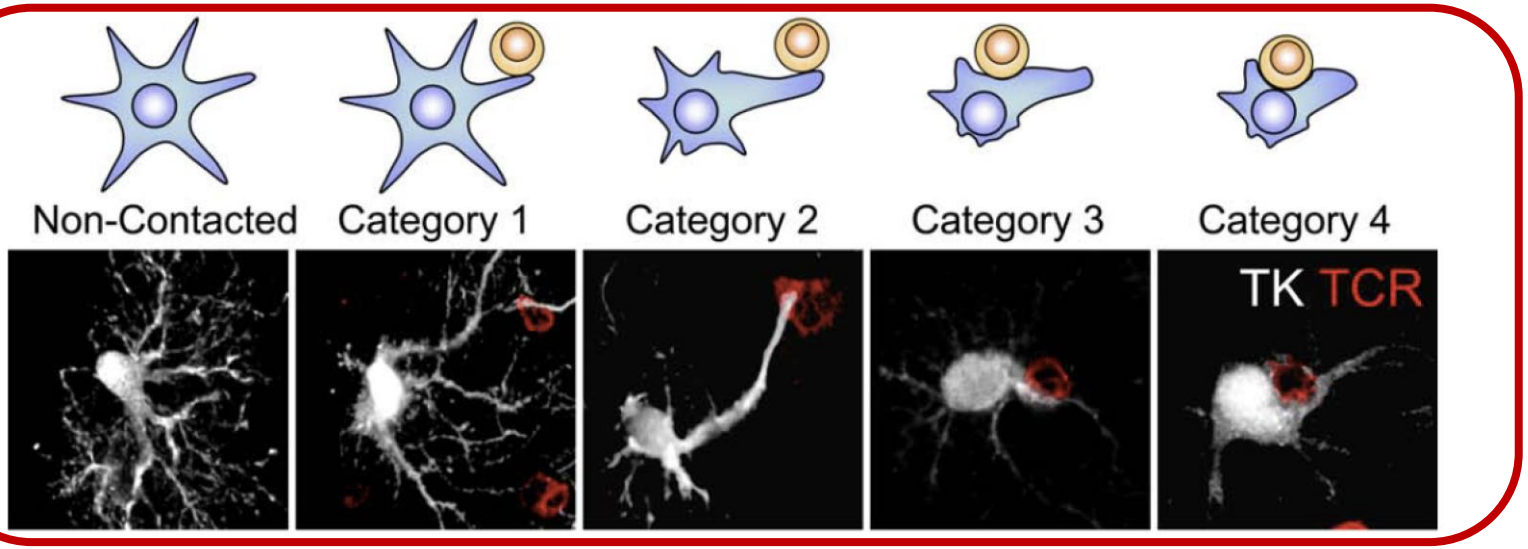
Activated T-Cells May Play a Role in HIV Persistence in the CNS







Peluso et al, CROI 2019, Abstract 125



Barcia et al, PLoS ONE 3(8): e2977. doi:10.1371/journal.pone.0002977

Which Cells Harbor HIV DNA in the CNS?

Strongest Evidence

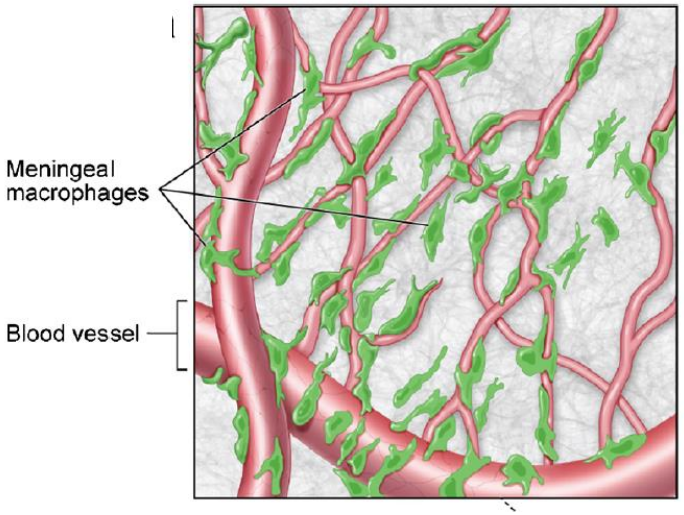
- Brain macrophages
- Microglia
- Migrating monocytes
- Migrating T-cells

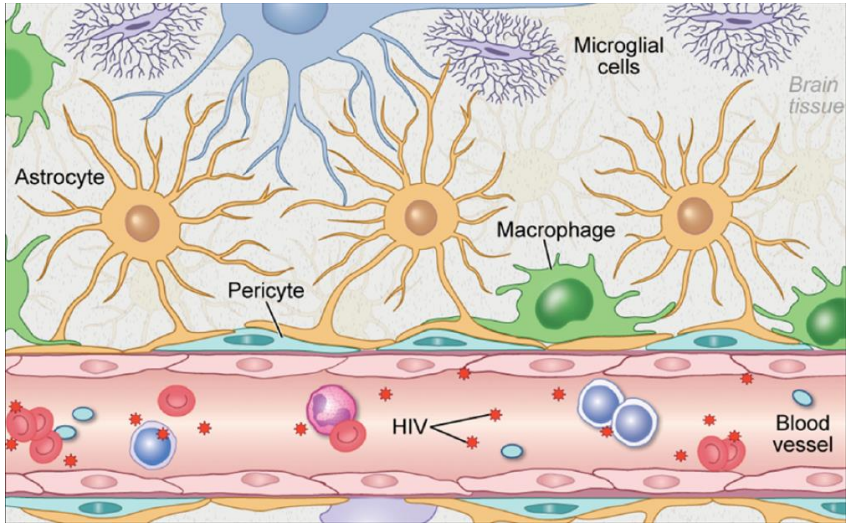
Inconsistent or Limited Evidence

- Astrocytes
- Oligodendrocytes
- Brain microvascular endothelial cells
- Pericytes
- Ependymal cells
- Neural precursor cells

Evidence of Absence

- Neurons

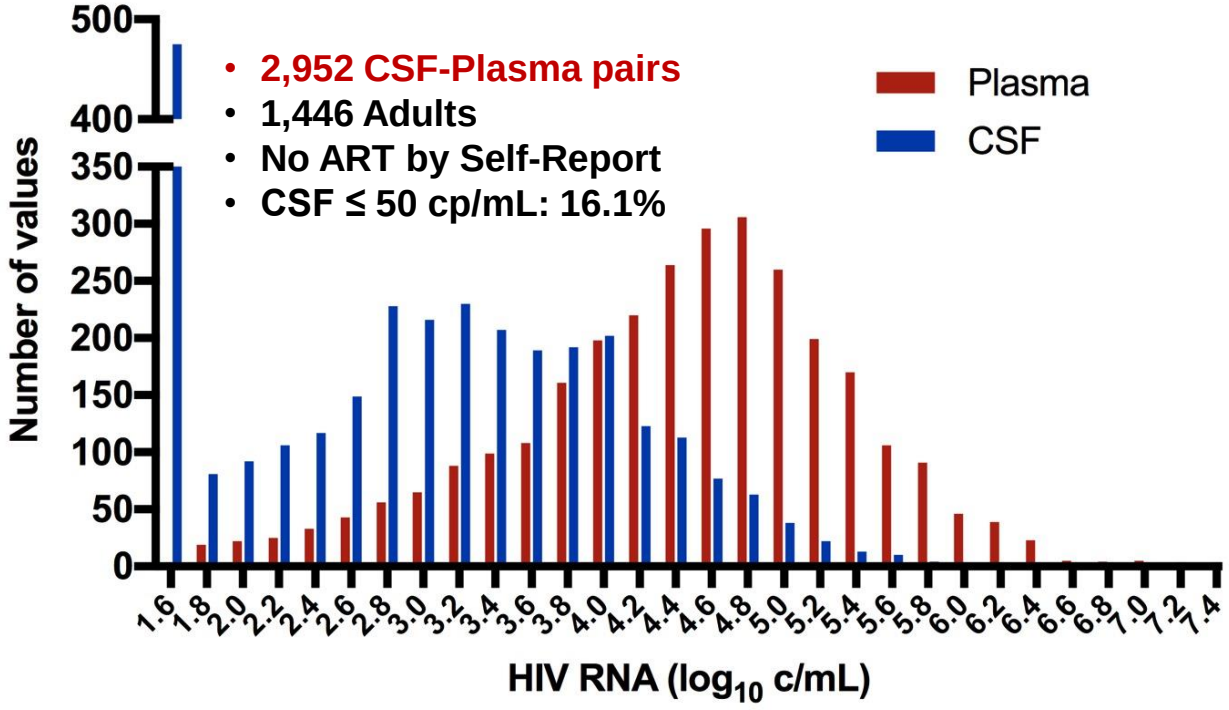


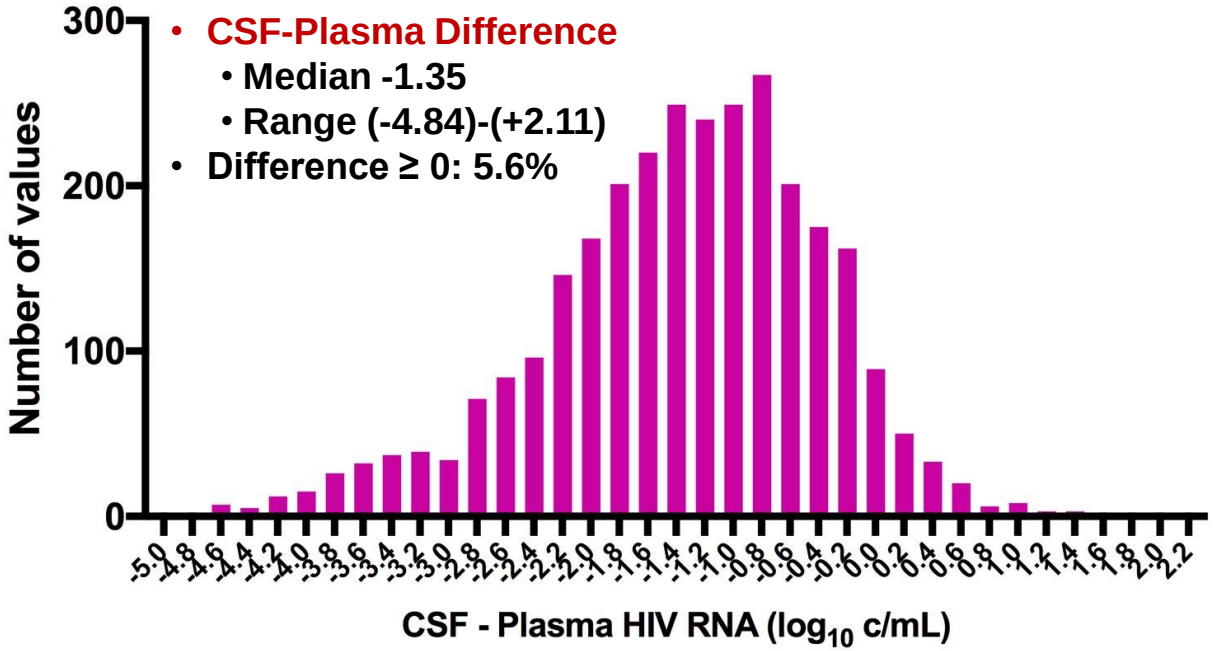


Nath A, J. Neurovirol. (2015) 21:227–234

LAST GIFT

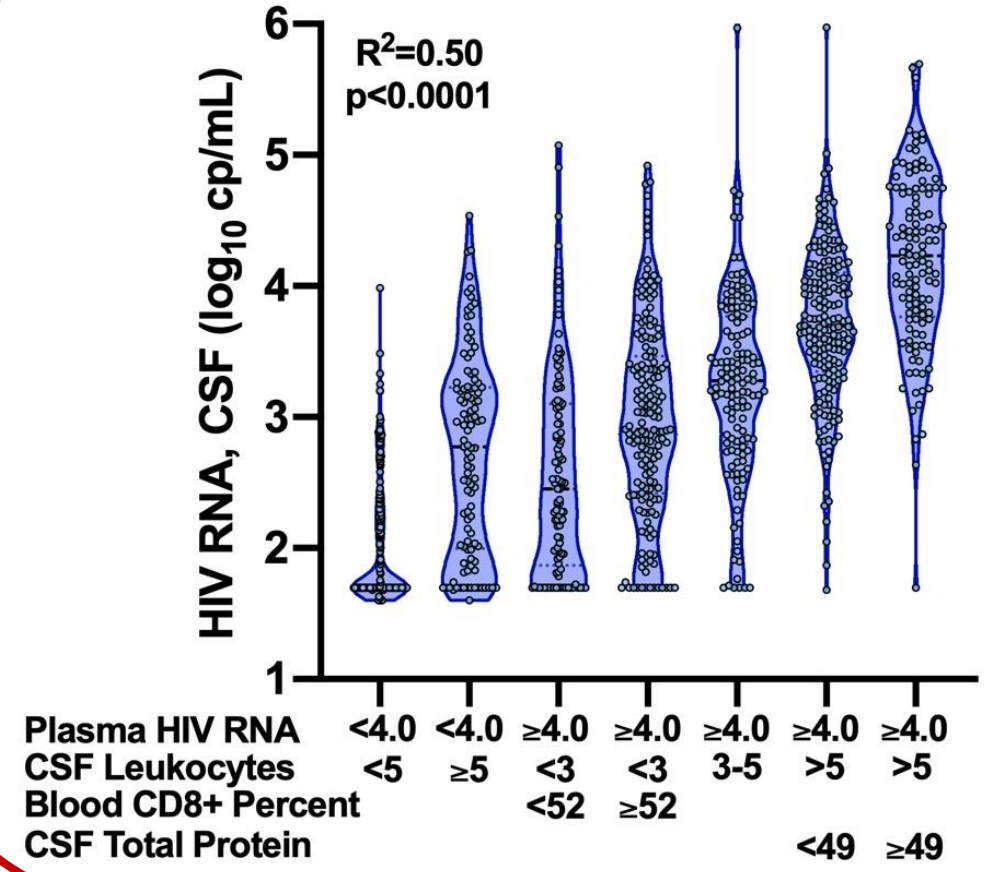
A UC San Diego Study





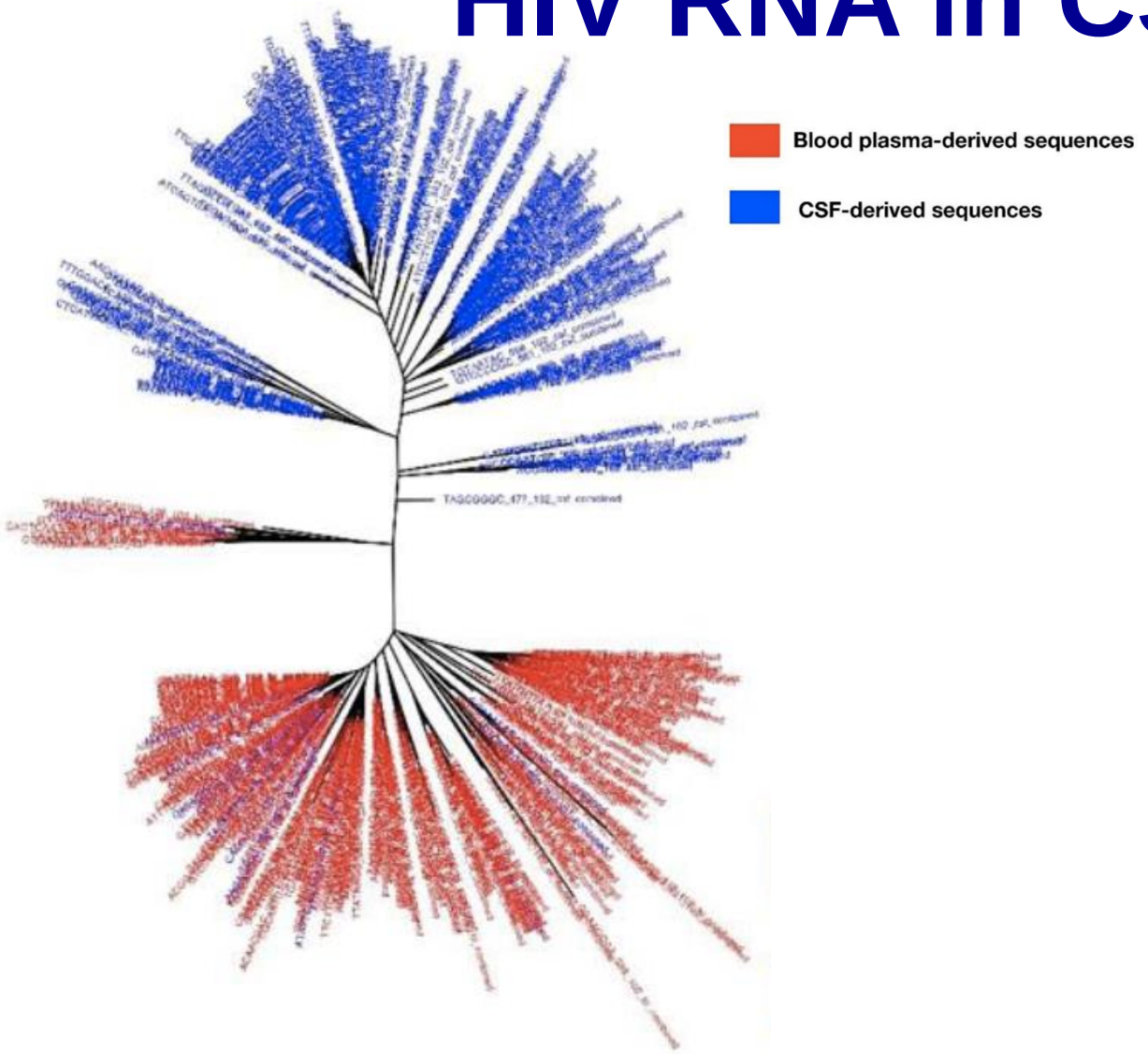
Correlates of HIV RNA in CSF off ART

- Higher HIV RNA in blood
- More CSF leukocytes
- Fewer CD4+ T-cells
- Higher CD4+ and CD8+ percent
- Lower serum albumin
- Higher total protein in CSF and blood
- Lower CSF glucose

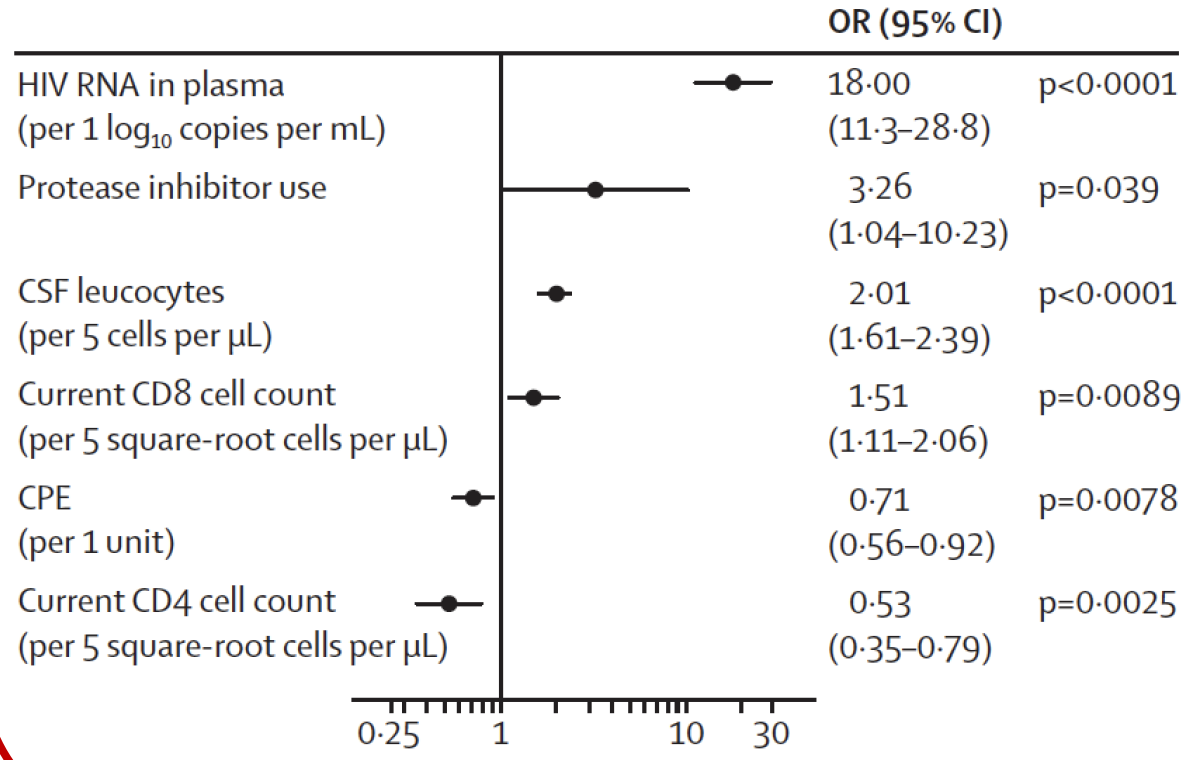


Okwuegbuna et al, CROI 2020, Accepted

Compartmentalization & HIV RNA in CSF During ART



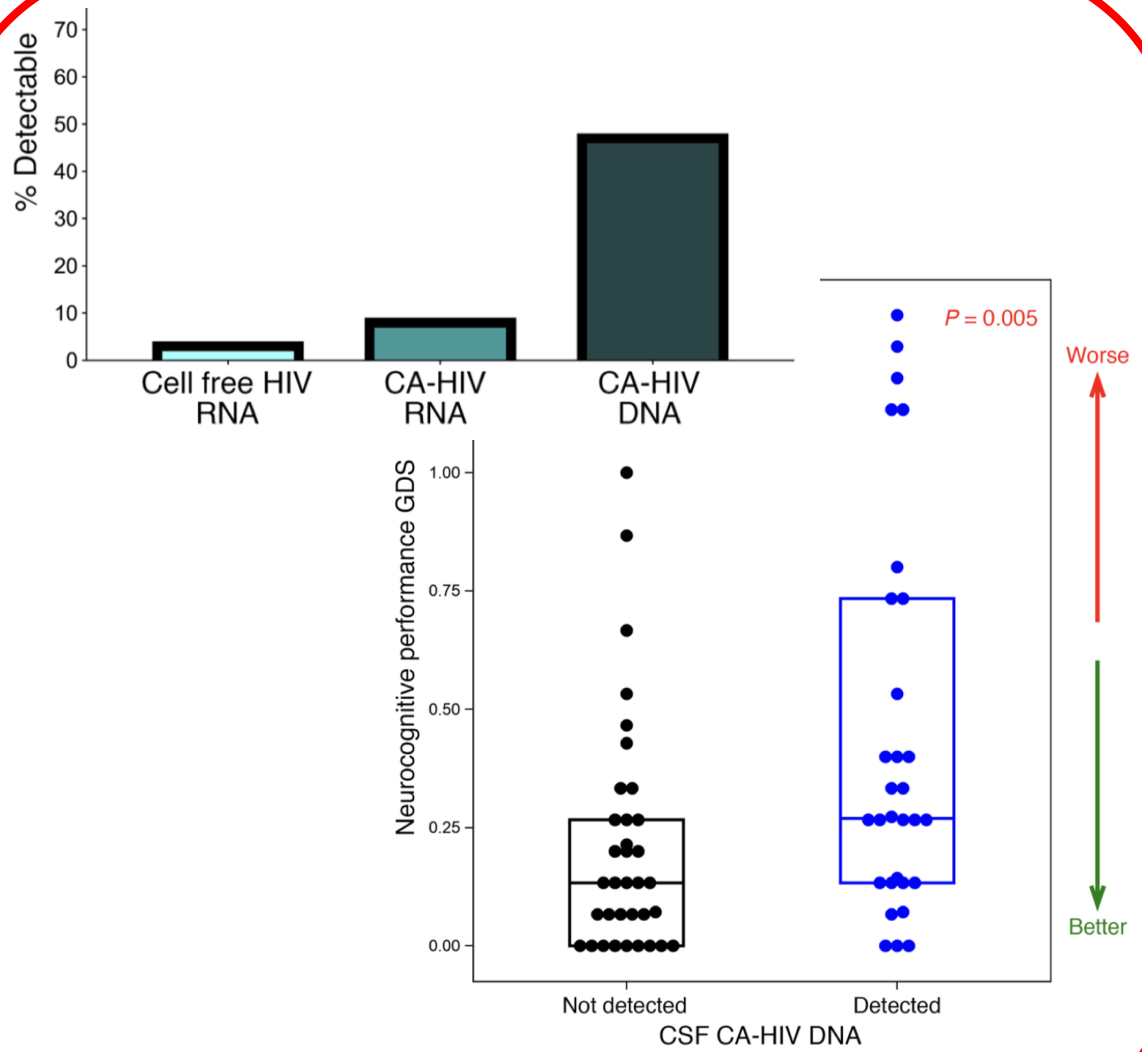
Correlates of HIV RNA in CSF during ART



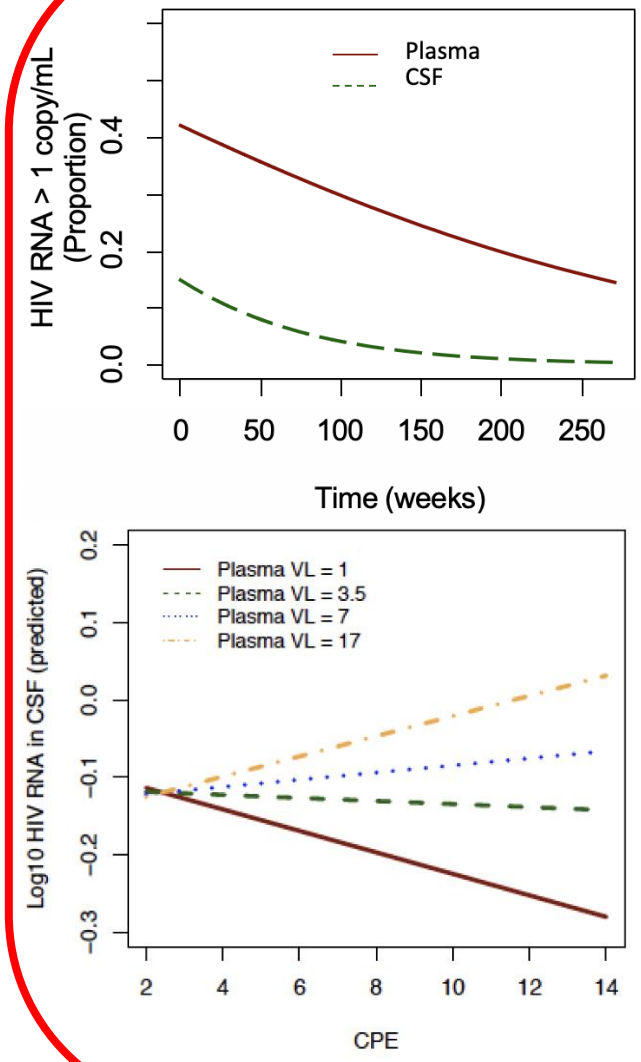
Bowman et al, CROI 2016, Abstract 401

Livelli, et al, Lancet HIV 2019; S2352-3018(19)30182-1

Low-Level HIV RNA or Cell-Associated HIV DNA in CSF



Spudich et al, J Clin Invest. 2019; 129(8):3339-3346



Detectable HIV RNA in Cell-Free CSF

	P value
Global	0.01
Processing Speed	0.006
Recall	0.012
Motor	0.026
Learning	0.12
Executive Functioning	0.42
Working Memory	0.47
Verbal Functioning	0.74

Anderson et al, J Infect Dis. 2019, Submitted

Highlights of the Global HIV-1 CSF Escape Consortium Meeting

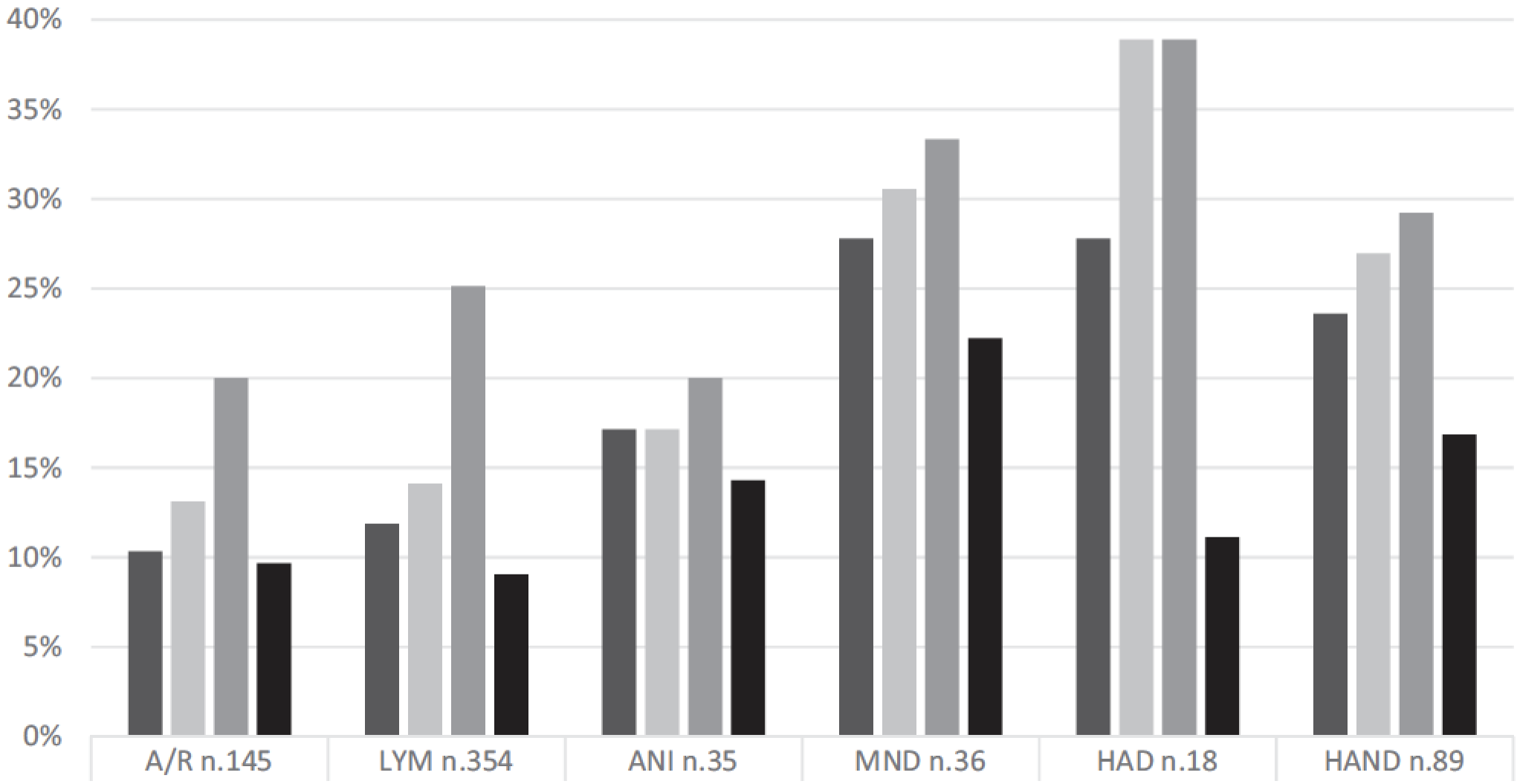
Jeymohan Joseph*[1], Paola Cinque[2], Deborah Colosi[1], Ameet Dravid[3], Luminita Ene[4], Howard Fox[5], Dana Gabuzda[6], Magnus Gisslen[7], Sarah Beth Joseph[8], Scott Letendre[9], Shibani S. Mukerji[6,10], Avindra Nath[11], Ignacio Perez-Valero[12], Deborah Persaud[13], Richard W. Price[14], Vasudev R. Rao[1], Ned Sacktor[15], Ronald Swanstrom[8], Alan Winston[16], Valerie Wojna[17], Edwina Wright[18] and Serena Spudich[19]

Speakers	Study site	Total number of cases	Number of cases of HIV-1 CSF escape	Neurosymptomatic	Asymptomatic	Criteria for determining CSF escape	Estimated prevalence[1]
Price, Gisslen, Cinque, Spudich, Joseph S	Multiple[2] (San Francisco, New Haven, Chapel Hill, USA; Sweden; Italy)	N/A	81	42	39	Symptomatic: PVL<50 & CVL>100 or PVL 50–100 & CVL 2 × PVL; or Asymptomatic: PVL<50 & CVL>50	N/A
Joseph S	THINC Study Sites (Chapel Hill, San Francisco, New Haven, USA)	97	6	N/A	6	PVL<40 & CVL>40 or CVL>PVL	6%
Winston (UK)	UK	142	30	3	27	PVL<50 & CVL>200 or $\log_{10}$ CVL>1.5 × $\log_{10}$ PVL	21%
Winston (Europe)	EU	134	1	1	N/A	CVL>PVL	0.7%
Ene	Romania/Adult	91	4	2	2	CVL>0.5 log of PVL	4.4%
Perez	Spain	125	4	4	N/A	PVL: not detectable; CVL: detectable	3.2%
Sacktor	Uganda	91	9	4	5	PVL: not detectable; CVL: detectable	10%
Wright	Australia	167	6	3	3	PVL: 6 months not detectable; CVL: detectable	3.5%
Dravid	India	62	17	17	0	CVL: detectable with PVL: not detectable; CVL>1 log of PVL	27.4%
Letendre	CHARTER/HNRC sites	849	60	23	37	CVL>PVL with PVL: not detectable; CVL>1 log of PVL	7%
Nath	Washington DC	56	11	7	4	PVL<40; CVL>20	20%
Gabuzda	Boston, MA/NNTC (four sites)	200/426 (626)	11/29 (40)	11/17	0/12	PVL<50, CVL>50; CVL>0.5 log of PVL	6.4%
Wojna	Puerto Rico**	380	10	3/9	6/9	CVL>PVL	2.6%

Range: 0.7%-27.4%

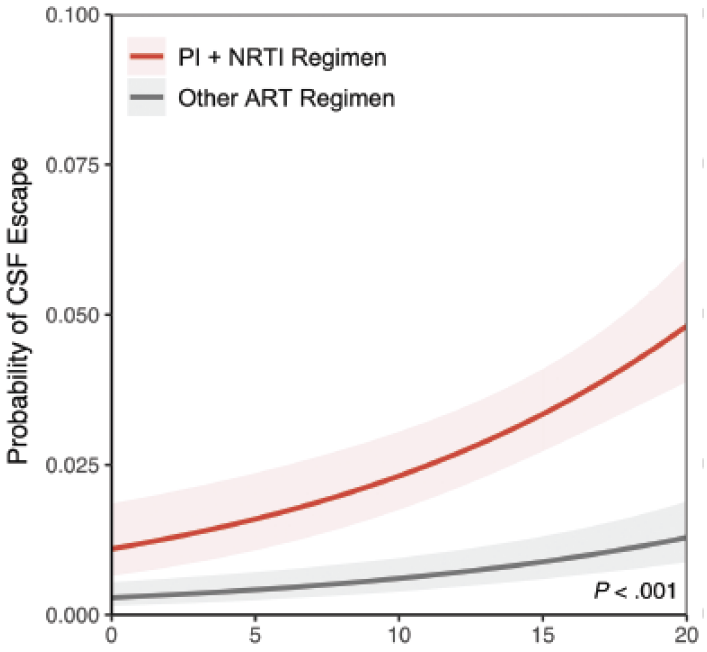
Journal of Virus Eradication

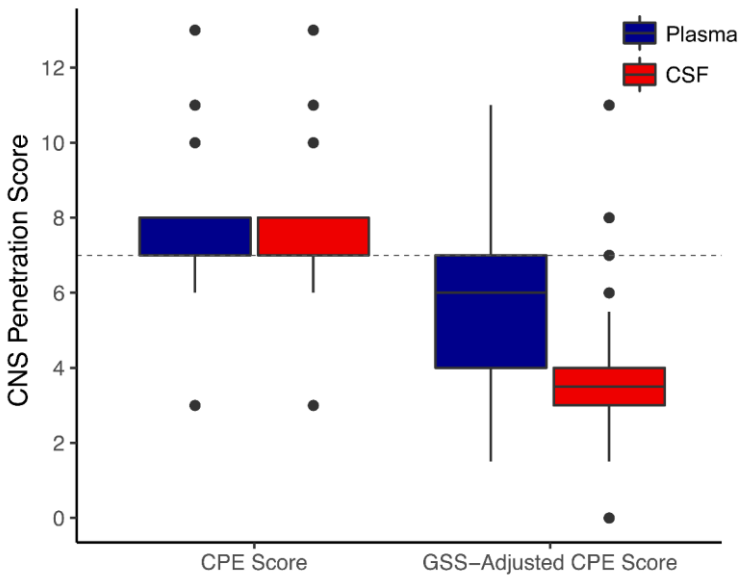
CSF Escape Frequency Varies with Definition

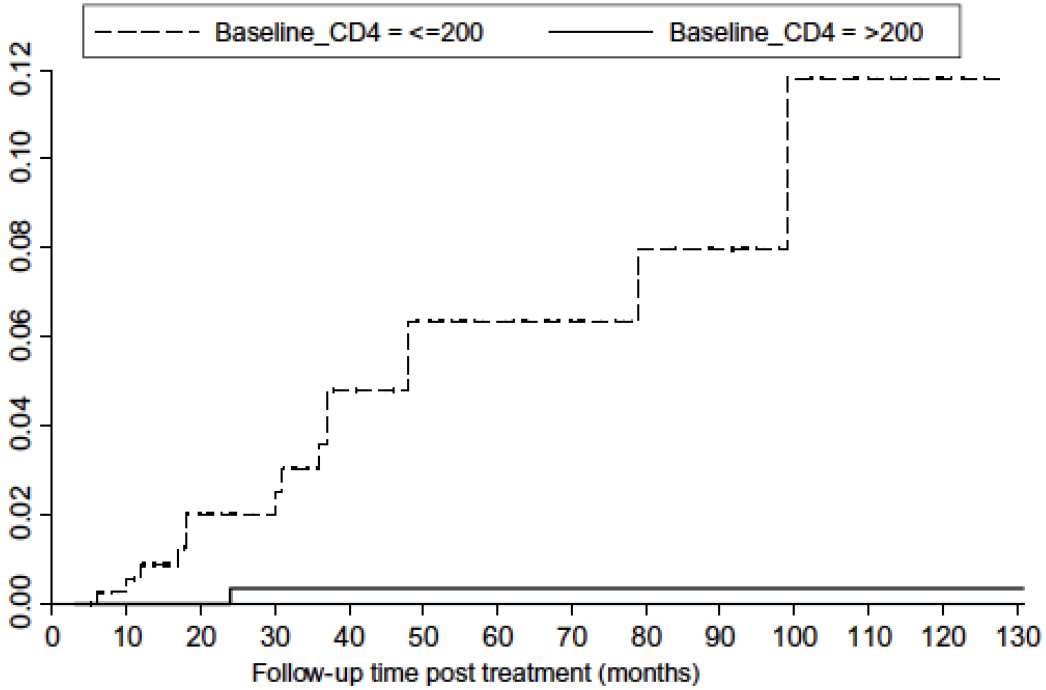


Trunfio, et al, AIDS 2019; DOI:10.1097/QAD.0000000000002091

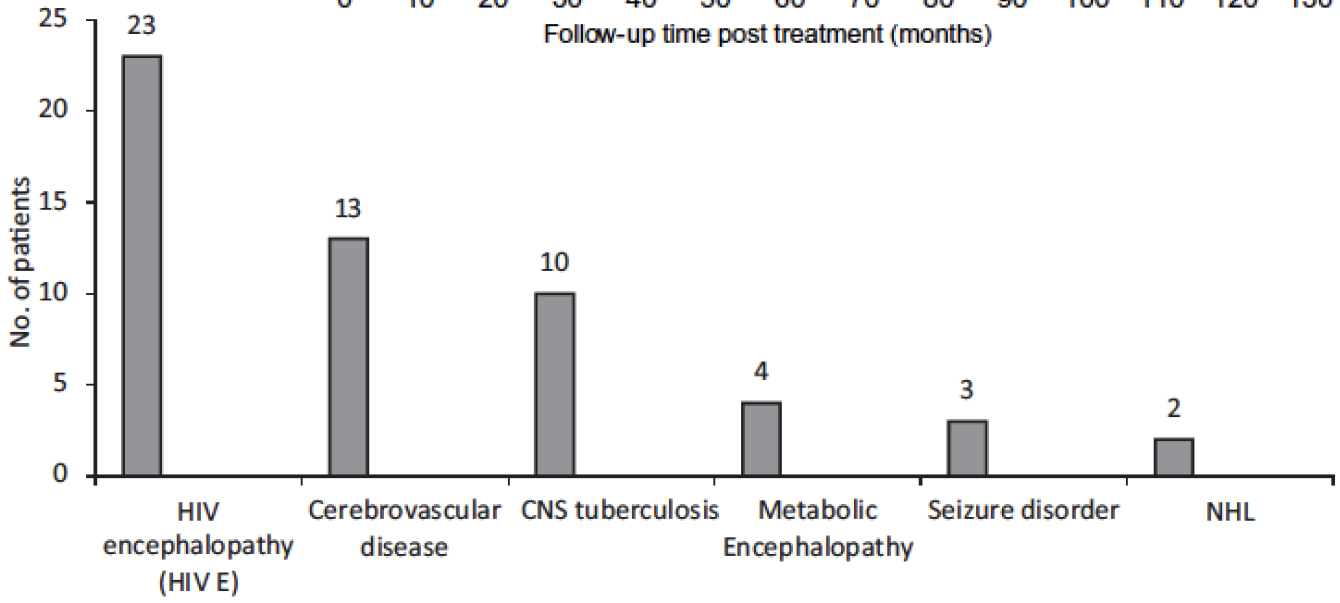
Correlates of CSF Viral Escape





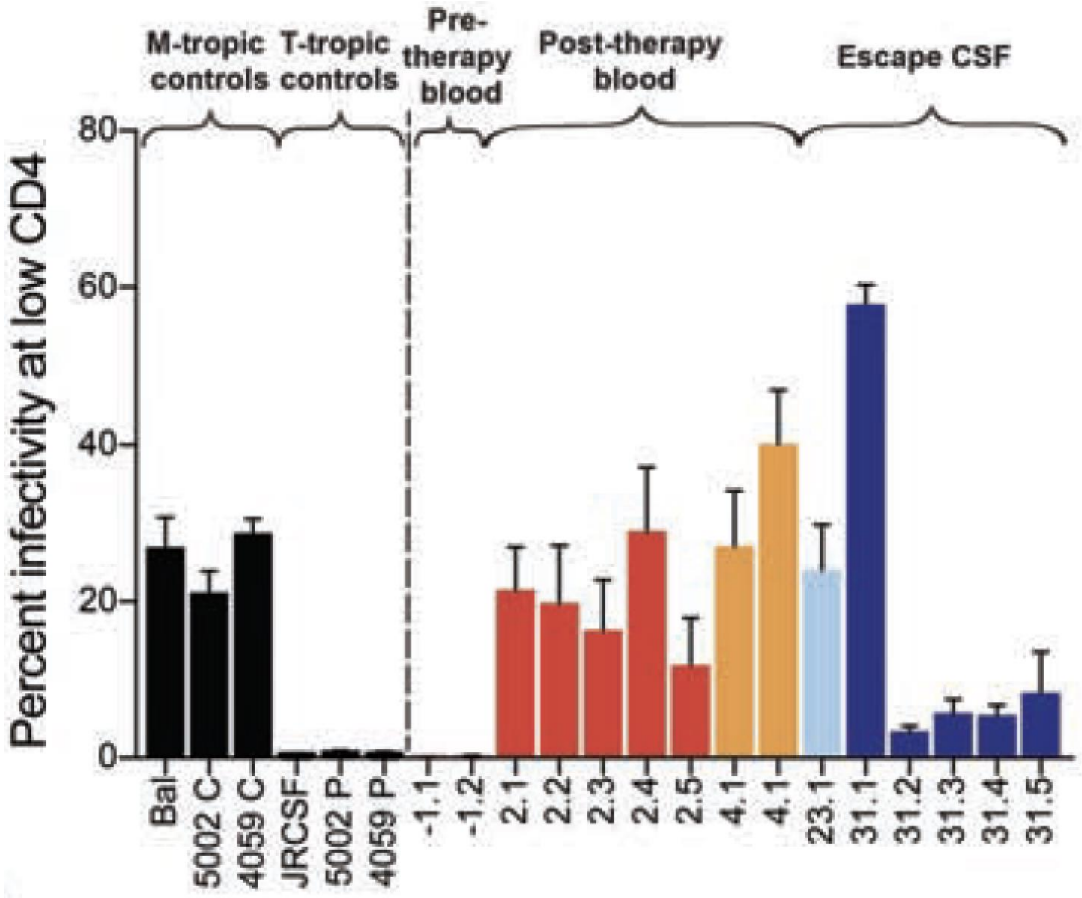


Mukerji, et al, Clin Infect Dis. 2018; 67(8):1182–90
Patel, et al, Journal of NeuroVirology (2018) 24:498–505
Dravid et al, Medicine (2018) 97:8(e9969)

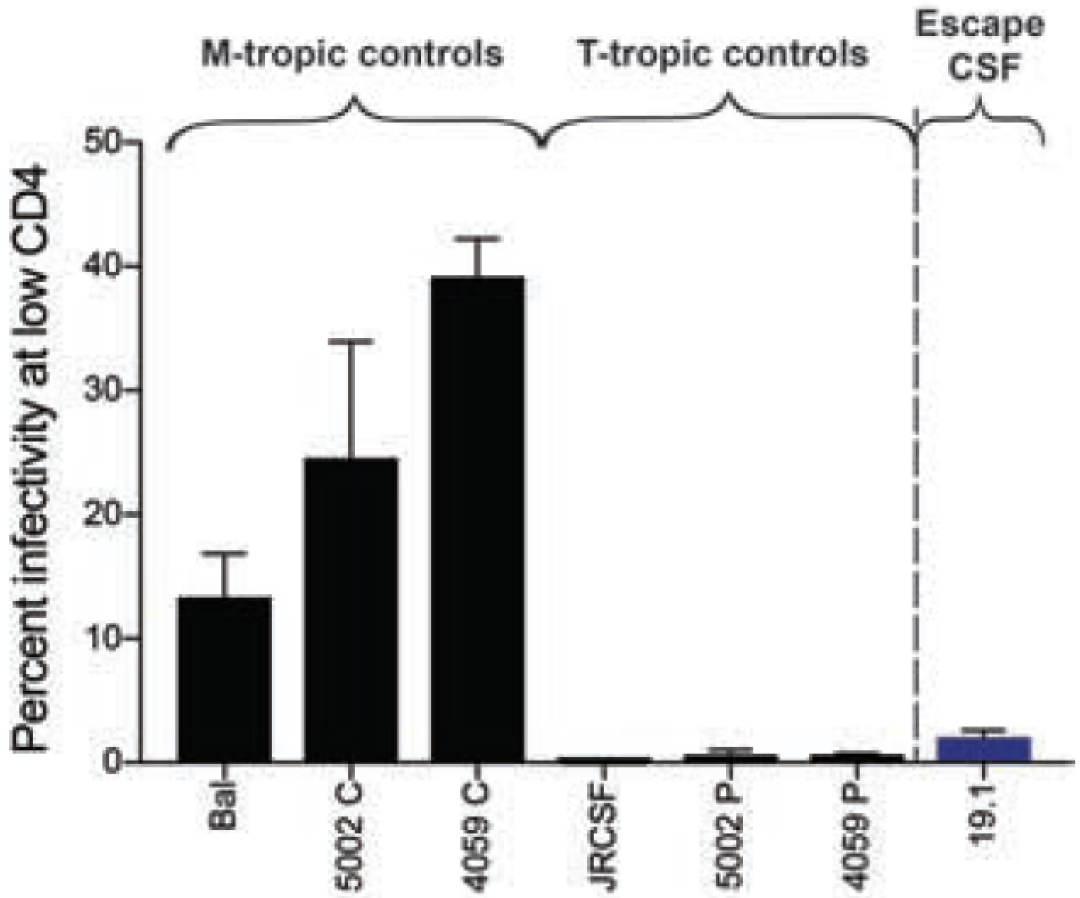


CSF Viral Escape can Occur with M-Tropic or T-cell-Tropic HIV

Persistent Escape: M-Tropic

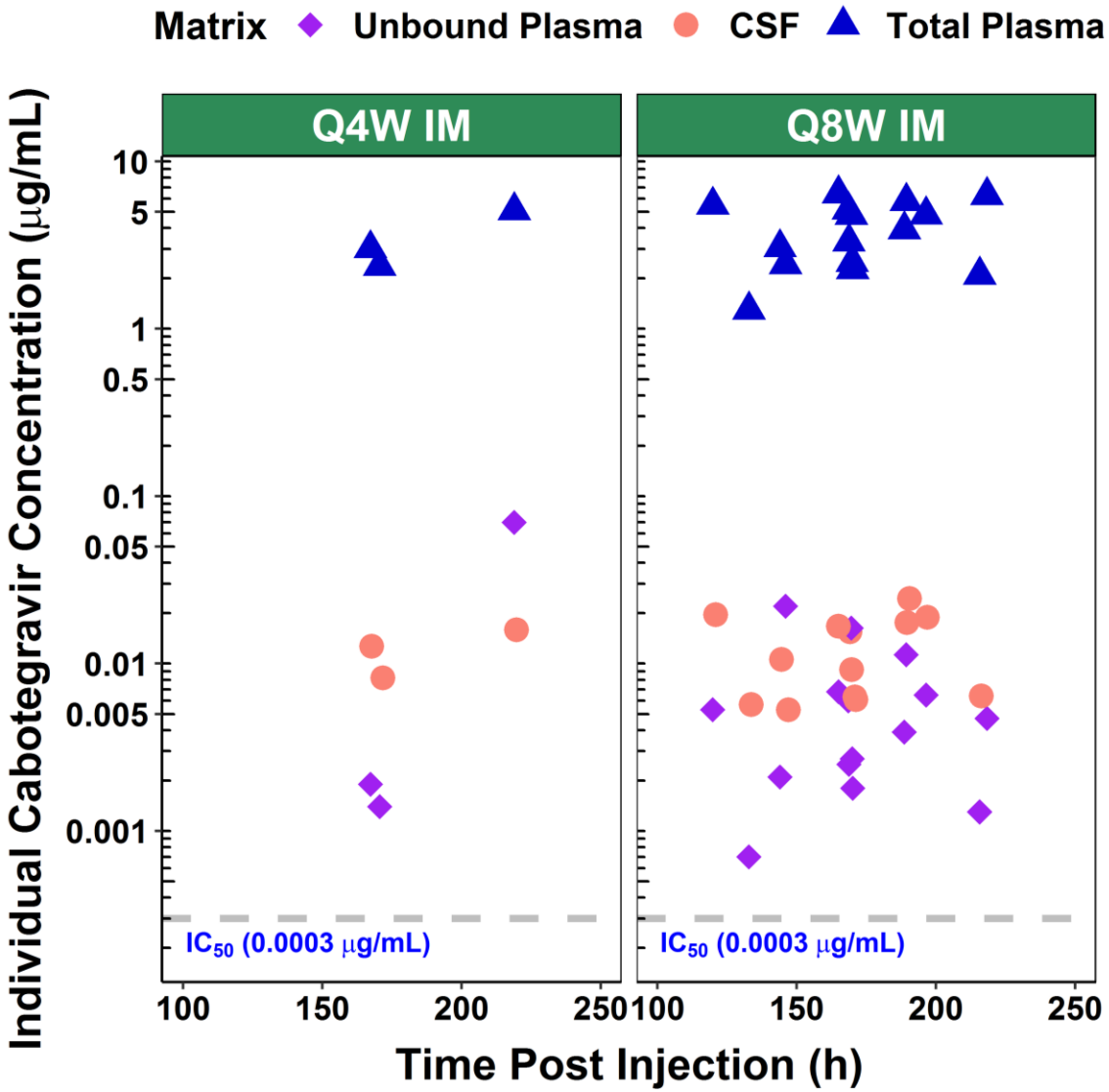


Transient Escape: T-Tropic

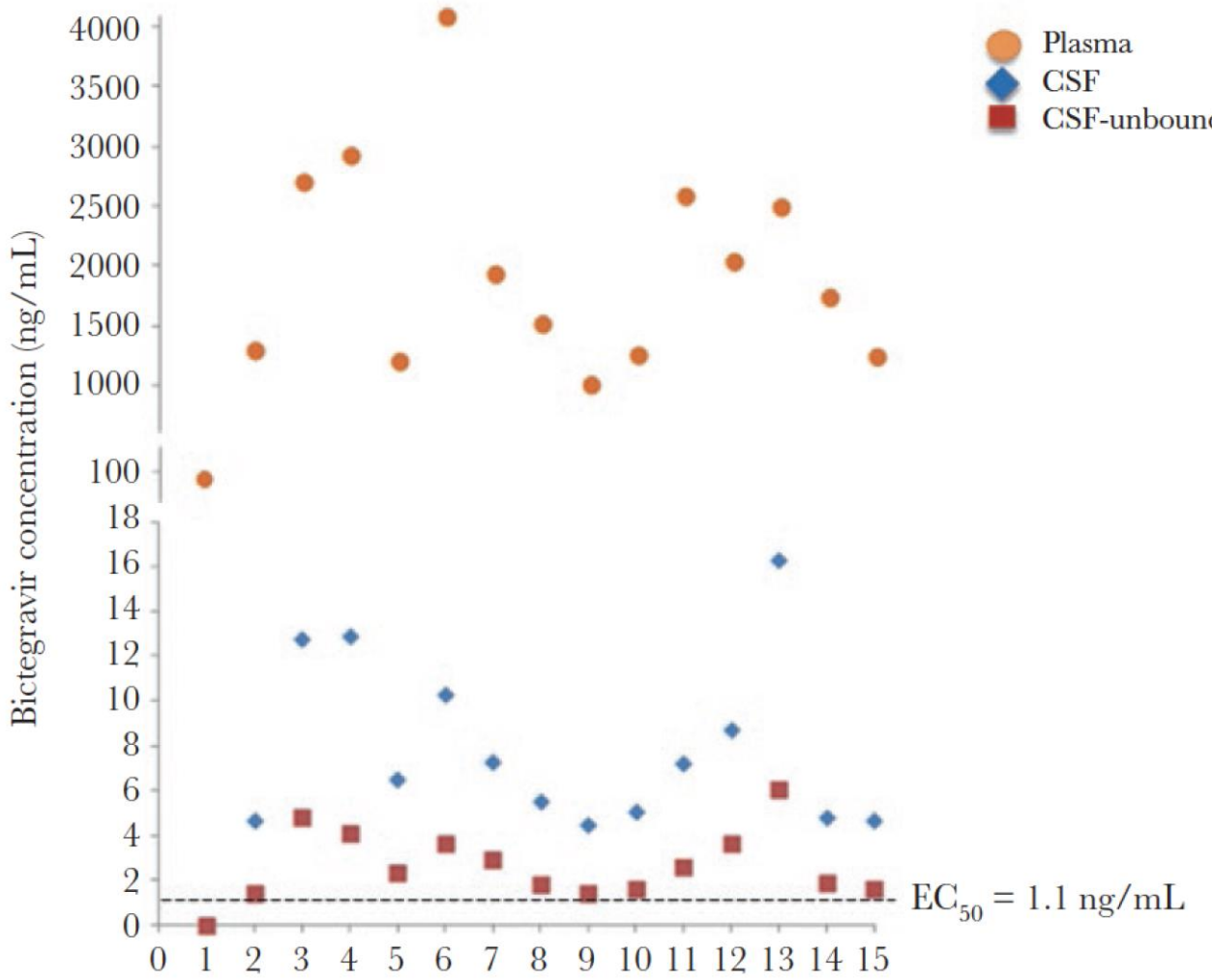


Joseph, et al, Clinical Infectious Diseases 2019;69(8):1345-52

Concentrations of CAB and BIC in CSF

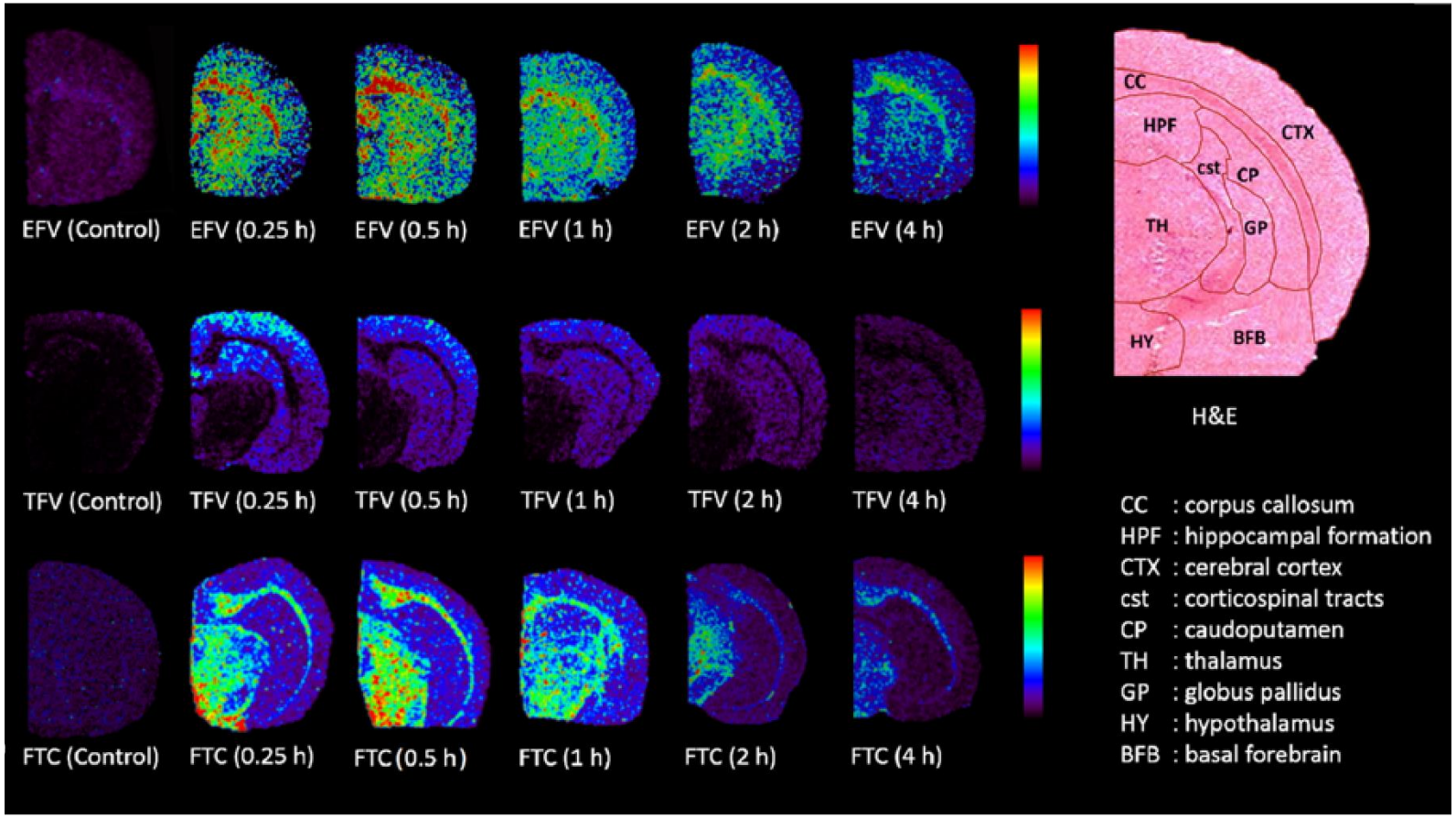


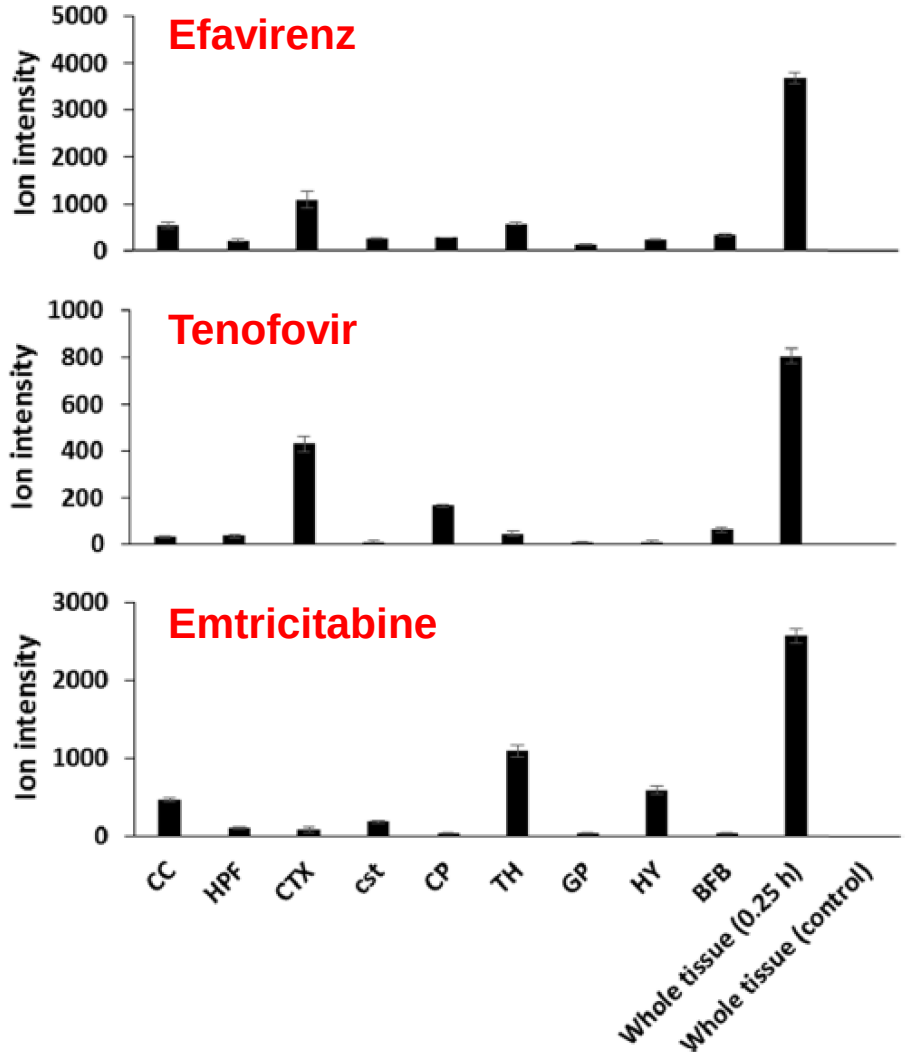
Letendre et al. HIV Glasgow; 2018. Oral O346.



Tiraboschi et al. J Infect Dis 2019, PMID: 31784745

Brain Regional Variation of ART Concentrations in Rats





Ntshangase et al. ACS Omega 2019, 4, 21169−21177

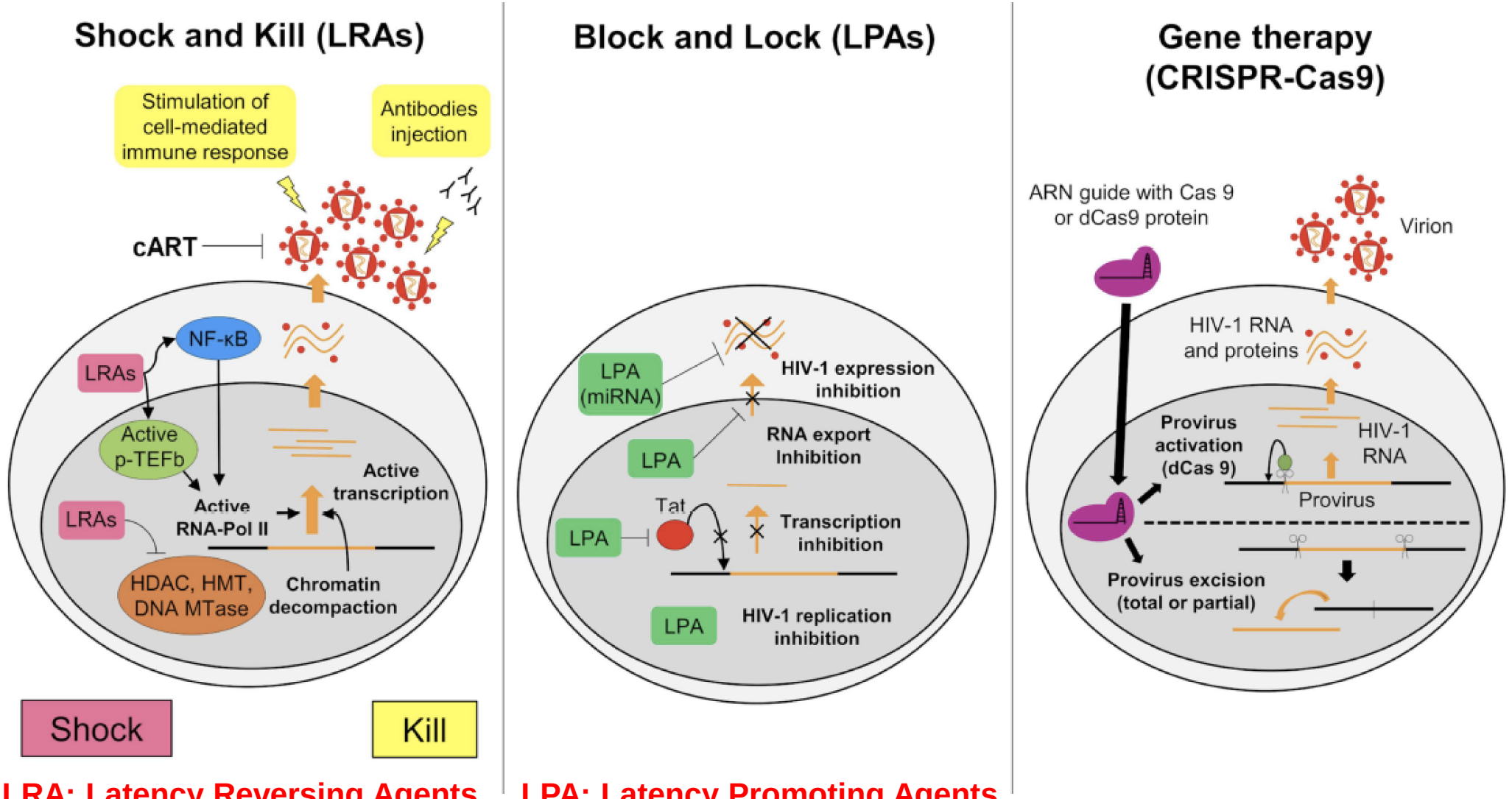
Inconsistent Results on InSTI Neurotoxicity

First author	Abstract	Sample Size	Drugs	Design	Neurobehavioral Findings	Neuroimaging Findings
Vera	122	12	Raltegravir Dolutegravir	Switch 120 Days	Global NP: No difference PRO: No difference	fMRI: No difference FC: Increase in 3 resting-state networks
Mora-Peris	443	20	Raltegravir Dolutegravir	Switch 120 Days	Global NP: No difference PRO: No difference	^{1}H-MRS: Higher NAA/Cr with DTG (p=0.07)
Prats	439	42	InSTIs	Early vs. Chronic HIV 48 Weeks	NPZ12: No differences Depressive, Anxiety, and Stress: Worse at Baseline in Early HIV	sMRI: Decrease in medial orbital frontal cortex in Chronic HIV
O'Halloran	442	202	InSTIs vs. Non-InSTIs	Clinical cohort	Global & Learning/Memory: InSTIs worse	sMRI: Lower total and subcortical GM with InSTIs
Chan	440	254	Dolutegravir	Switch 48 Weeks	NPZ4: Improved PHQ-9 Somatic: Worsened	None reported

PRO=Patient-Related Outcome
FC=Functional Connectivity
InSTI=Integrase Strand Transfer Inhibitors
PHQ=Patient Health Questionnaire

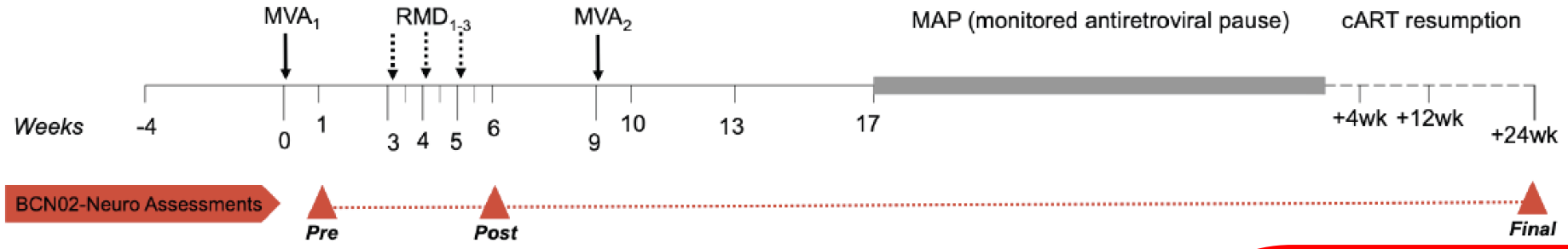
CROI
Conference on Retroviruses and Opportunistic Infections

HIV Eradication Strategies

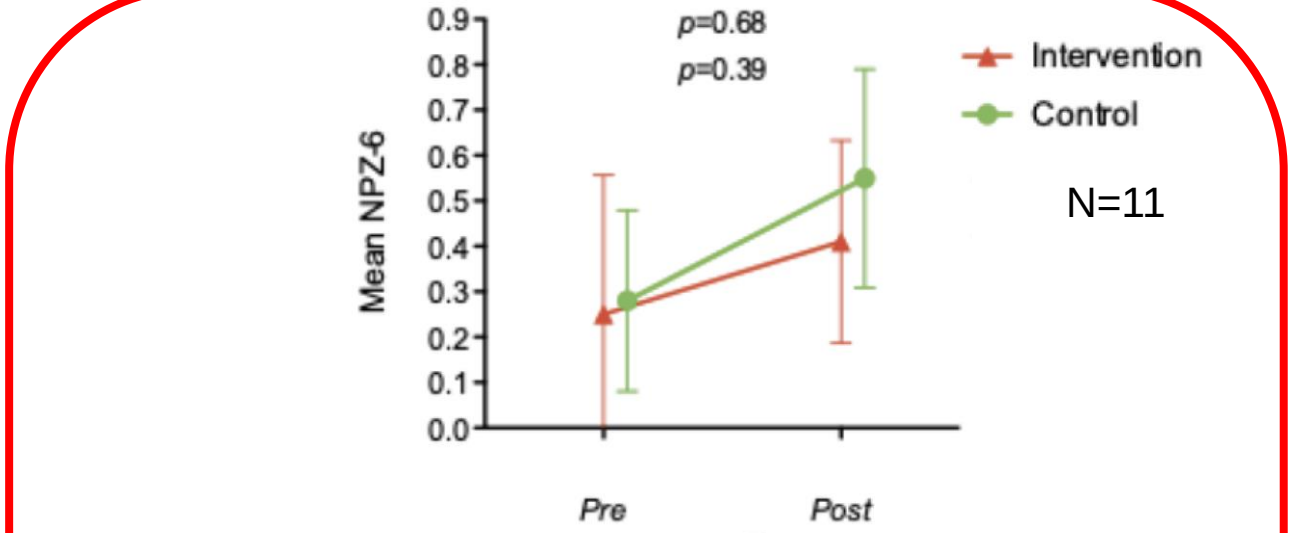


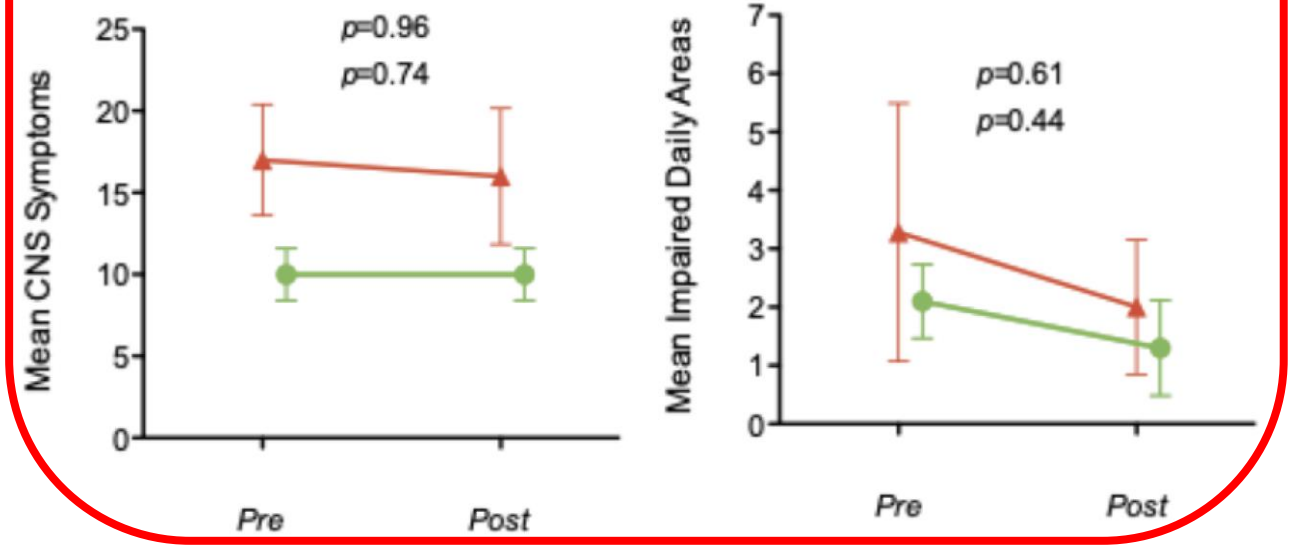
LRA: Latency Reversing Agents **LPA: Latency Promoting Agents**

Wallet et al, Frontiers in Cellular and Infection Microbiology 2019, doi: 10.3389/fcimb.2019.00362

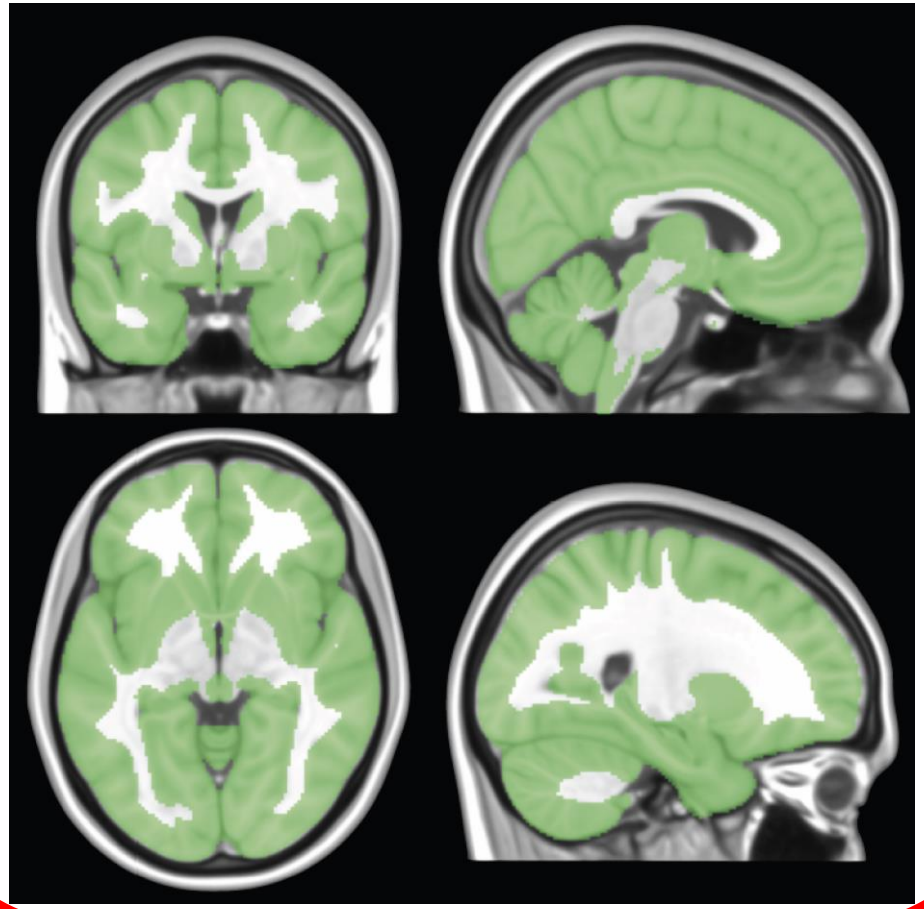


MVA: MVA.HIVconsv vaccine
RMD: Romidepsin
MAP: Monitored ART Pause

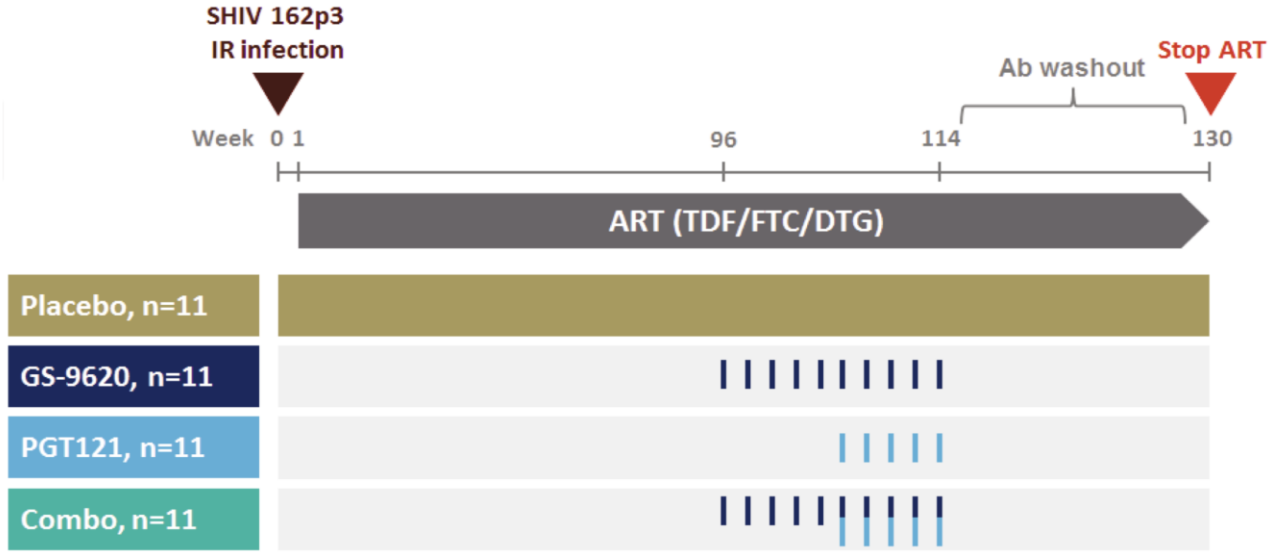


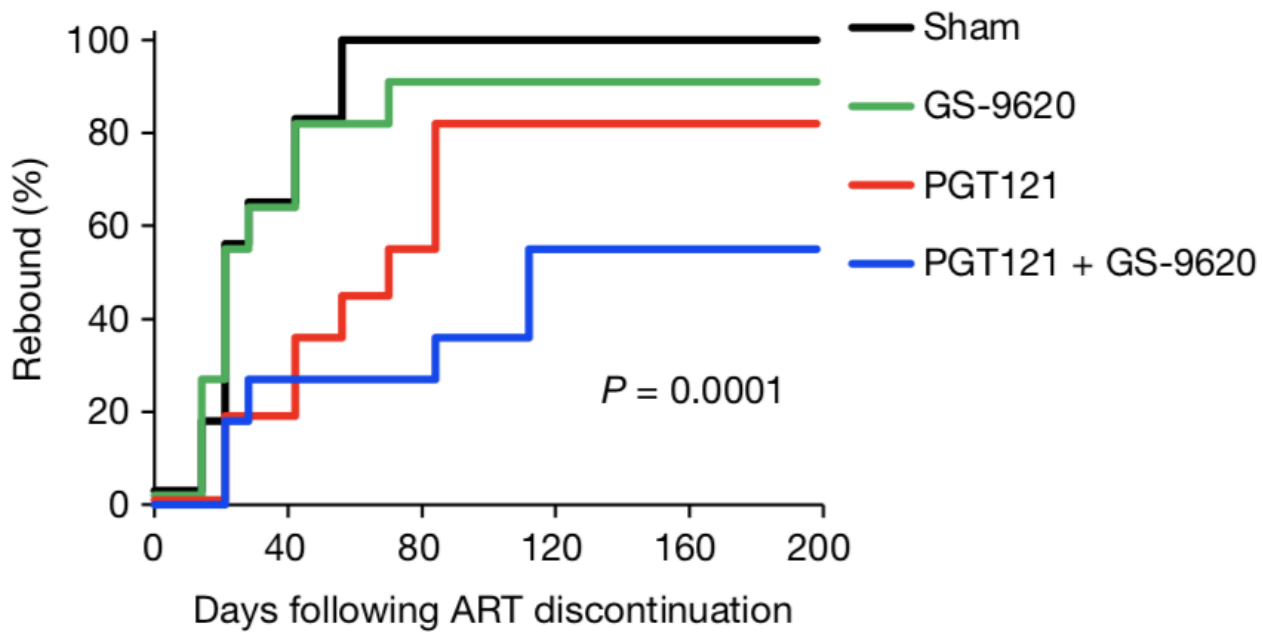


Structural, T1-weighted, 3T MRI

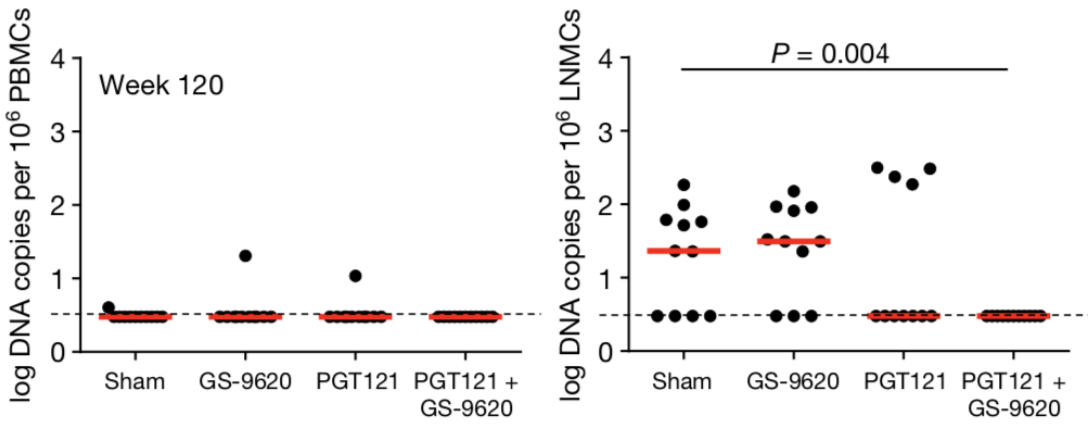


Carrillo-Molina, et al, CROI 2019, Abstract 438





Before ART Discontinuation



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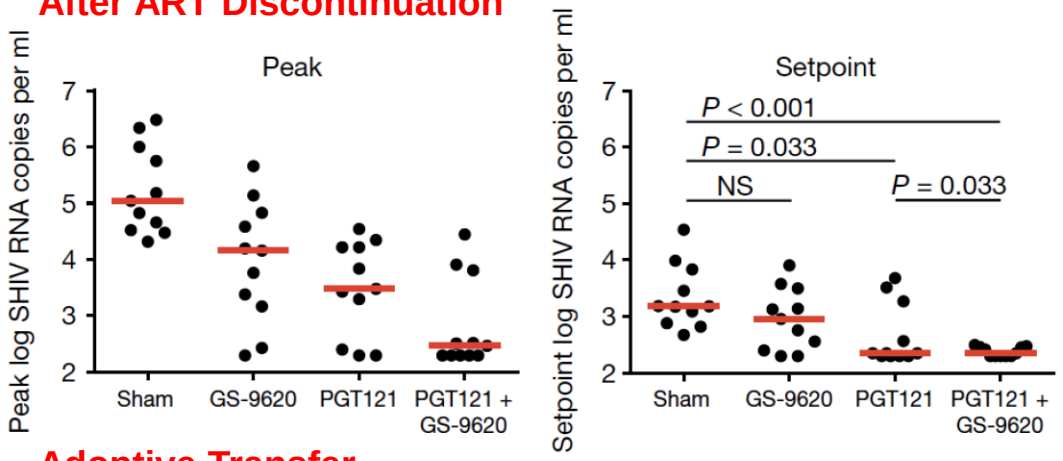
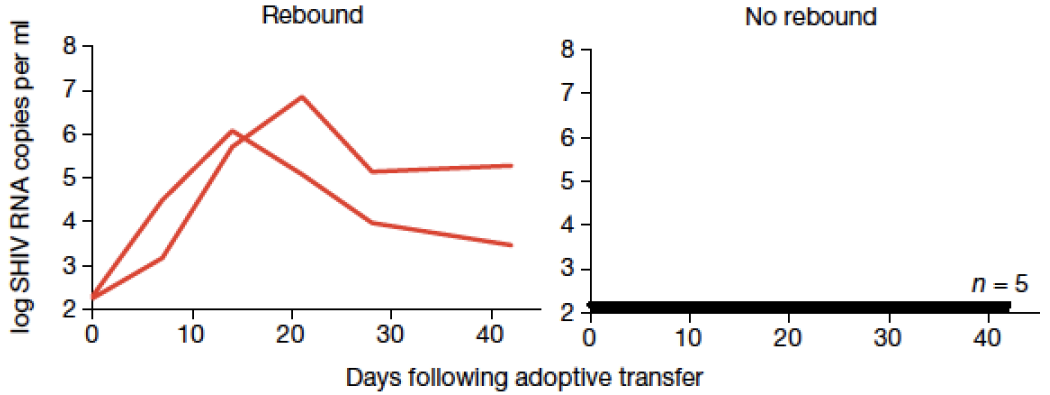
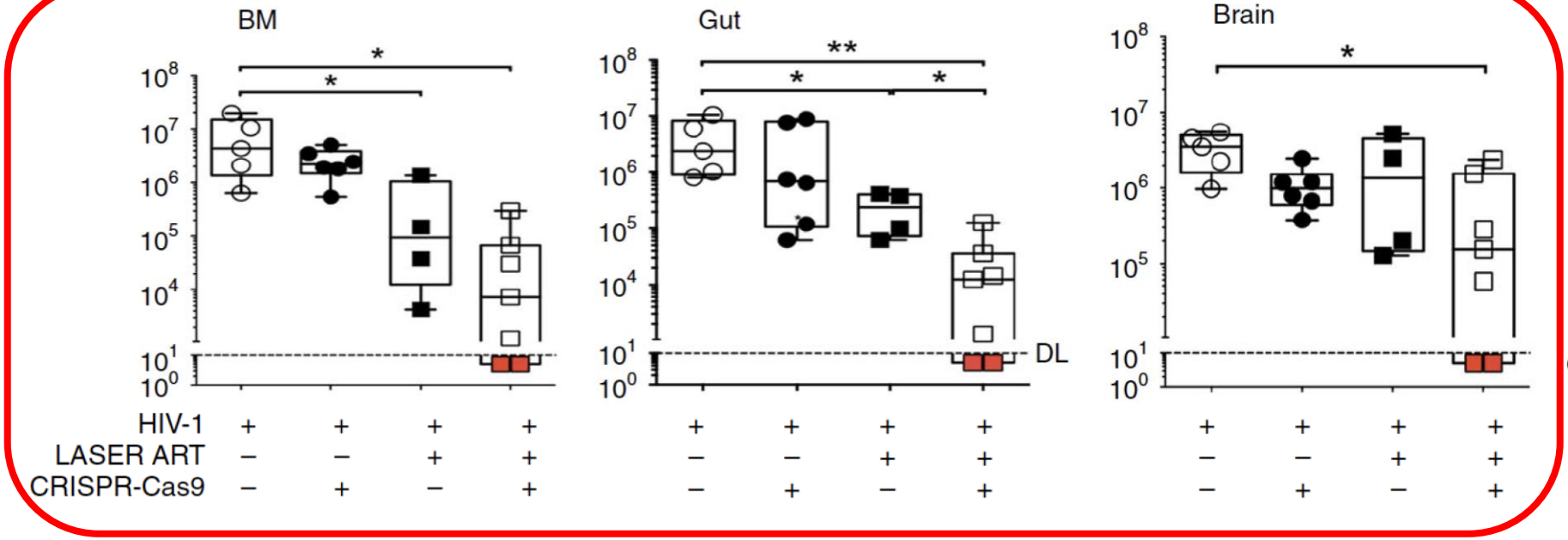


Adoptive Transfer

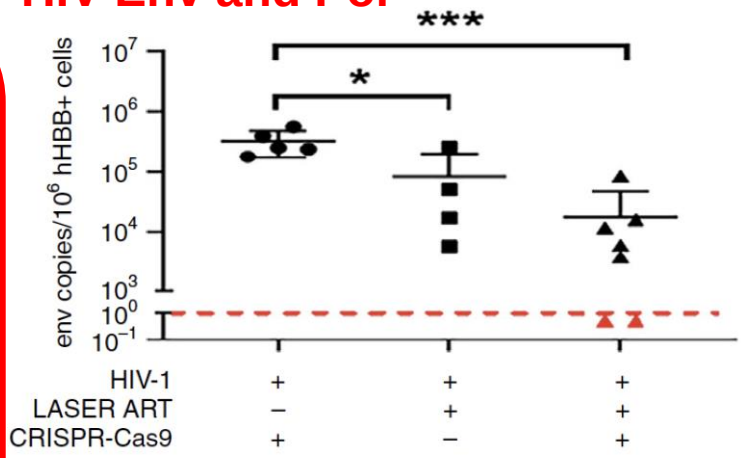


Borducchi et al, Nature 2018, doi.org/10.1038/s41586-018-0600-6

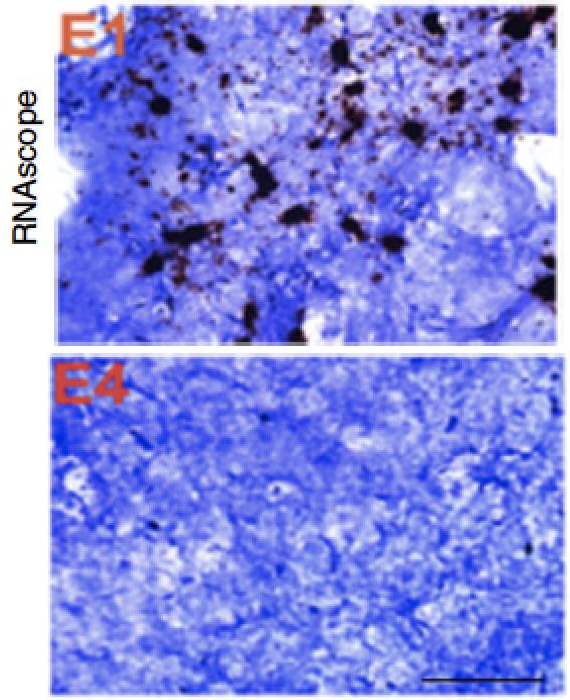
HIV RNA



HIV Env and Pol

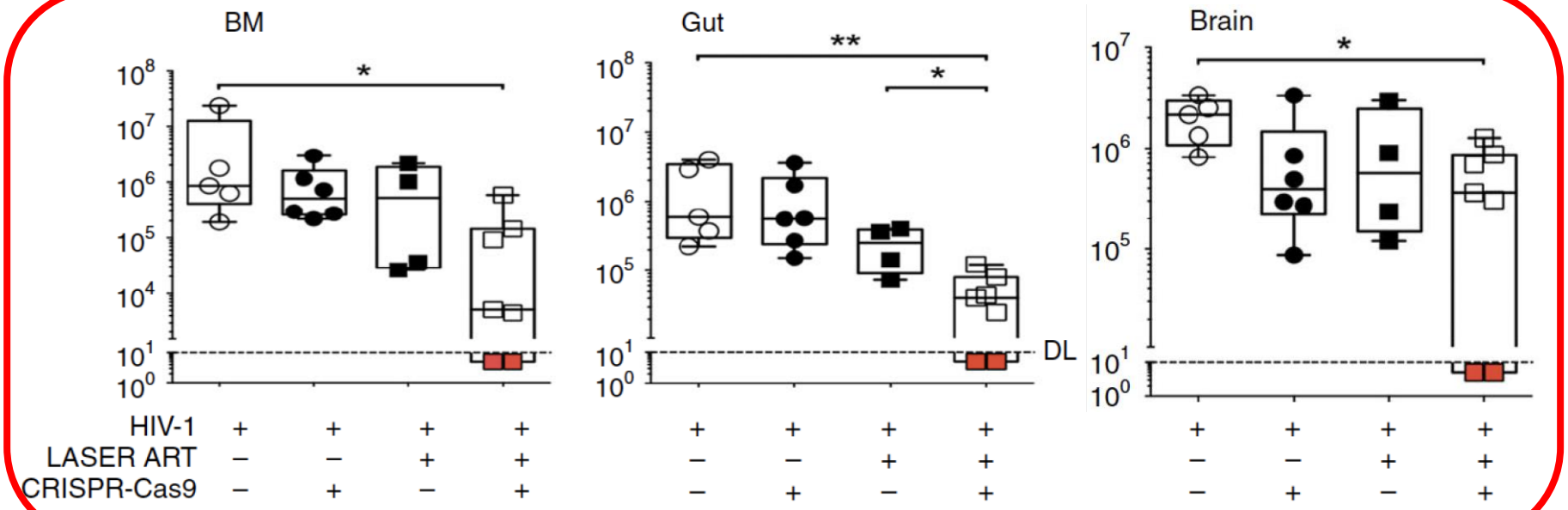


HIV RNA in Situ



HIV DNA

LASER: Long-acting slow-effective release



Dash et al, Nature Communications 2019
doi.org/10.1038/s41467-019-10366-y

Will the Same Intervention Eradicate HIV from the CNS of All PWH?

- Younger
- Early presenter
- Shorter HIV duration
- Early ART initiator
- Integrase inhibitor
- Fewer coinfections
- No addiction
- Equilibrated HIV
- Smaller CNS reservoir

Most PWH

- Older
- Late presenter
- Longer HIV duration
- Late ART initiator
- Older ART drugs
- More coinfections
- Drug use disorder
- Compartmentalized HIV
- Larger CNS reservoir

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HNRP
HIV NEUROBEHAVIORAL RESEARCH PROGRAM

CFAR
SAN DIEGO | CENTER FOR AIDS RESEARCH

Trainees

- Qing Ma (Buffalo)
- Bert Anderson (Emory)
- Jenny Iudicello
- Kemi Okwuegbuna
- Josue Perez Santiago
- Micol Ferrara
- Ameet Dravid

NIH National Institute of Mental Health

NIH National Institute on Drug Abuse
Advancing Addiction Science

NIH National Institute of Allergy and Infectious Diseases

NIH National Institute on Aging