News From the Reservoirs: Central Nervous System

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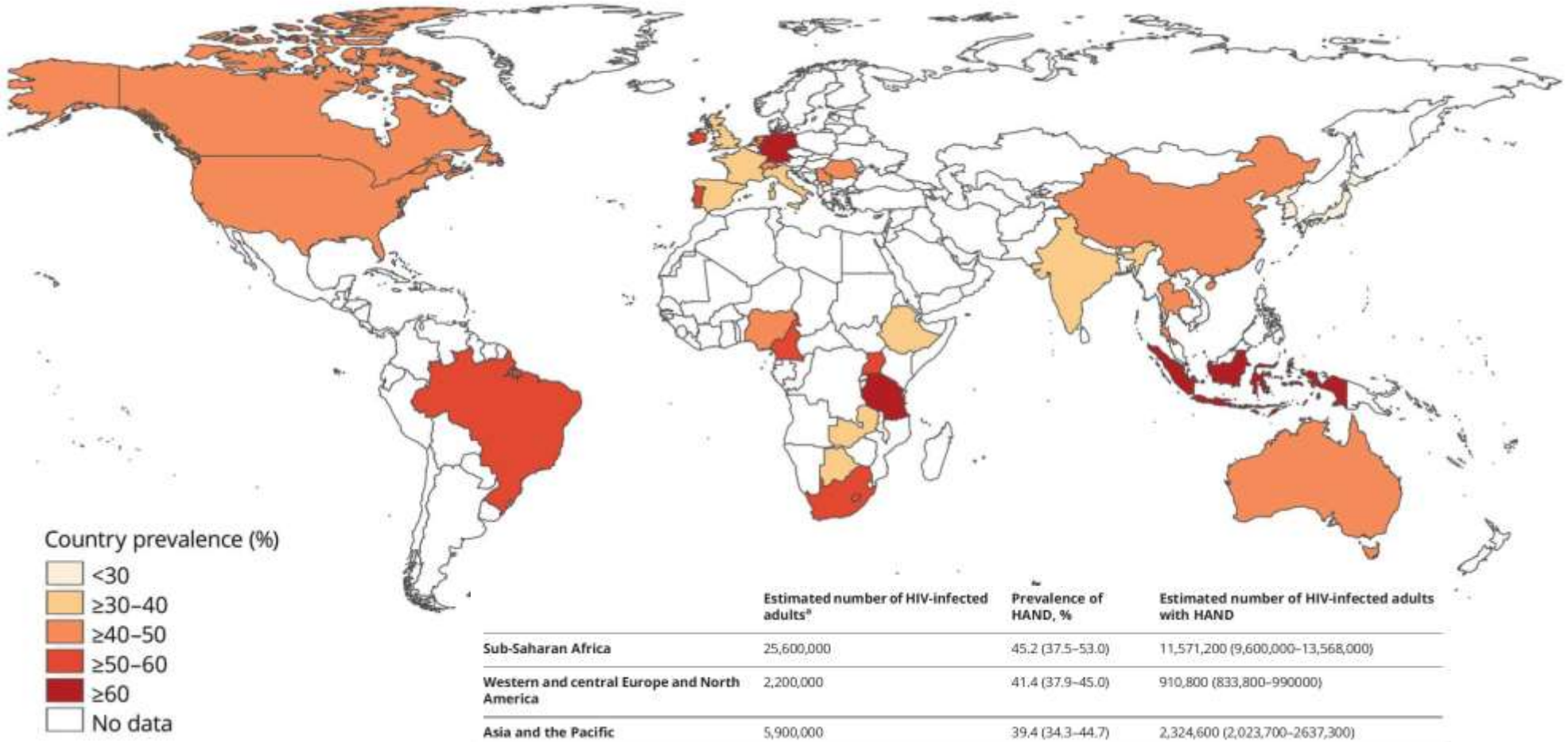
Disclosures

Research awards paid to UC San Diego:

- National Institutes of Health
- Merck & Co., Inc.

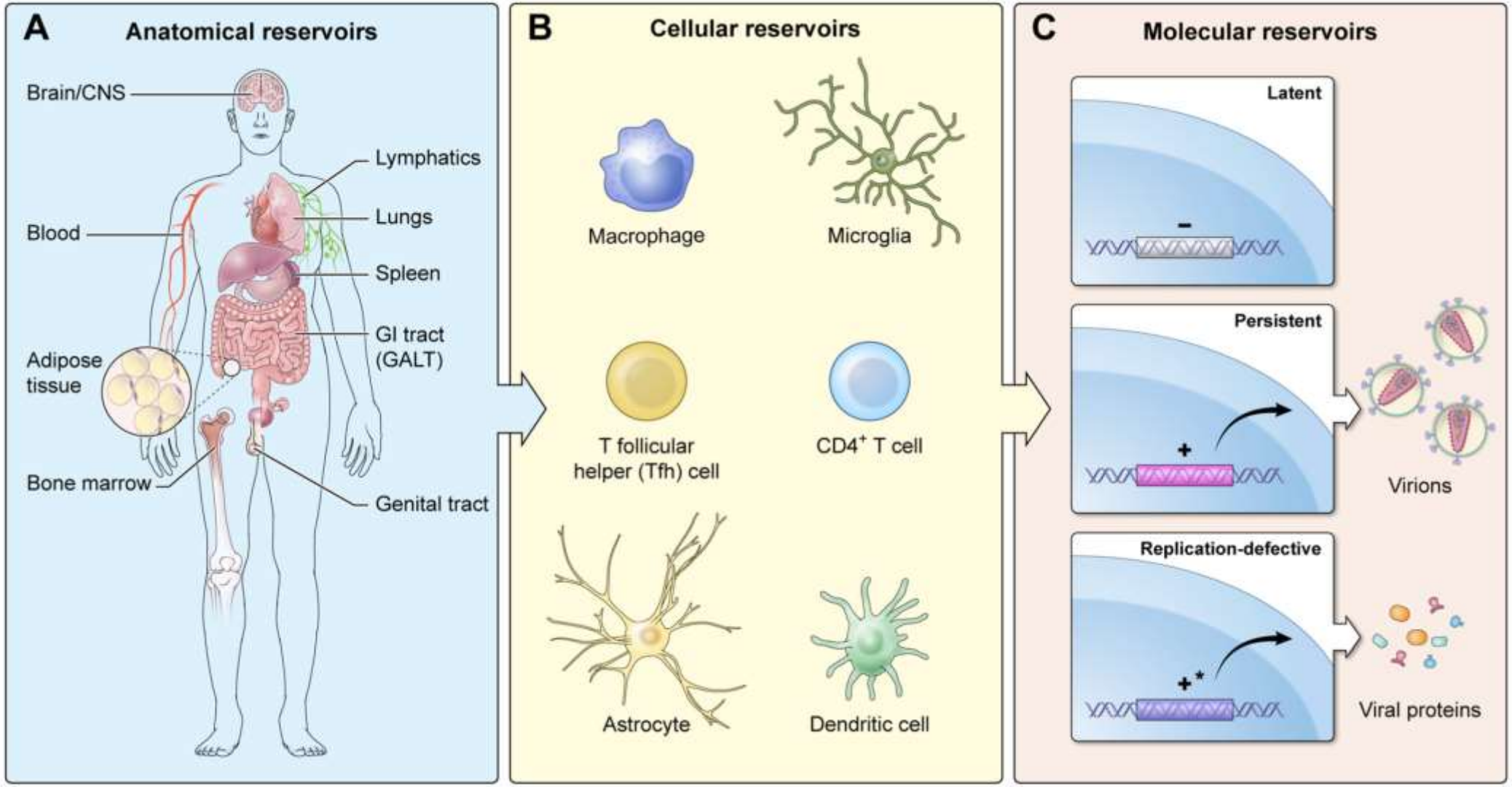
Meta-Analysis of Regional HAND Prevalence



	Estimated number of HIV-infected adults[a]	Prevalence of HAND, %	Estimated number of HIV-infected adults with HAND
Sub-Saharan Africa	25,600,000	45.2 (37.5–53.0)	11,571,200 (9,600,000–13,568,000)
Western and central Europe and North America	2,200,000	41.4 (37.9–45.0)	910,800 (833,800–990000)
Asia and the Pacific	5,900,000	39.4 (34.3–44.7)	2,324,600 (2,023,700–2637,300)
Middle East and North Africa	240,000	—	—
Latin America and the Caribbean	2,240,000	59.0 (48.5–69.0)	1,321,600 (1,086,400–1545,600)
Eastern Europe and central Asia	1,700,000	—	—
Global totals	37,900,000	42.6 (39.7–45.5)	16,145,400 (15,046,300–17,244,500)

Wang et al, Neurol 2020. 95:e2610-e2621

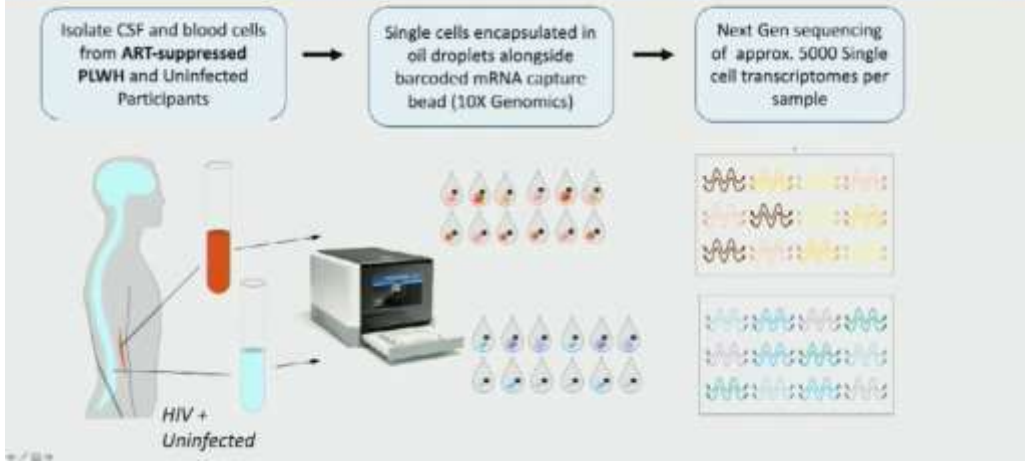
Other Cell Types Can Harbor HIV



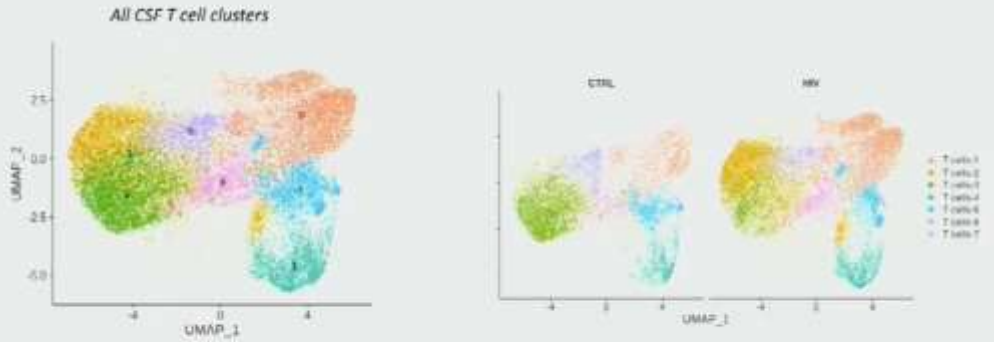
Henderson et al, J Virol 2020; 94: e00375-19.

Single Cell Genomics Analysis of T Cells in CSF

Approach: Generating single cell transcriptomes from CSF and blood



CSF T cell subset frequencies in HIV compared to uninfected



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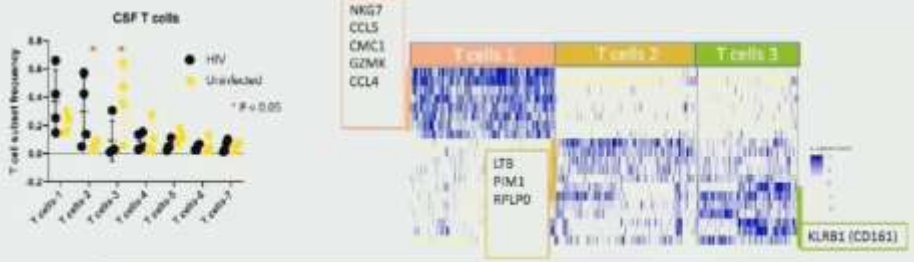
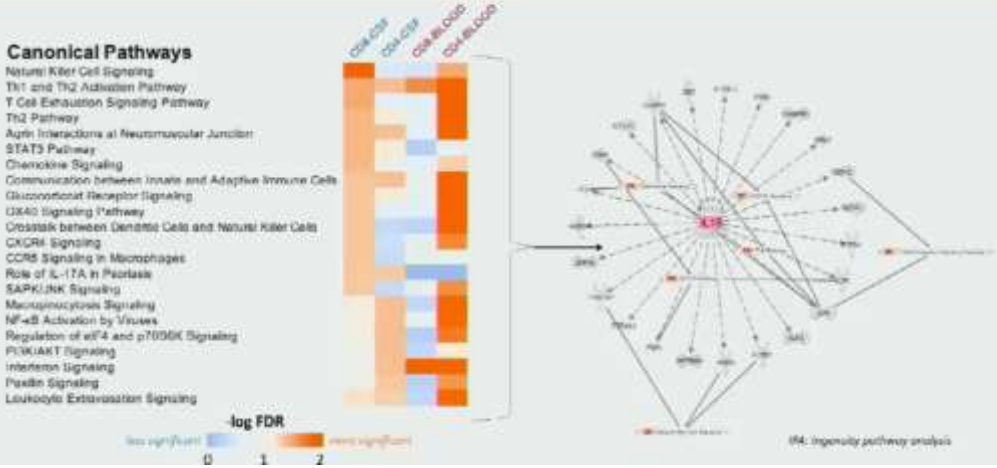


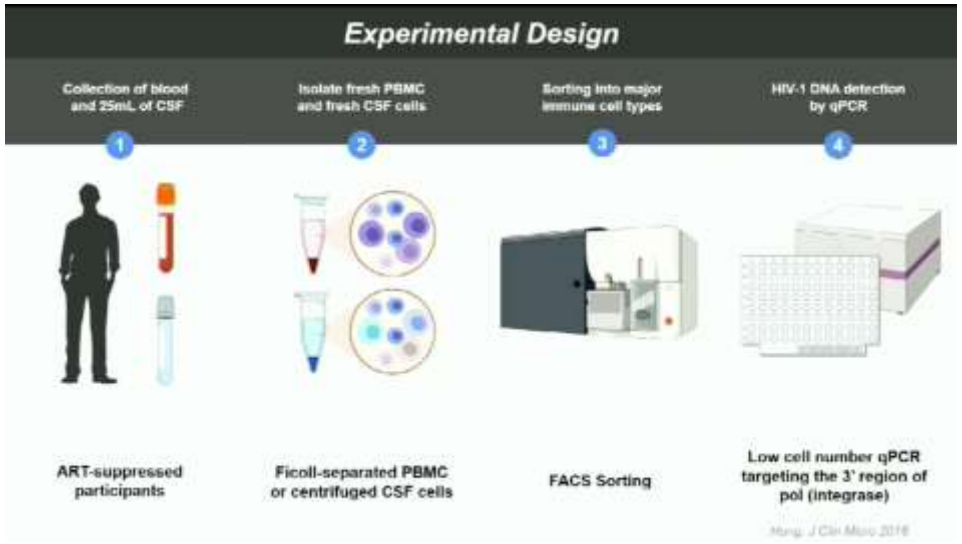
- Overall T cell types do not differ between PLWH on ART and Uninfected
- Increased **frequency** of exhausted and of activated effector CD8 cells in HIV
- Increased **frequency** of cycling CD4 cells in HIV
- Lower **frequency** of CD161+ (TH17-like) in HIV

T cell exhaustion and CCR5 signalling pathways are hallmarks of the CNS but not the peripheral CD8 T cell response to HIV infection during ART



Farhadian et al. CROI 2020, Abstract 27

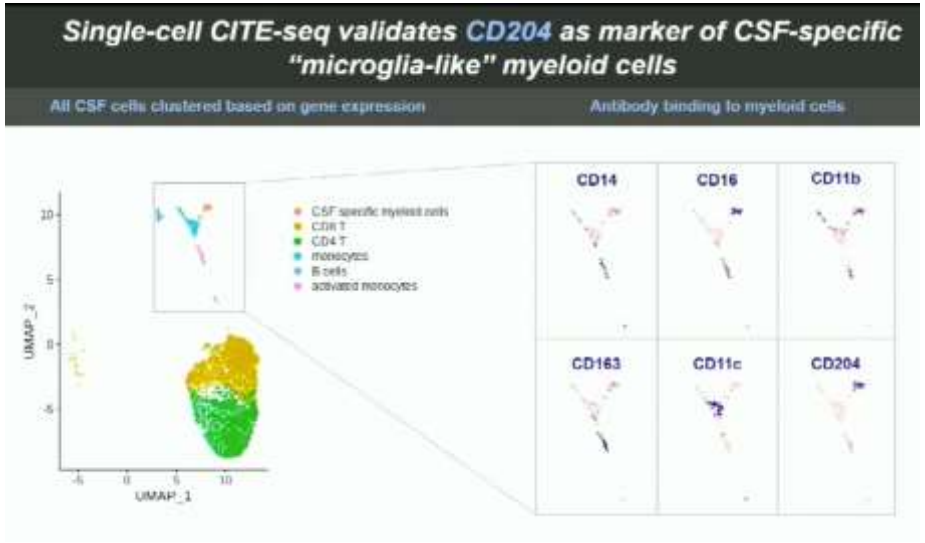
HIV DNA Higher in CD4+ T-Cells in CSF than in Blood



Participant Characteristics

Donor	Age	Sex	CD4⁺ T cells (/mm³)	Nadir CD4⁺ T cells (/mm³)	Years of ART Suppression	Plasma HIV-1 RNA (copies/mL)	CSF HIV-1 RNA (copies/mL)	Current ART Regimen	Neurological Problems
1	48	Male	1032	432	10	TND	95	TAF/FTC/EVG/Cobi	none
2	69	Male	518	308	24	TND	<20	TDF/FTC, RAL, ETR	none
3	27	Male	936	187	4	<20	TND	ABC/3TC/DTG	prior O.I.
4	55	Male	834	600	22	<20	163	TAF/FTC/RPV+DTG	none
5	65	Male	729	109	20	TND	TND	TAF/FTC, DTG	memory loss
6	61	Male	555	55	23	TND	TND	ABC/3TC/DTG	prior O.I.
7	56	Male	652	251	9	748	87	off therapy x 2 mo	memory loss
Median	56	-	729	251	20	-	-	-	-

All participants enrolled in the HIV Associated Reservoirs and Comorbidities (HARC) Study at the Yale School of Medicine



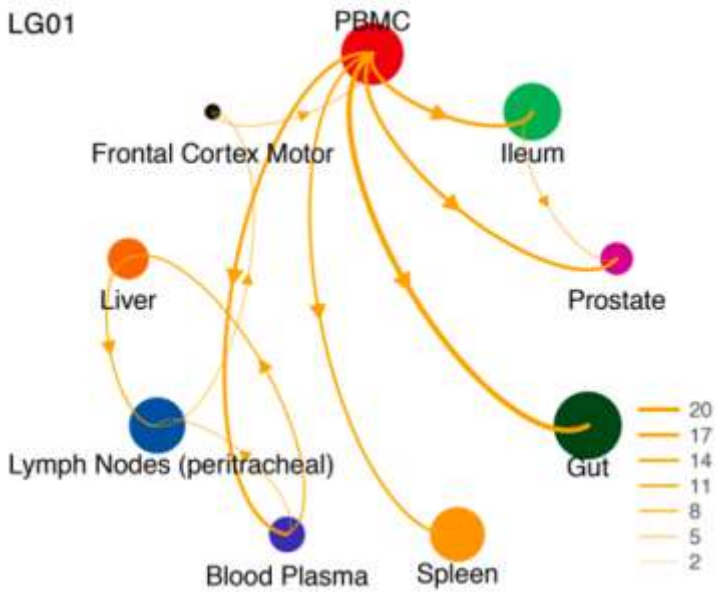
HIV-1 DNA detection in cell subsets

Donor	Sample	HIV RNA copies/mL	Sorted Cell Type Assayed for HIV-1 DNA	Sorted Cell Counts	Total Cell Equivalents Assayed	HIV-1 DNA copies per 1M Cell Equivalents
4	Blood	<20	CD4⁺ T cells	-	58050	0
			CD8⁺ T cells	-	46450	57
	CSF	163	CD4⁺ T cells	22000	6915	132
			CD8⁺ T cells	19000	16330	0
			CD204⁺ cells	432	585	0
5	Blood	TND	CD4⁺ T cells	-	144450	1112
			CD8⁺ T cells	-	237000	0
	CSF	TND	CD4⁺ T cells	5700	18270	391
			CD8⁺ T cells	4800	5586	0
			CD204⁺ cells	15	0	0
6	Blood	TND	CD4⁺ T cells	-	109050	1411
			CD8⁺ T cells	-	44550	211
	CSF	TND	CD4⁺ T cells	10280	2984	10793
			CD8⁺ T cells	5765	2057	0
			CD204⁺ cells	395	92	0
7	Blood	748	CD4⁺ T cells	-	111600	401
			CD8⁺ T cells	-	34050	0
	CSF	87	CD4⁺ T cells	5562	5160	2769
			CD8⁺ T cells	6005	0	0
			CD204⁺ cells	**203**	**527**	**4368**

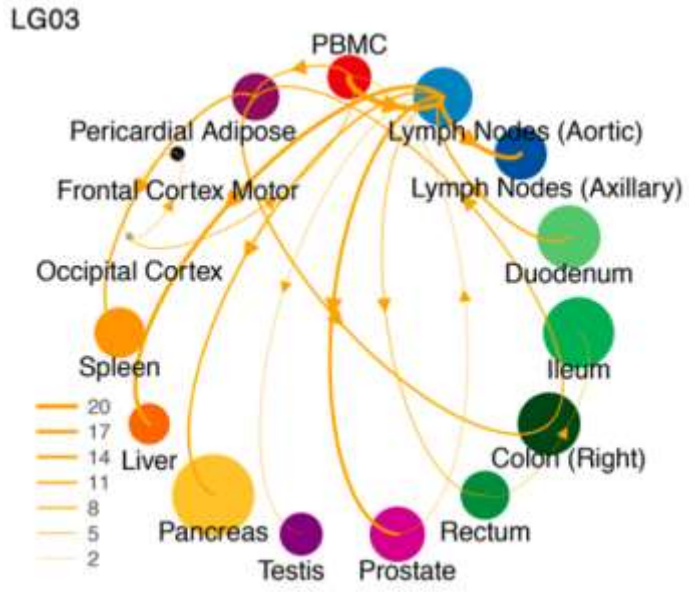
Farhadian et al. CROI 2020, Abstract 31

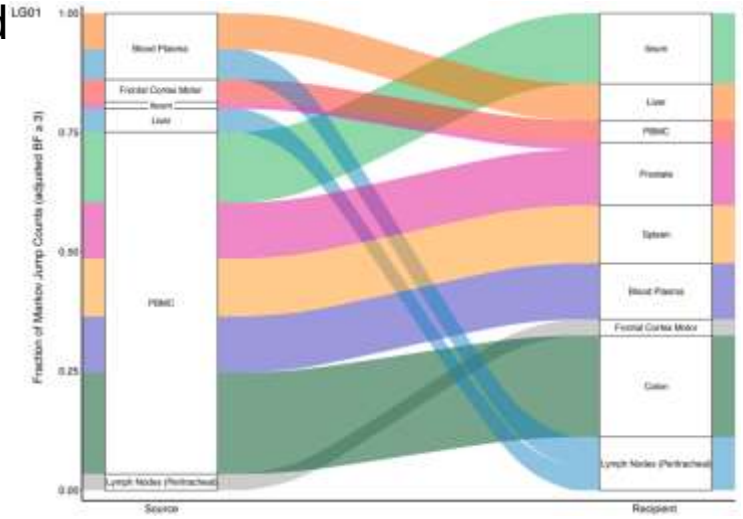
- 6 PWH provided serial blood samples before death and their bodies for rapid autopsy. 4 had viral suppression until death, 2 stopped ART prior to death.
- HIV reservoirs were characterized by ddPCR, single-genome amplification, and sequencing of full-length envelope HIV. Phylogeographic methods were used to reconstruct HIV spread.
- **Analysis showed:**
  (a) emergence of large, identical, intact HIV RNA populations in blood after cessation of therapy, which repopulated tissues throughout the body;
  (b) multiple sites acted as hubs for HIV dissemination but blood and lymphoid tissues were the main source;
  (c) **viral exchanges occurred within brain areas and across the blood-brain barrier**; and
  (d) migration was associated with low HIV divergence between sites and greater diversity at the recipient site.

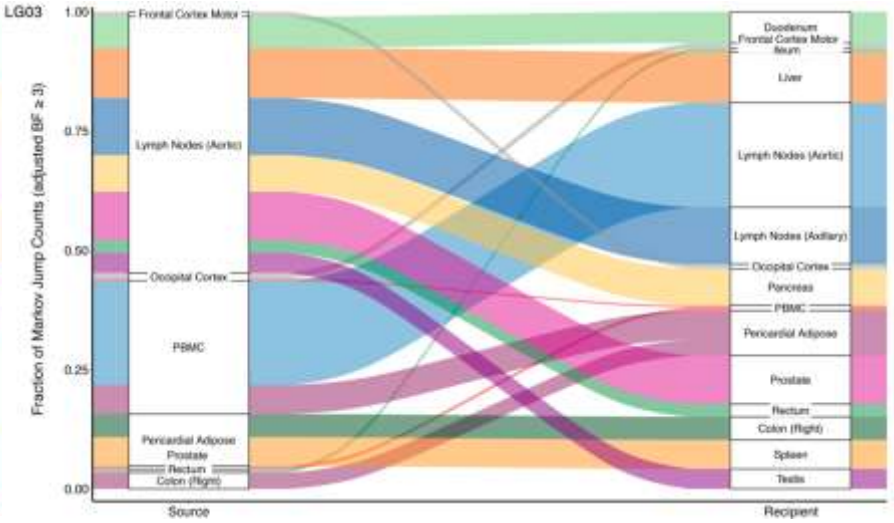
On ART



Off ART



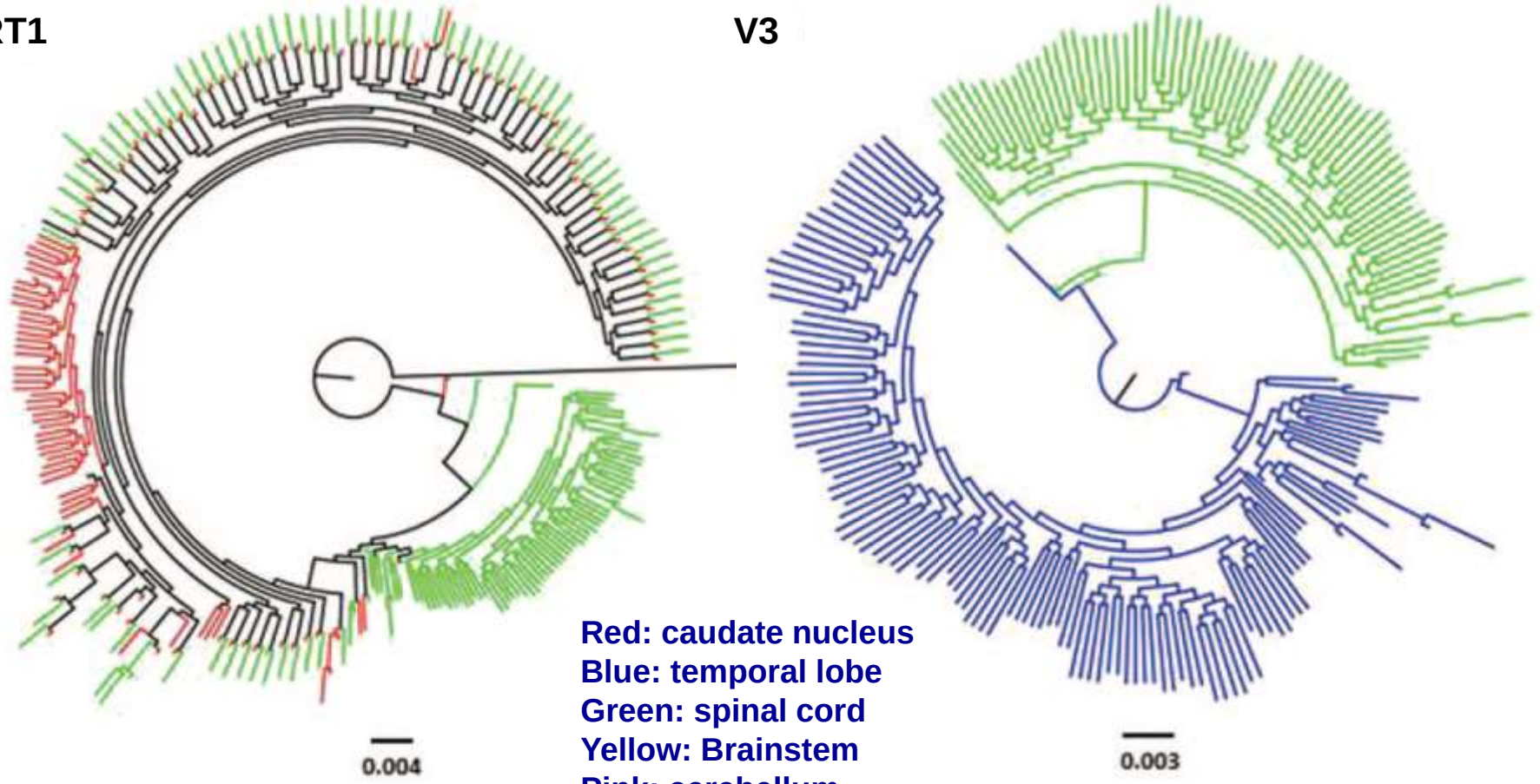




Chaillon et al, J Clin Invest. 2020;130(4):1699-1712

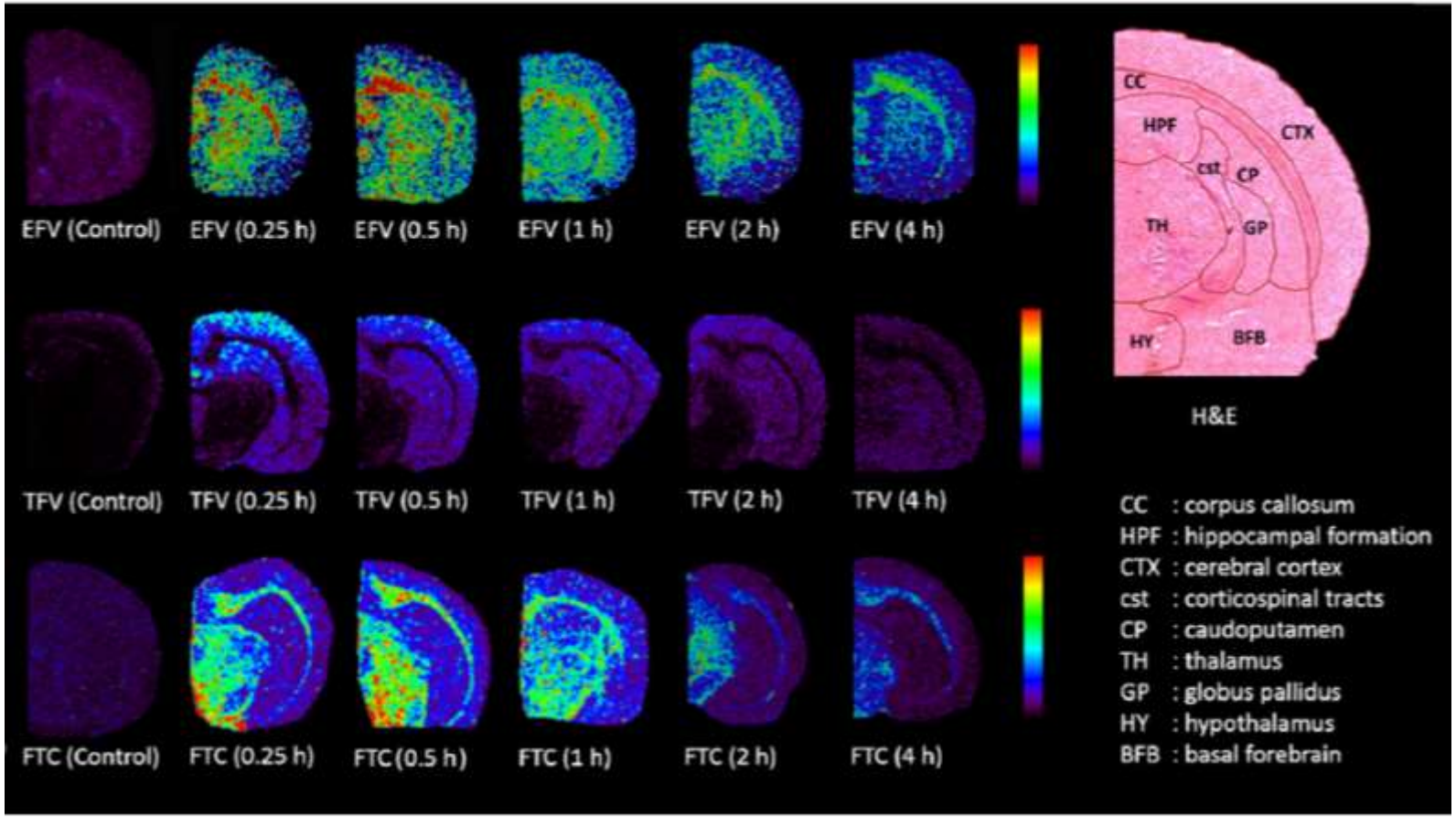
Brain Regional Genetic Variation Using Ultradeep Sequencing

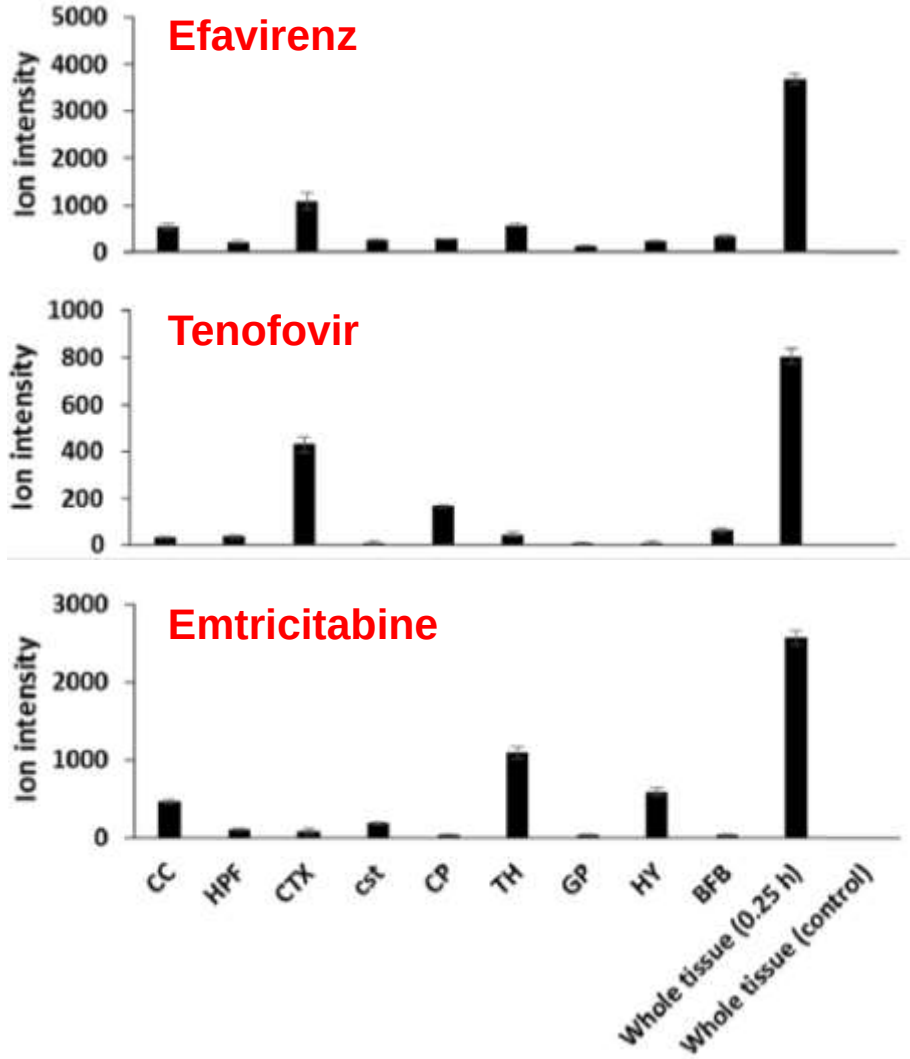
- **Some regions shared HIV variants.**
  - **Most harbored a specific HIV subpopulation reflecting HIV compartmentalization in the CNS.**
- **The proportion and distribution of resistance mutations to nucleoside and nonnucleoside reverse transcriptase inhibitors differed among different brain areas.**



Giatsou et al, AIDS 2020, 34:1609–1614

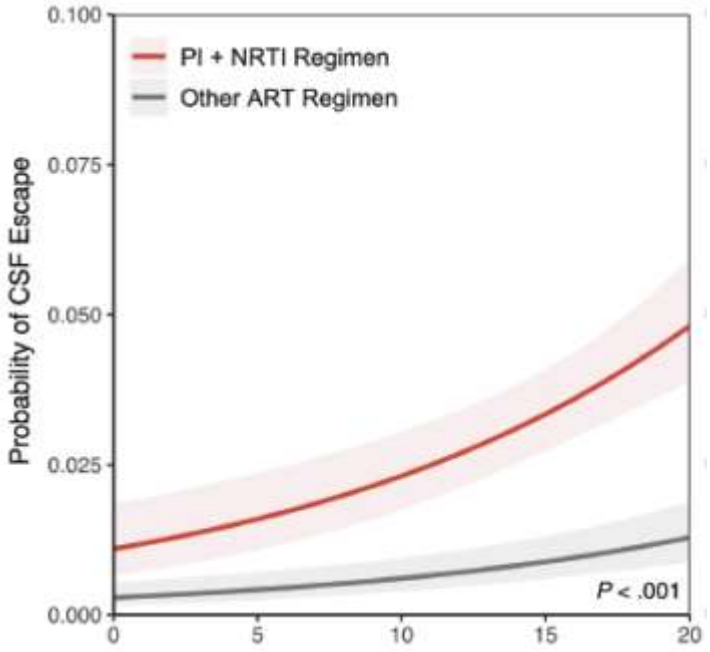
Brain Regional Variation of ART Concentrations in Rats

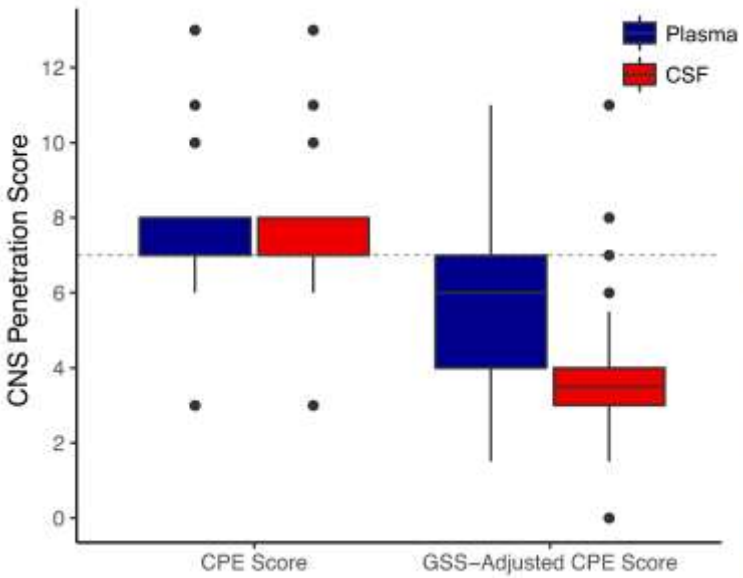


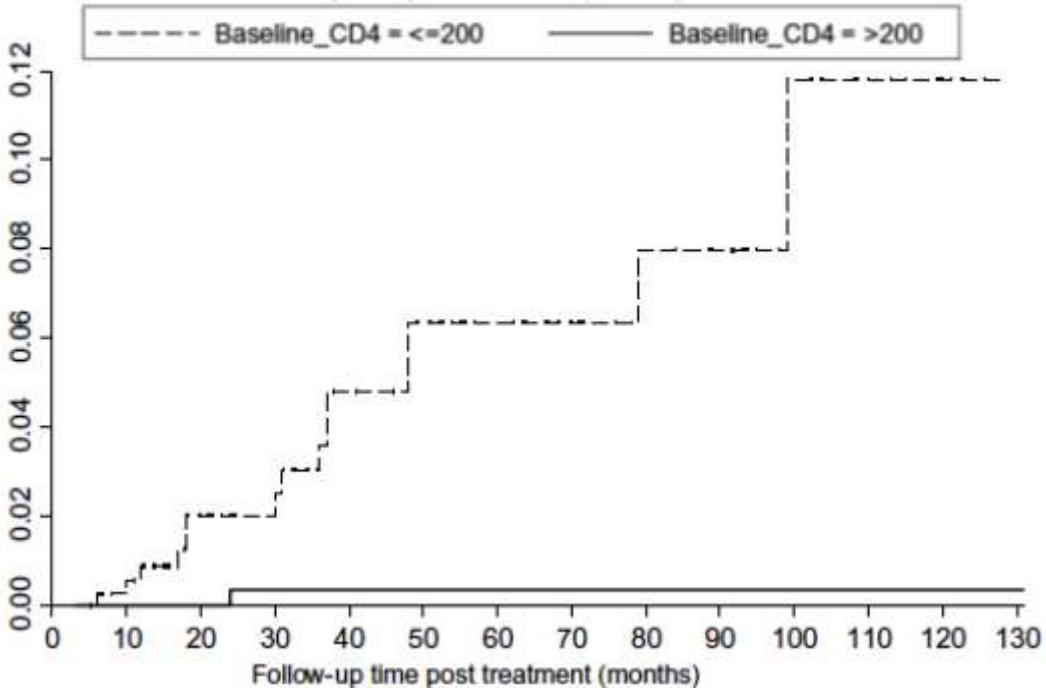


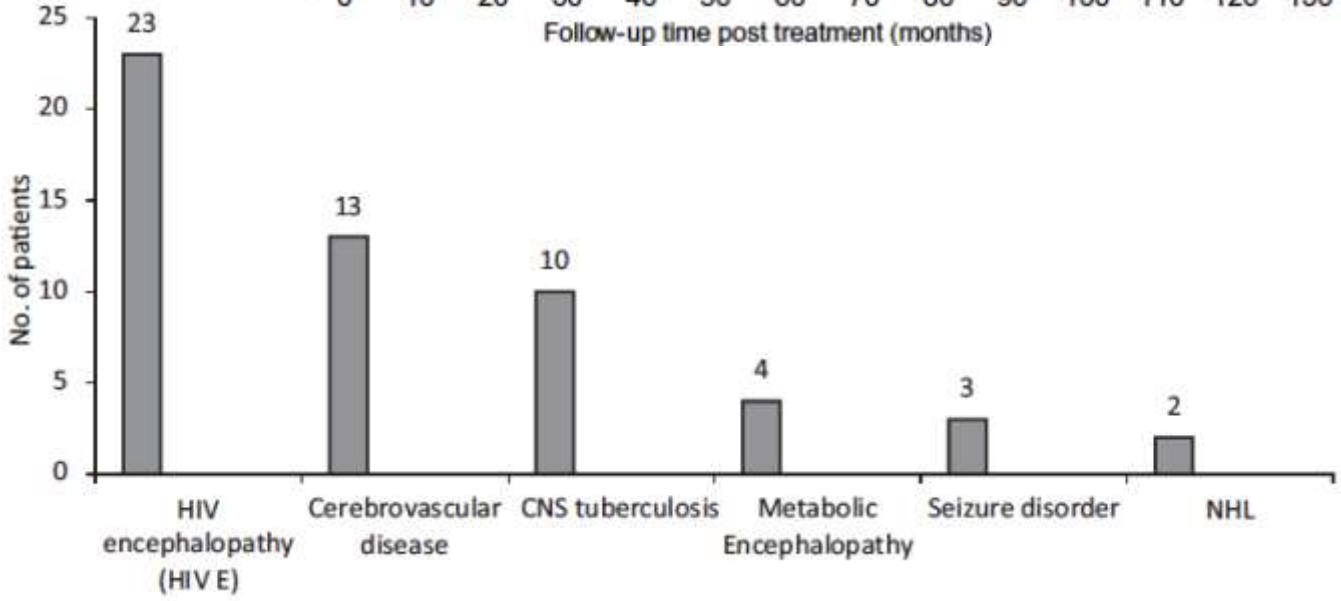
Ntshangase et al. ACS Omega 2019, 4, 21169−21177

Correlates of CSF Viral Escape



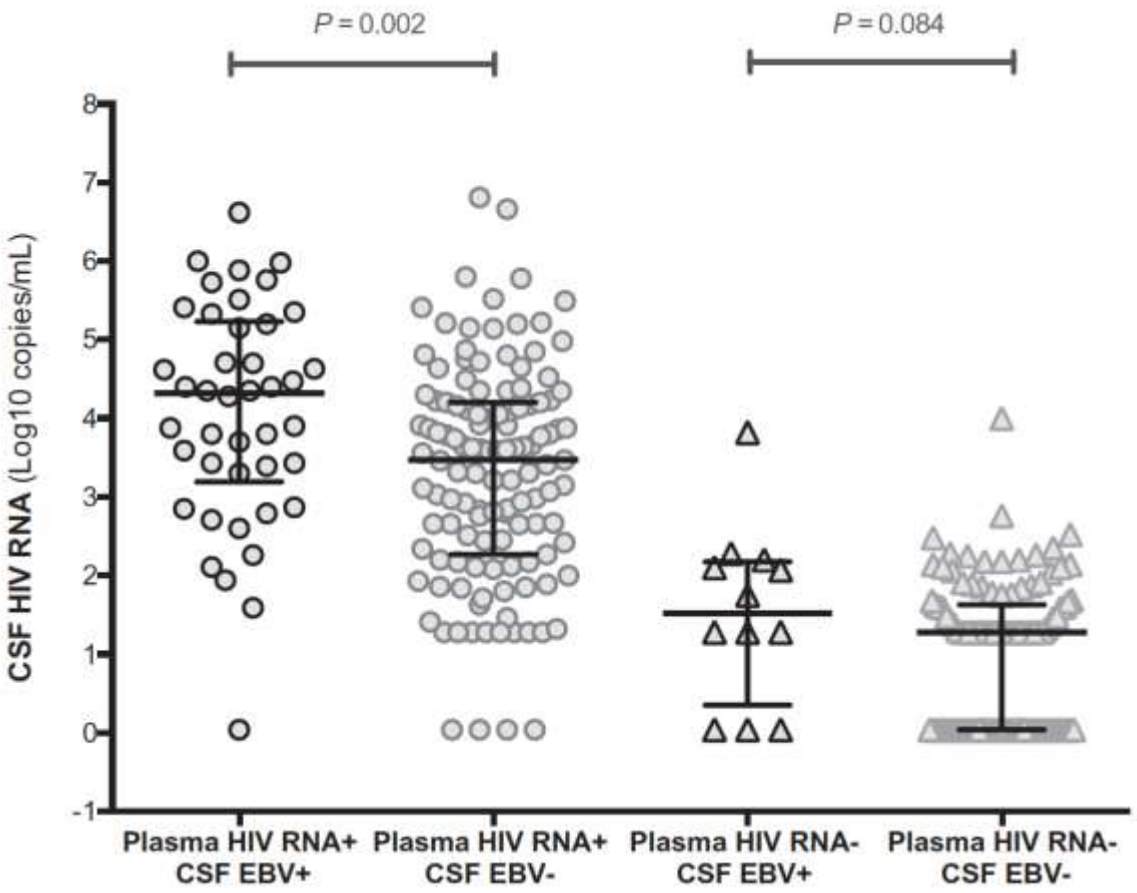


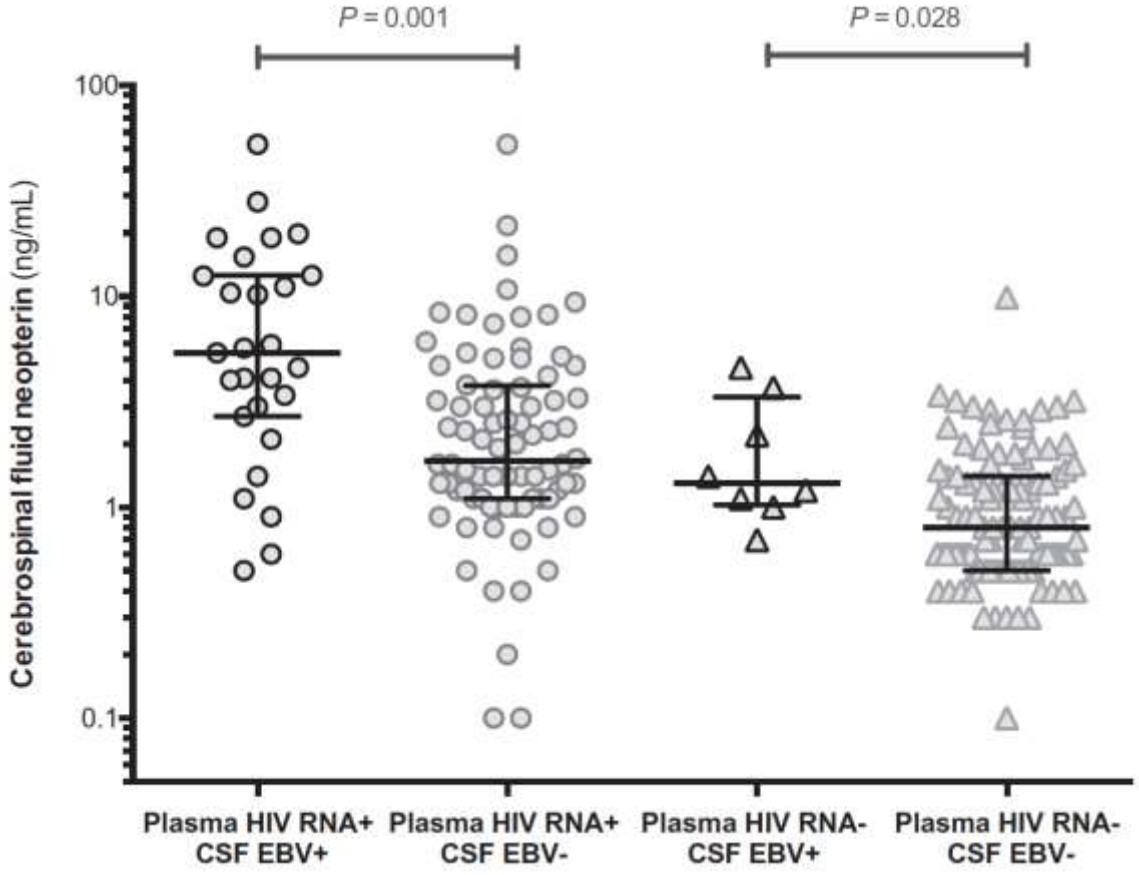




Mukerji, et al, Clin Infect Dis. 2018; 67(8):1182–90
Patel, et al, Journal of NeuroVirology (2018) 24:498–505
Dravid et al, Medicine (2018) 97:8(e9969)

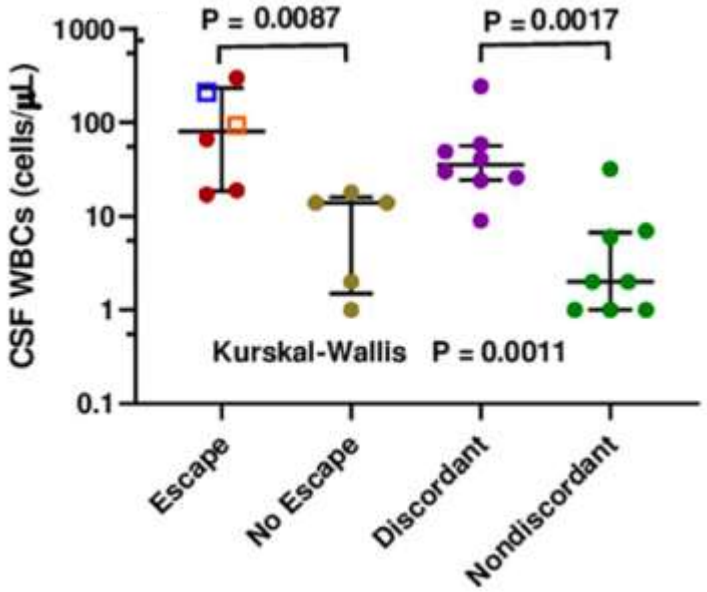
EBV DNA in CSF is Associated with Pleocytosis and Higher CSF HIV RNA

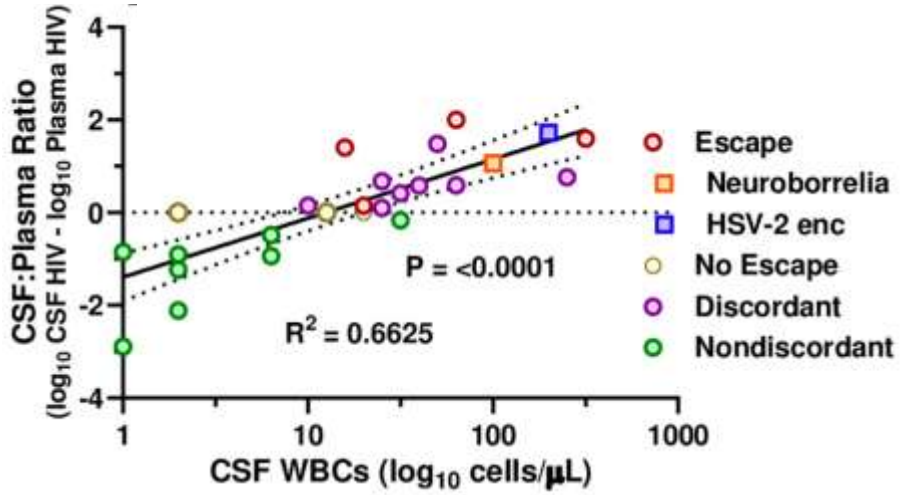


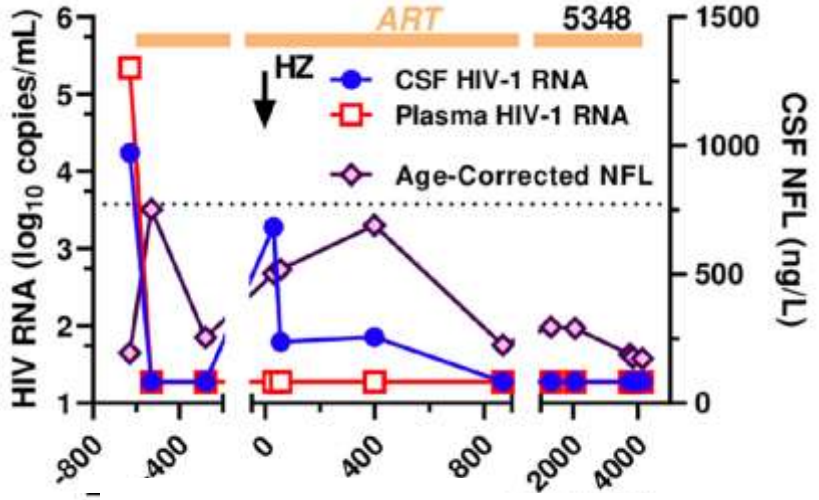


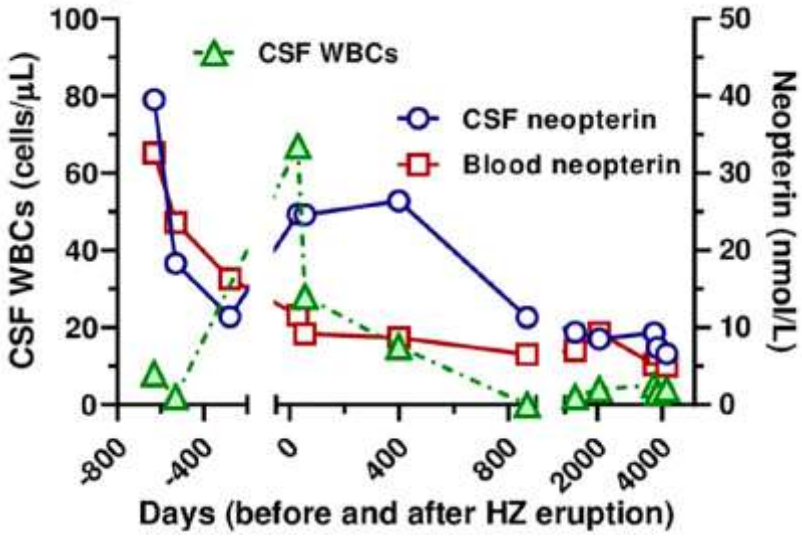
Lupia et al, AIDS 2020, 34:373–380

VZV Infection, CSF Escape, and Persistent CSF Abnormalities



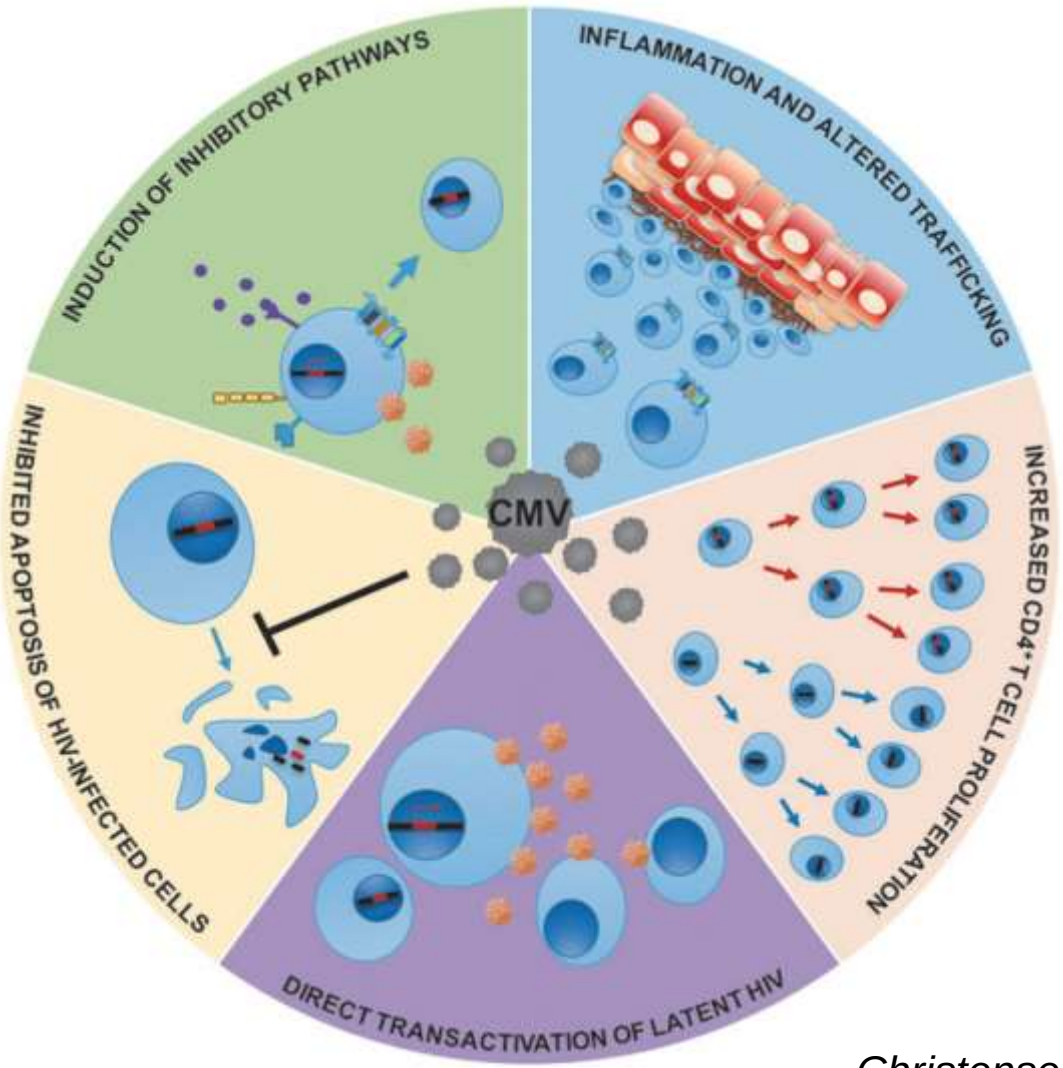


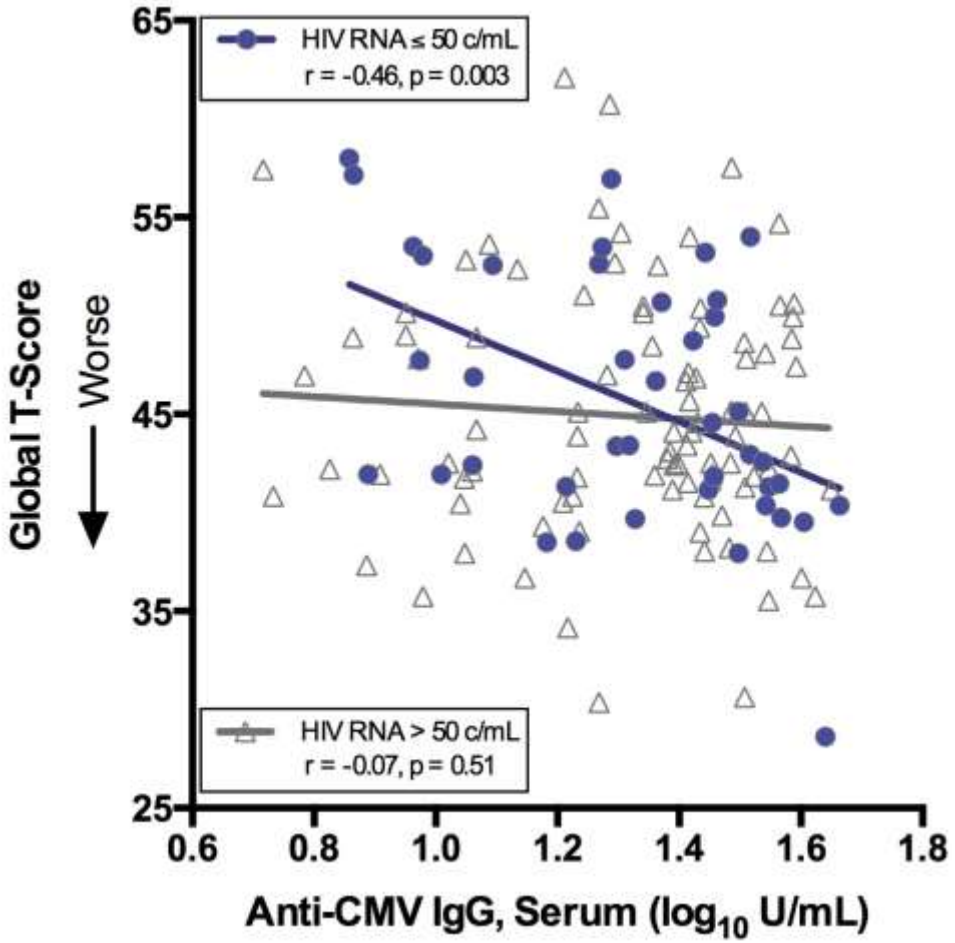




Hagberg et al, PLoS ONE 15(7): e0236162.

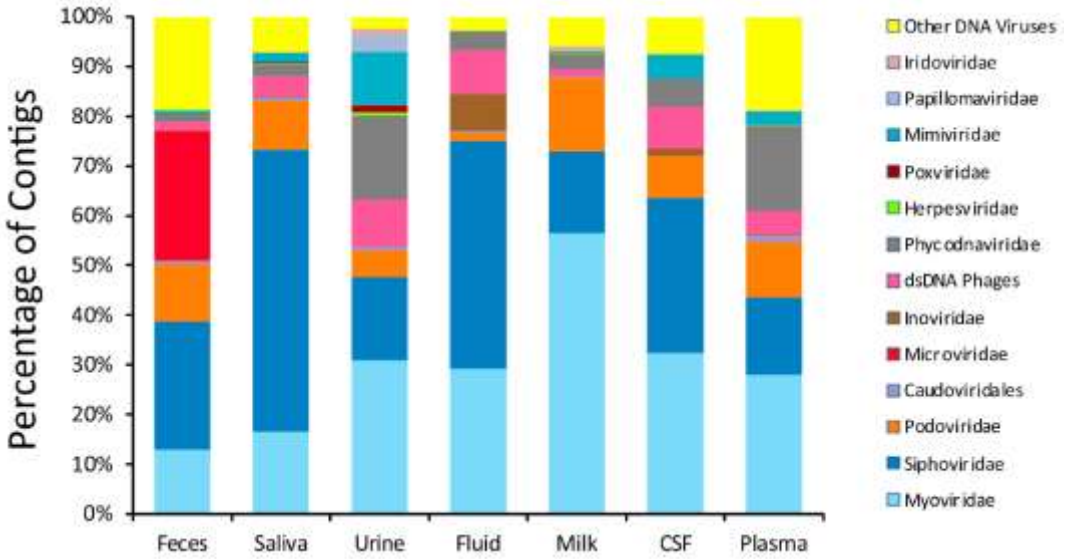
CMV Can Transactivate Latent HIV



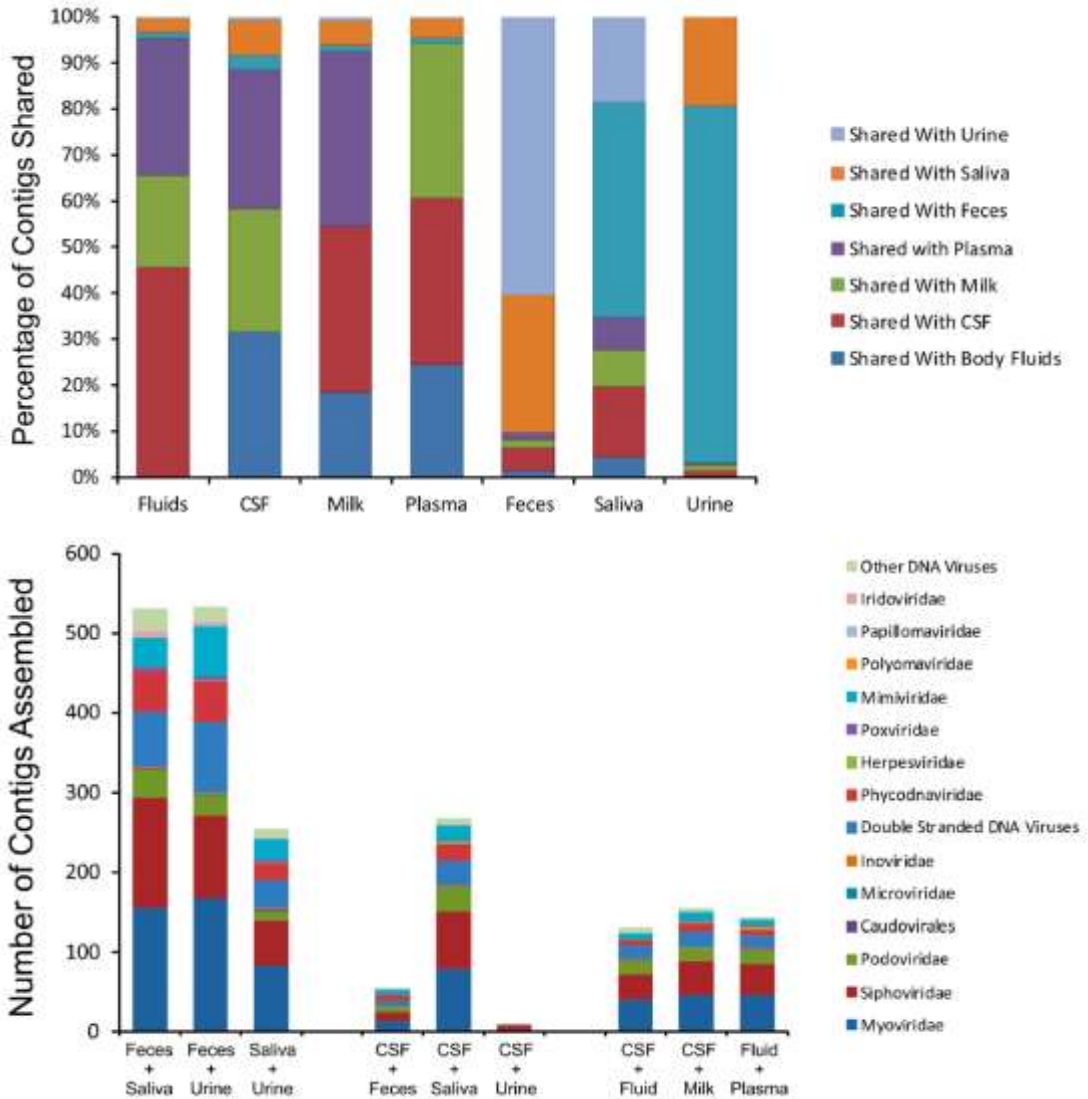


Christensen-Quick et al, AIDS Res Hum Retrovir 2017. doi: 10.1089/aid.2017.0145
Letendre, et al. Clin Infect Dis. 2018. doi: 10.1093/cid/ciy170

The Virome of “Sterile” CSF



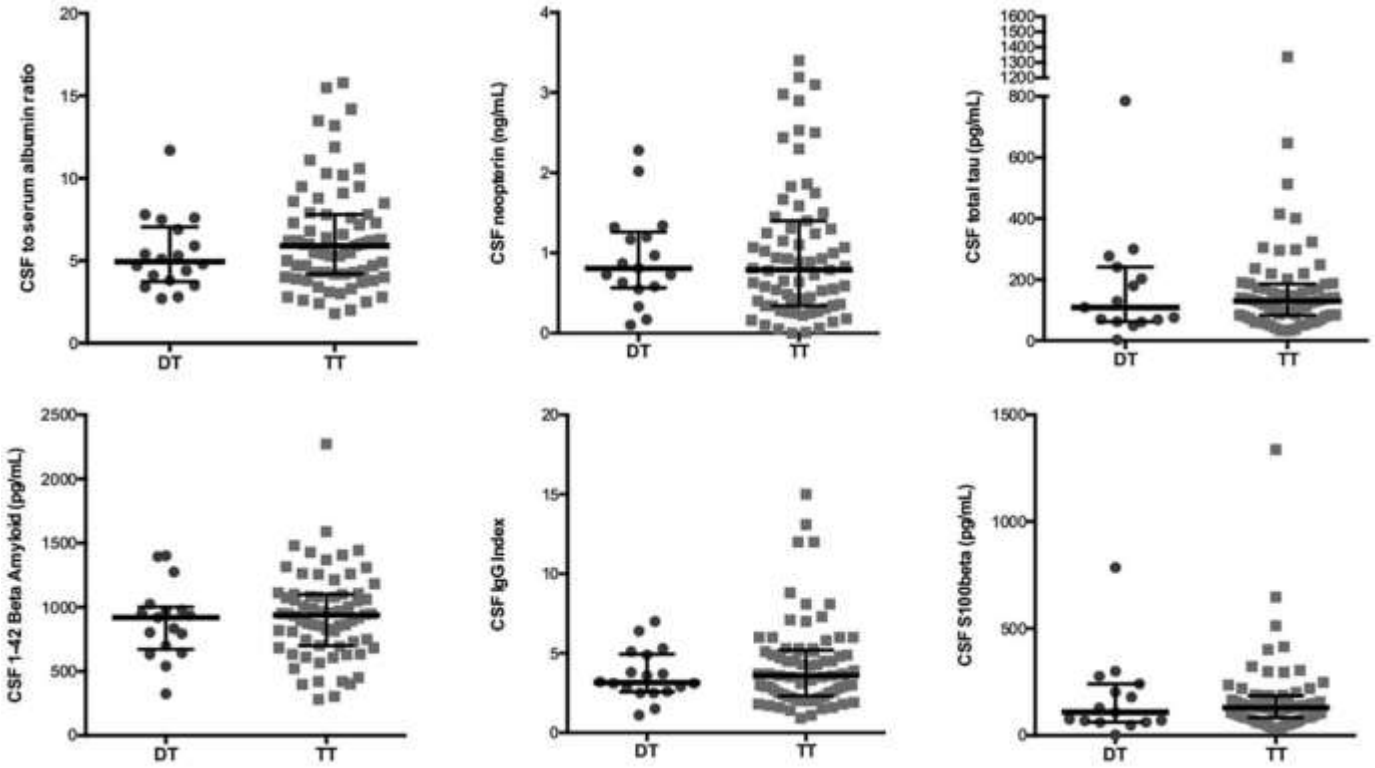
By subject	Percent homologous within sample type[a]	Percent homologous between sample types[a]	*P*-value[b]
CSF	17.38 ± 0.02	4.89 ± 0.07	0.0984
Body fluids	6.78 ± 0.03	5.32 ± 0.06	0.3878
Milk	17.00 ± 0.15	2.83 ± 0.06	0.1870
Plasma	11.20 ± 0.08	6.97 ± 0.09	0.3033
Stool	19.18 ± 0.12	2.00 ± 0.03	**0.0382**
Saliva	54.42 ± 0.05	1.76 ± 0.04	**<0.0001**
Urine	9.89 ± 0.08	1.77 ± 0.04	0.0925



Ghose et al, Front. Microbiol, 2019. 10:2061

CNS Safety of Dual ART

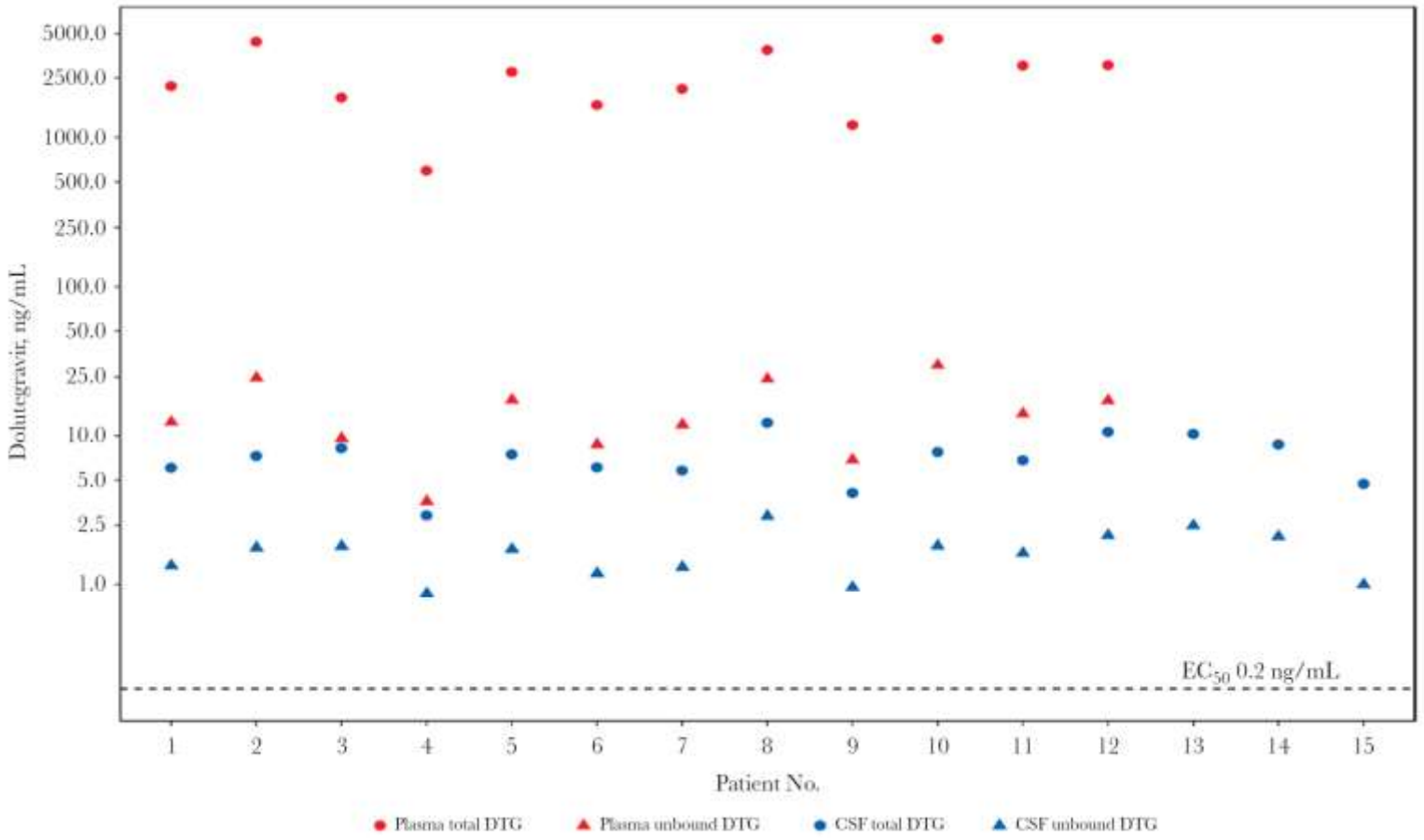
- **78 PWH on triple therapy and 19 on dual therapy were included.**
  - Dual therapies: 12 InSTI+bPI, 3 InSTI+NNRTI, 2 bPI+NNRTI, 2 bPI+NRTI.
- **Time on current regimens 18 months (8–29). Length of plasma suppression was 32 months (14–94).**
- **Groups did not differ in terms of HAND, demographic, or viro-immunological features.**
- Undetectable CSF HIV RNA (73.7% in dual therapy vs. 78.2% in triple therapy, p=0.67) and CSF escape (21.1% in dual therapy vs. 19.2% in triple therapy, p=0.86) did not differ.
- No difference in depression, anxiety, neurocognition (in 63 participants) nor in inflammation, blood–brain barrier integrity, neuronal damage, or astrocytosis biomarker.



Trunfio et al. AIDS 2020, 34:1899–1906

CNS Safety of Dual ART (DTG+3TC)

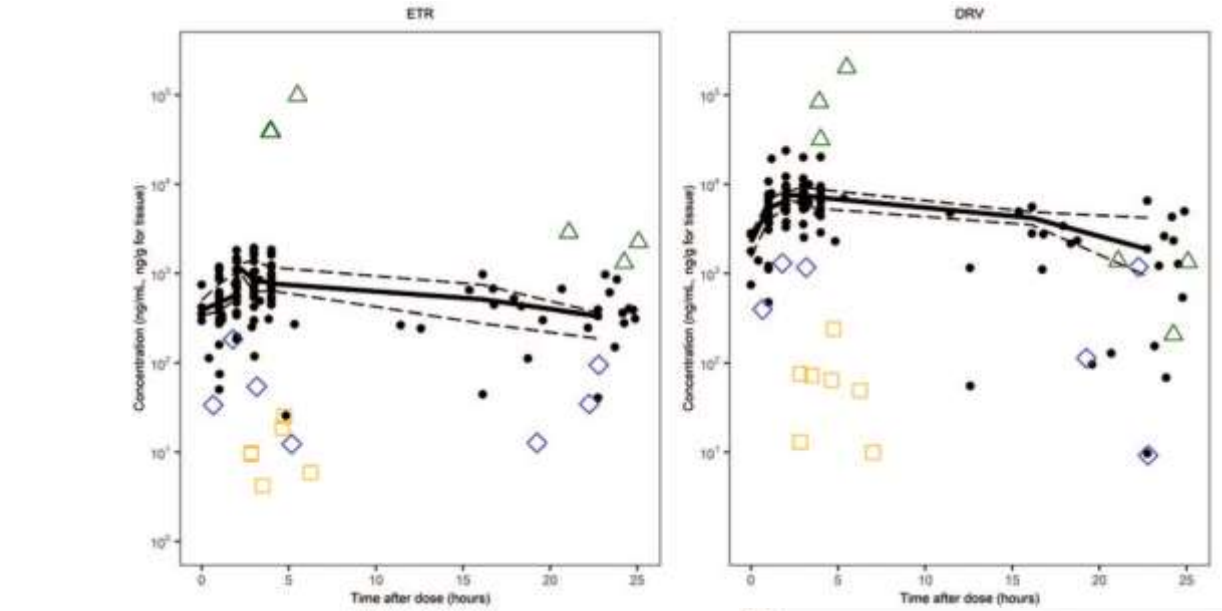
- Evaluated HIV RNA, neuronal injury, and inflammatory biomarkers and (DTG) exposure in CSF in 15 adults switching to DTG+3TC
- All maintained viral suppression in plasma and CSF at week 48
- No increase in CSF biomarkers of inflammation or neuronal injury
- Median (interquartile range) total and unbound DTG concentration in CSF were 7.3 (5.9–8.4) and 1.7 (1.2–1.9) ng/mL

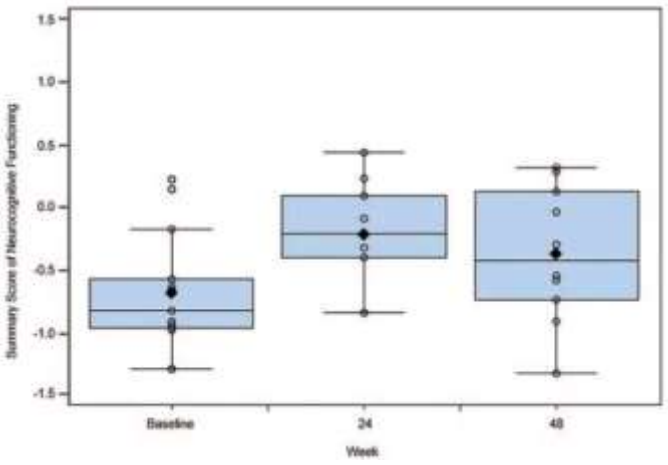


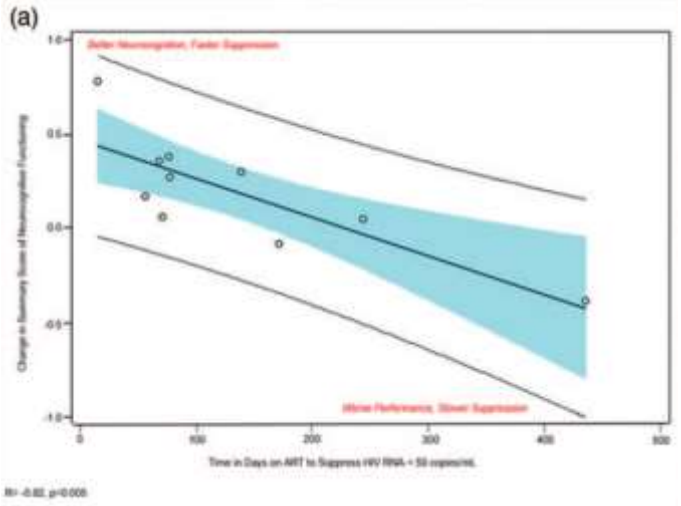
Tiraboschi et al. J Infect Dis 2020, PMID: 33049035

CNS Safety of Dual ART (DRV+ETR)

- Single-arm, open-label pilot study of PWH initiating ritonavir-boosted darunavir and etravirine within 30 days of acute HIV diagnosis
- At baseline, 8 of 13 (61%) participants were impaired, 33% were impaired at 24 weeks and, 30% impaired at 48 weeks.
- Statistically significant improvement in overall neurocognitive performance over time (P=0.03), with the greatest improvement occurring between baseline and week 24
- Two of the three participants who did not improve failed to achieve virologic suppression.
- More rapid HIV RNA suppression correlated with improved neurocognitive performance (r=0.82, P<0.005)







Gay et al. AIDS 2020, 34:1923–1931

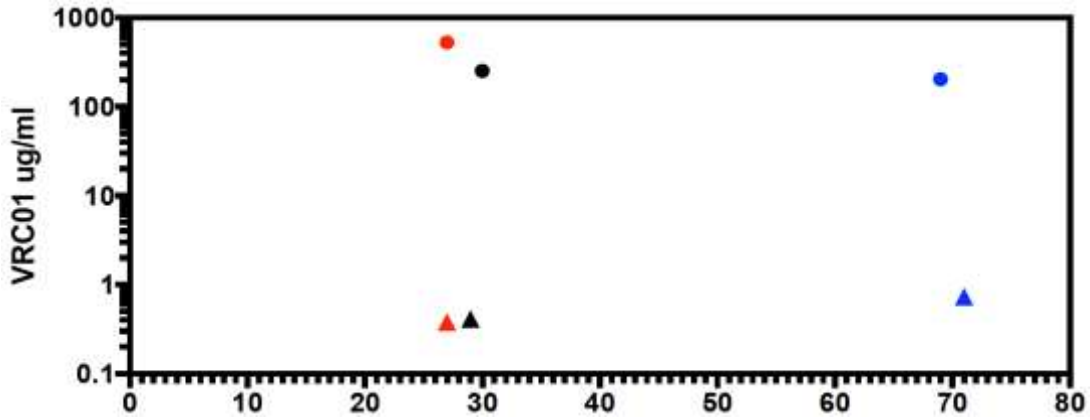
CNS Safety of Monoclonal Antibodies

Ibalizumab

Class	Resistance mutations in plasma RNA	Resistance mutations in PBMC DNA	Resistance mutations in plasma RNA at week 30	Resistance mutations in CSF RNA at week 30	ART exposure since first regimen
NRTI	M41L, E44D, D67N, K70Q, V75M, F77L, M184I, L210W, T215Y, K219R	M41L, E44D, D67N, K70Q, V75M, F77L, M184I, L210W, T215Y, K219R	M41L, E44D, D67N, V75M, F77L, Y118I, M184I	M41L, E44D, D67N, V75M, F77L, M184I, L210W, T215Y	3TC, FTC, DDI, D4T, DDC, AZT, ABC, TDF, TAF
NNRTI	E138A, G190A	E138A, G190A	E138A, V179F, Y181V	E138A, V179F, Y181V	EFV, NVP, ETV, RPV TPV, SQV, FPV, NFV, LPV, DRV, ATV
PI	Major mutations: V32I, M46L, I54A, I84V, L90M Accessory mutations: L33F, T74P	Major mutations: V32I, M46L, I54A, I84V, L90M Accessory mutations: L33F, T74P	Major mutations: V32I, M46L, I54A, I84V, L90M Accessory mutations: T74P, L33F	Major mutations: V32I, M46L, I54A, I84V, L90M Accessory mutations: T74P L33F	RAL, DTG ENF
InSTI	Major mutations: Q148H, E138A, G140S Accessory mutations: T97A, G149A	Major mutations: Q148H, E138A, G140S Accessory mutations: T97A, G149A	Major mutations: Q148H, E138A, G140S Accessory mutations: T97A, G149A	Major mutations: Q148H, E138A, G140S Accessory mutations: T97A, G149A	MVC Fostemsavir
Tropism	CCR5 (FPR 69.8%)	CXCR4 (FPR 3.1%)	CCR5 (FPR 57.6%)	CCR5 (FPR 64%)	Ongoing ART before IBA start: DTG 50 mg BID + DRV/r 600/ 100 mg BID + 3TC 300 mg QD IBA associated with: DRV/r 600 mg BID + ENF 90 mg BID + MVC 150 mg BID + FTC/TAF/RPV 200/25/25 mg QD

Muccini et al. AIDS 2020. DOI:10.1097/QAD.0000000000002687

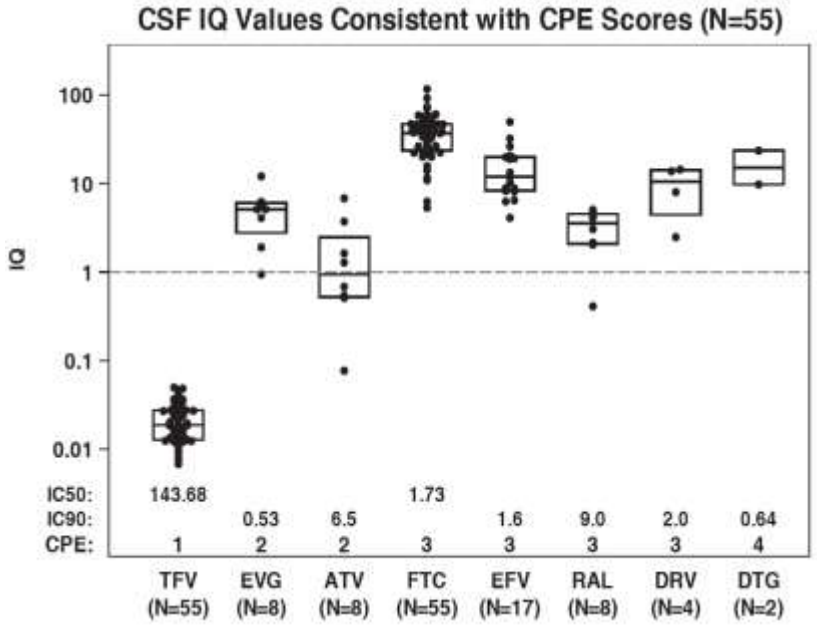
Broadly Neutralizing Antibodies

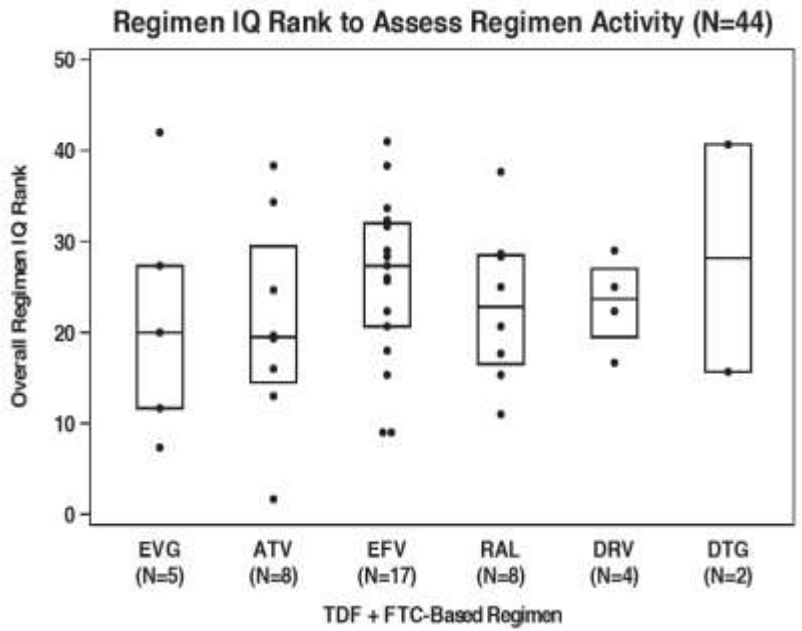


- **VRC01 concentrations in CSF were on average 1000-fold lower compared to concurrent plasma concentrations in 3 participants**
- **On average, VRC01 was 6% of all IgG in CSF compared with 2% of all IgG in blood plasma**

Prabhakaran et al. CROI 2020. Abstract 453

CSF Inhibitory Quotients Accounts for Interpatient Variability

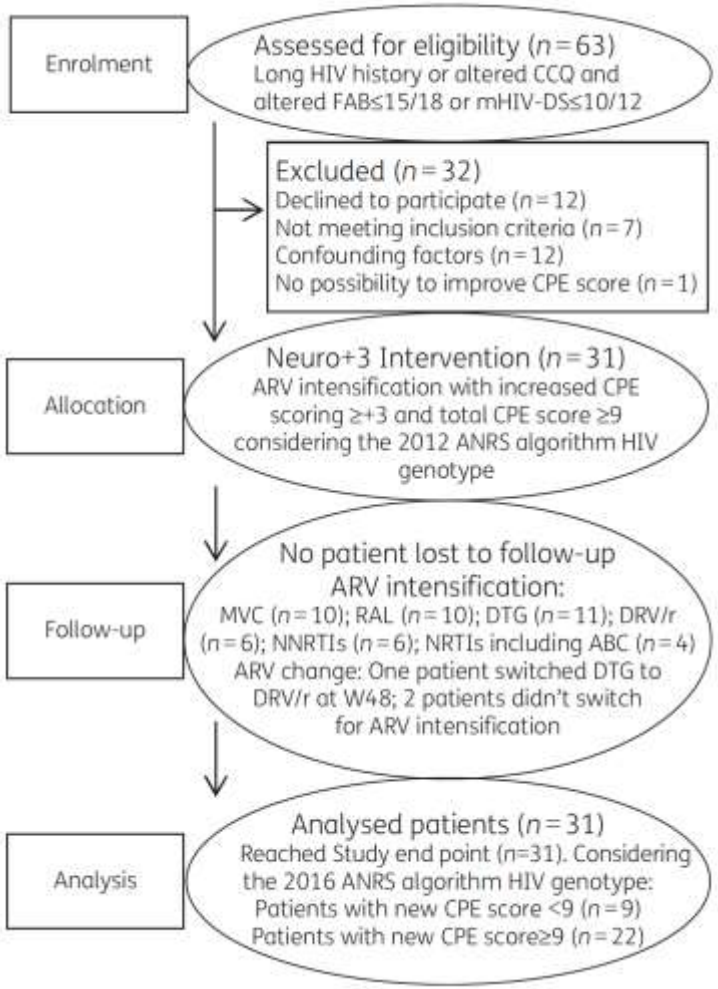


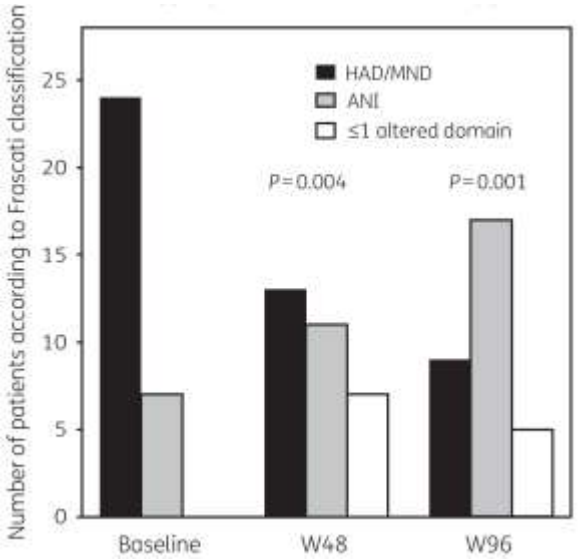


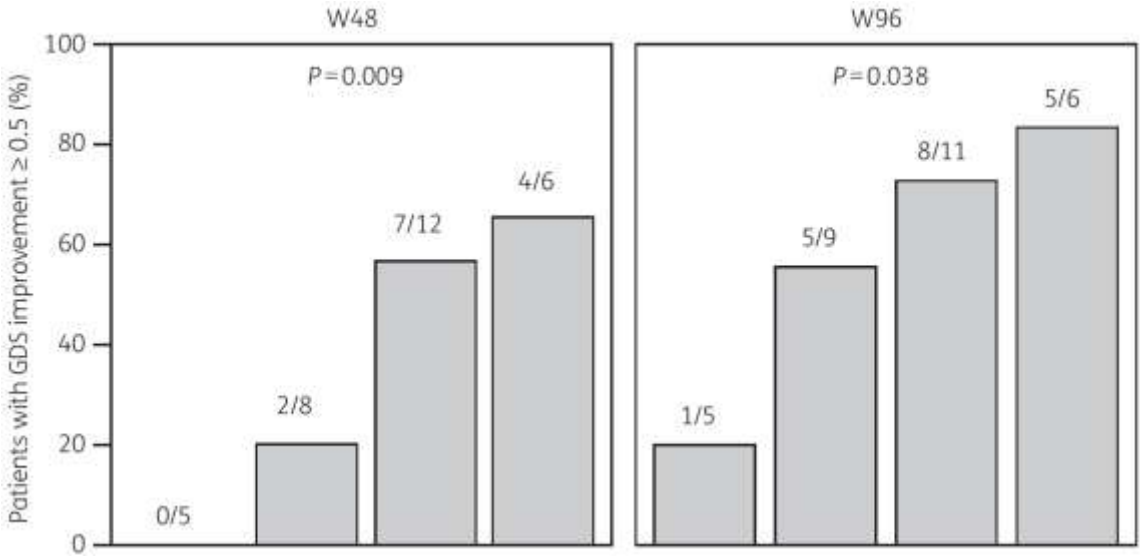
- **CSF ART drug concentrations were available on 55 participants on TDF/FTC-based regimens**
- **Inhibitory quotients (IQs) were calculated for each drug in ART regimen as ratio of measured CSF concentration to literature values for in vitro inhibitory concentration**
- **Participants were ranked (low to high) by IQs for TFV, FTC, and third ART drug, then drug ranks were averaged to give an overall rank for the regimen**
- **CSF IQ values are consistent with the hierarchy of CPE scores (higher IQ <–> higher CPE), but allow interpatient variability the CPE does not**

Fletcher et al. CROI 2020, Abstract 455

ART Intensification May Benefit People with HAD (Neuro+3)

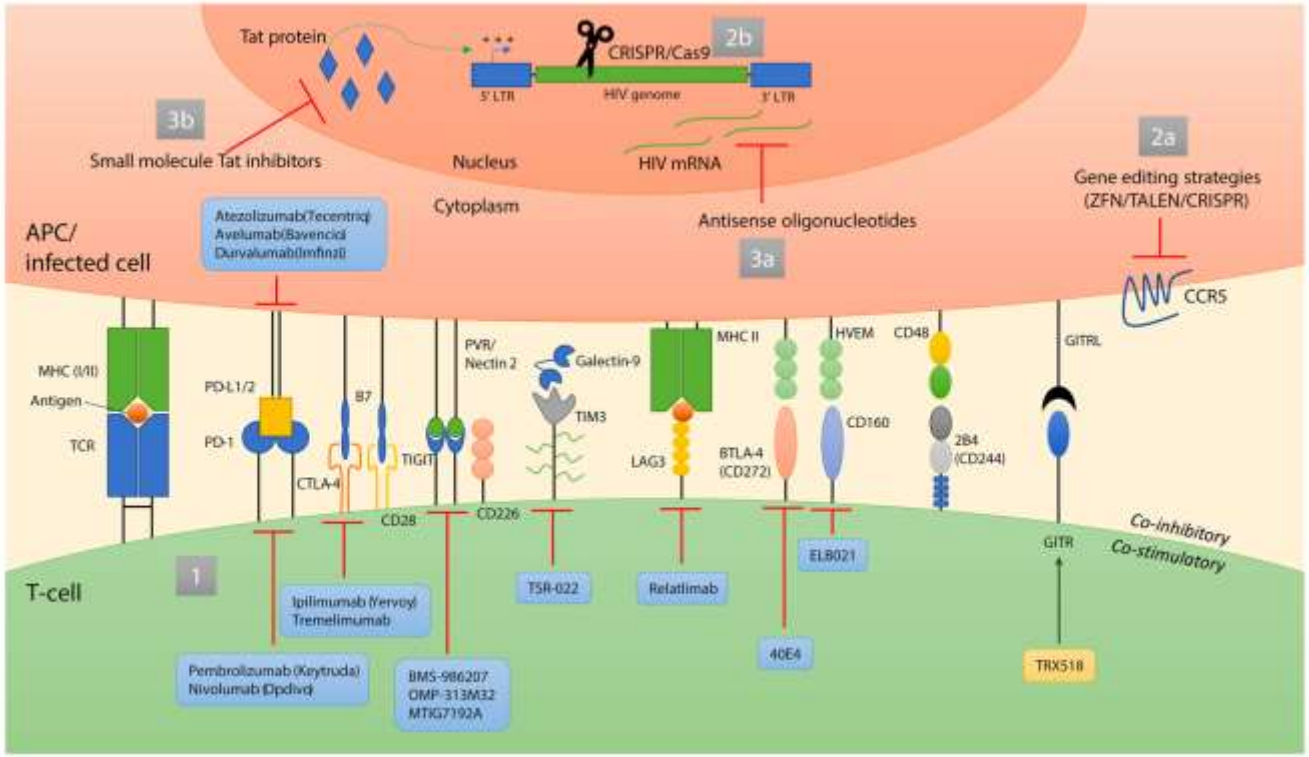






Force et al. J Antimicr Chemother 2020, doi:10.1093/jac/dkaa473

HIV Cure Strategies and Clinical Trials

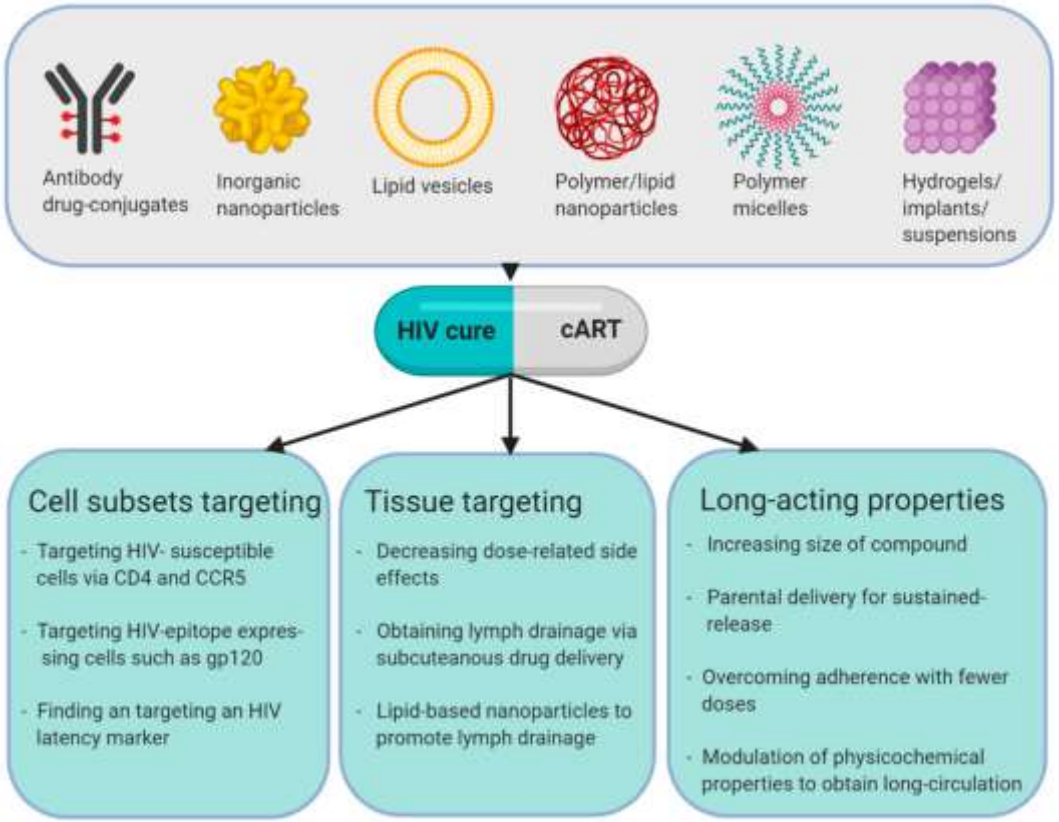


Trial	Study drug	Target(s)	Population	Phase
NCT03787095	Cemiplimab	PD1	Suppressed HIV on ART	1/2
NCT03239899	Pembrolizumab	PD-1	CNS HIV reservoir	1
NCT03367754	Pembrolizumab	PD-1	HIV with low CD4$^+$ cell count	1
NCT02595866	Pembrolizumab	PD-1	HIV and malignant neoplasms	1
NCT03304093	Nivolumab	PD-1	HIV and non-small-cell lung cancer	2
NCT02408861	Nivolumab and ipilimumab	PD-1, CTLA-4	HIV and malignant neoplasms	1
NCT03316274	Nivolumab	PD-1	HIV and Kaposi sarcoma	1
NCT03407105	Ipilimumab	CTLA-4	HIV	1
NCT03094286	Durvalumab	PD-L1	HIV and solid tumors	2

LRA	Secondary agent(s)	No. of patients	Status	Identifier
Nicotinamide (SIRT1 inhibitor)	Dendritic cell vaccine + auranofin + ART intensification	30	Active	NCT02961829
Vorinostat (HDACI)	ChAdV63.HIVconsv (ChAd) prime and MVA.HIVconsv boost vaccines	60	Active	NCT02336074
	Disulfiram	15	Terminated due to AE	NCT03198559
	HXTC[b]	12	Recruiting	NCT03212989
	Tamoxifen	30	Active	NCT03382834
	AGS-004 DC therapy	6	Terminated (AGS-004 supply unavailable)	NCT02707900 (VOR-VAX)
	VRC07-523LS	12	Recruiting	NCT03803605
Panobinostat (HDACI)	Pegylated IFN-α_{2a}	34	Recruiting	NCT02471430
Romidepsin (HDACI)	3BNC117	30	Active	NCT02850016[c]
	MVA vector HIV vaccine + HIVACAR01 (personalized HIV vaccine) + 10-1074	56	Not yet recruiting	NCT03619278
	3BNC117 ab	60	Recruiting	NCT03041012
	3BNC117 ab	42	Not yet recruiting	RV 438
Valproic acid (HDACI)	Pyrimethamine	28	Recruiting	NCT03525730
Chidamide (HDACI)	None	60	Active	NCT02902185
	CAR-T or TCR-T-cell therapy	40	Recruiting	NCT03980691
Euphorbia kansui (ingenol) (PKC agonist)	None	9	Recruiting	NCT02531295
Lefitolimod (MGN1703) (TLR9 agonist)	10-1047 + 3BNC117	48	Recruiting	NCT03837756[c]
GS-9620 (TLR7 agonist)	None	28	Active	NCT03060447[c]
Pegylated IFN-α_{2a}	None	54	Active	NCT02227277
	3BNC117 + 10-1074	21	Not yet recruiting	NCT03588715[c]
Recombinant human superagonist IL-15 (ALT-803/N-803)	None	10	Active	NCT02191098
	Haploidentical NK cell adoptive transfer	8	Recruiting	NCT03899480

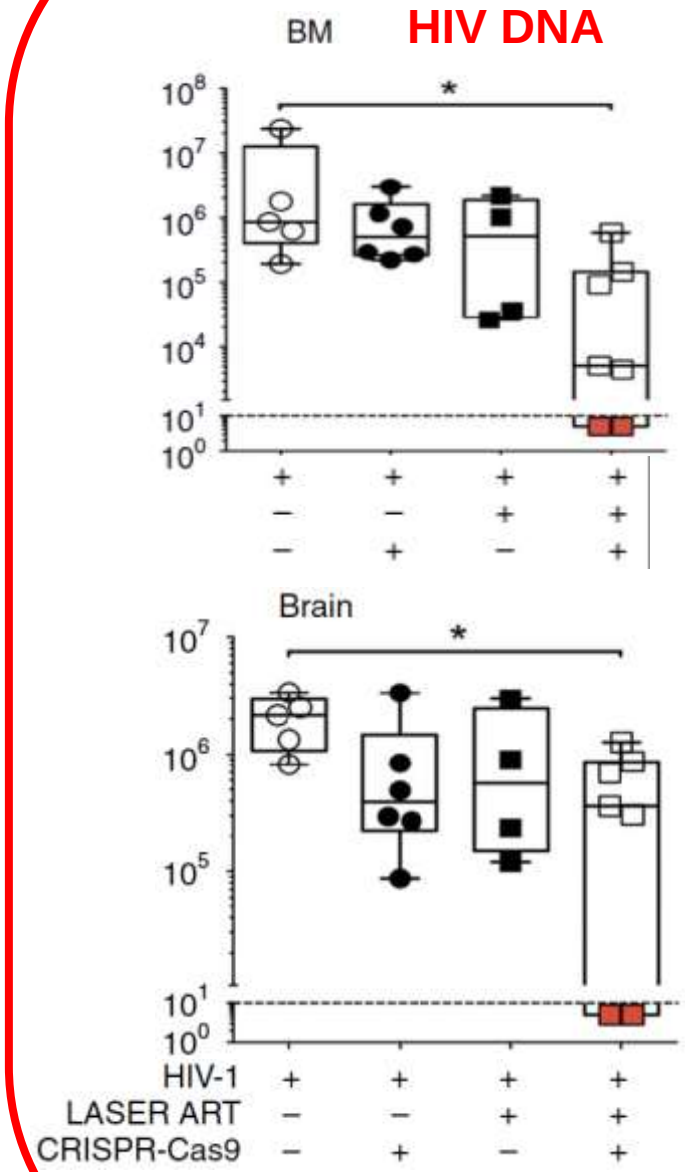
[a]Based on data from references 54 and 56. All treatments are in addition to ART, unless otherwise noted.
[b]HXTC, HIV antigen expanded specific T-cell therapy.
[c]These studies involve analytical treatment interruption (ATI).

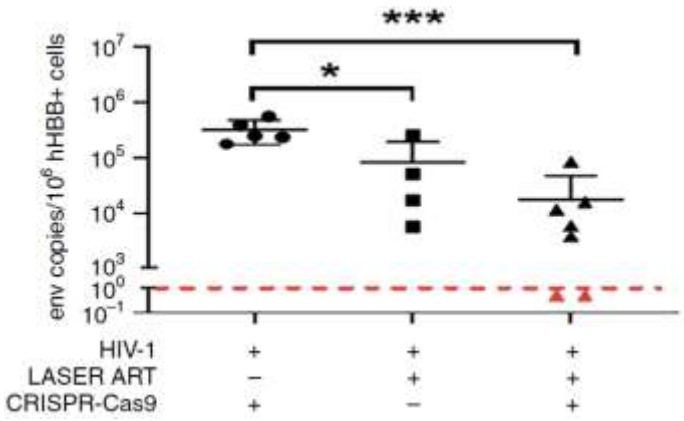
Henderson et al, J Virol 2020; 94: e00375-19.

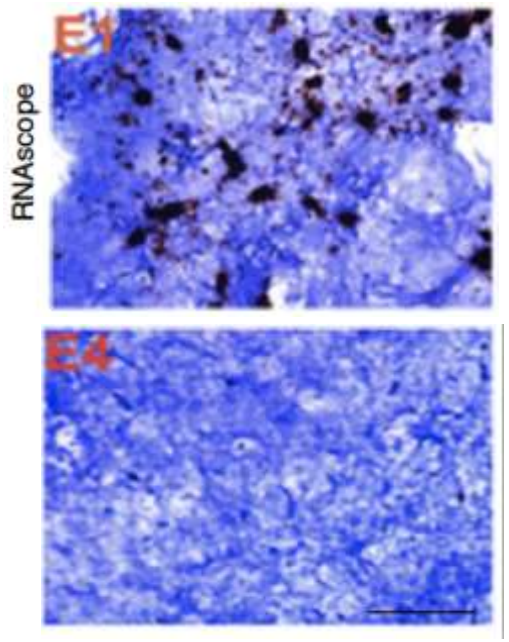


Andersen & Tolstrup. Viruses 2020, 12, 412; doi:10.3390/v12040412

LASER: Long-acting slow-effective release

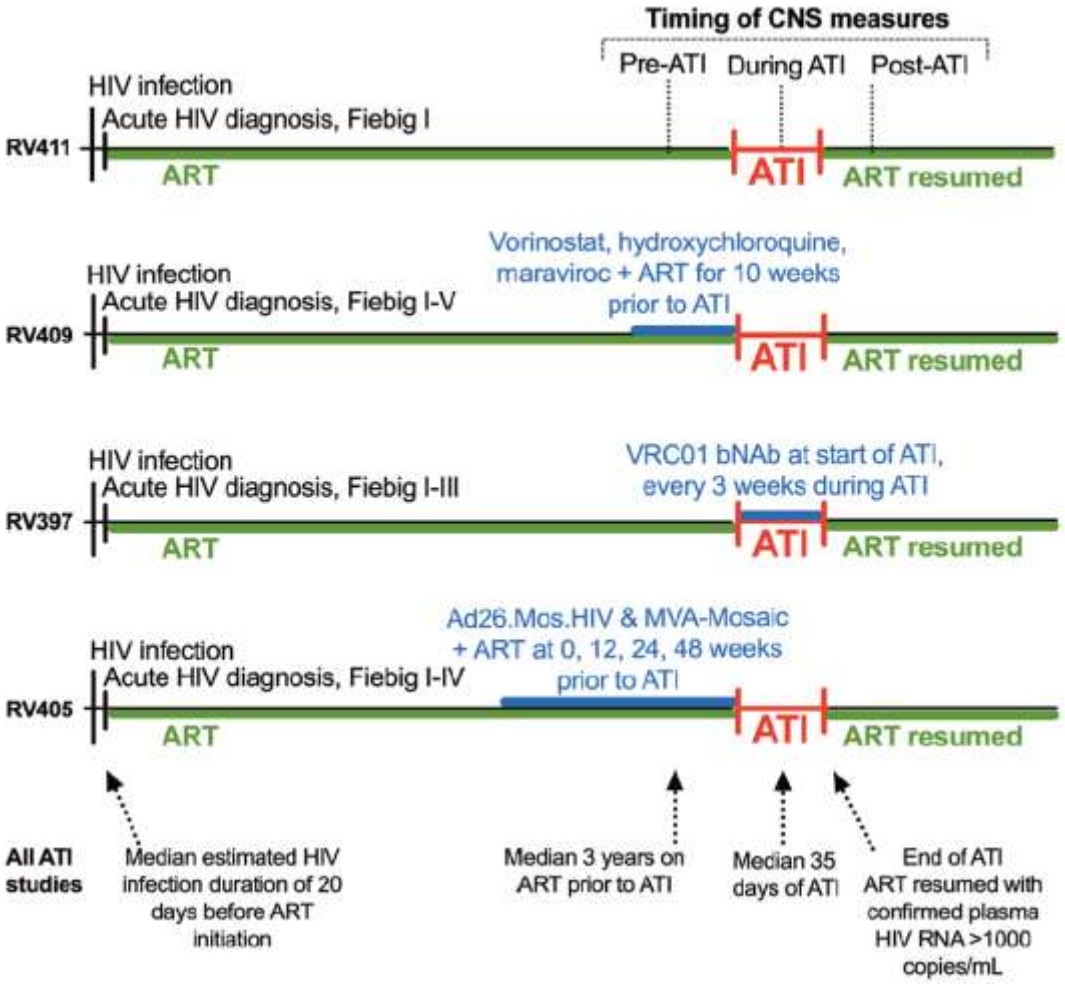


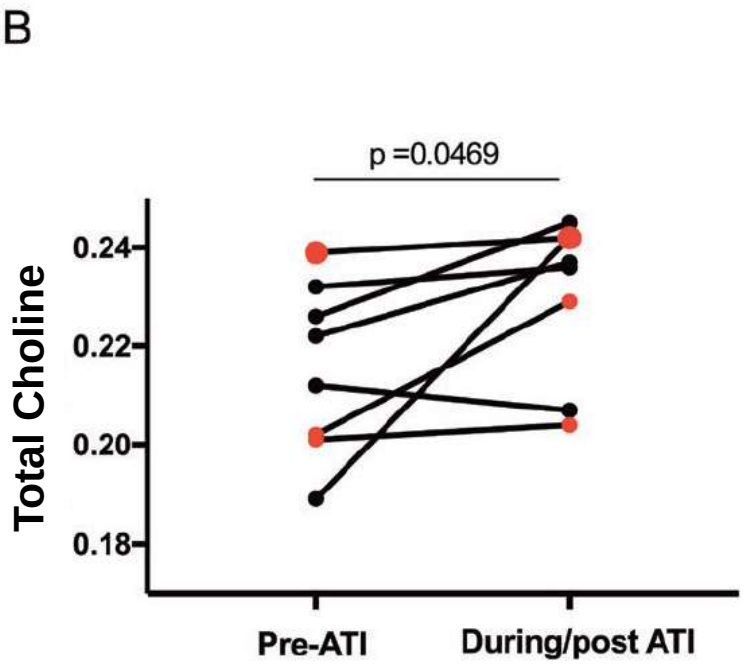




Dash et al, Nature Communications 2019 doi.org/10.1038/s41467-019-10366-y

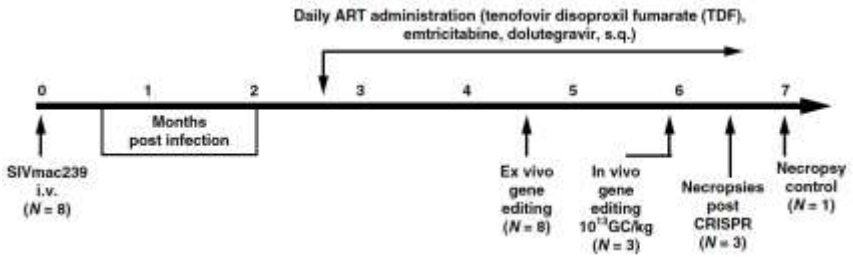
CNS Safety of Analytical Treatment Interruption

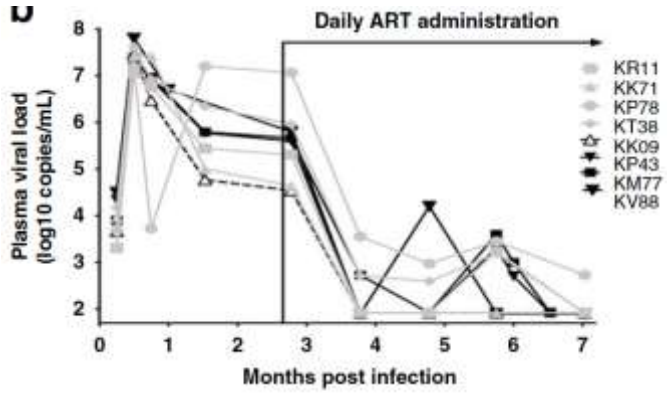


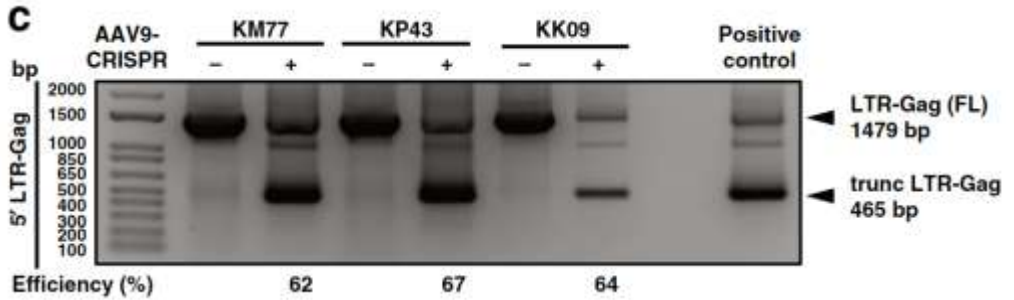


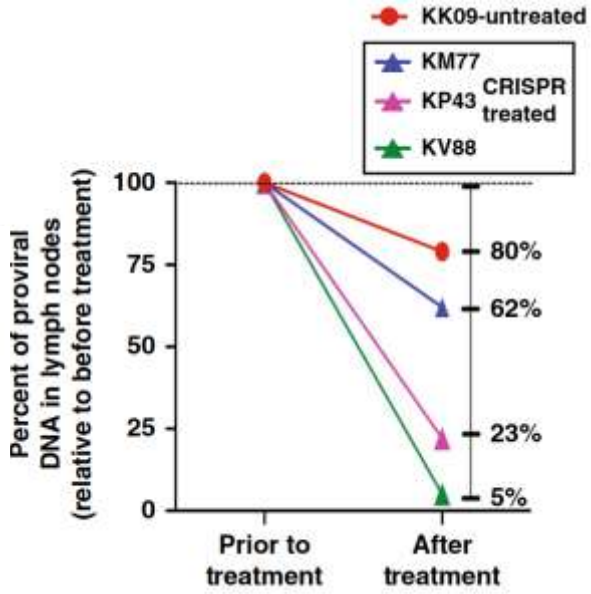
Hellmuth et al, Clin Infect Dis 2020. PMID: 32916708

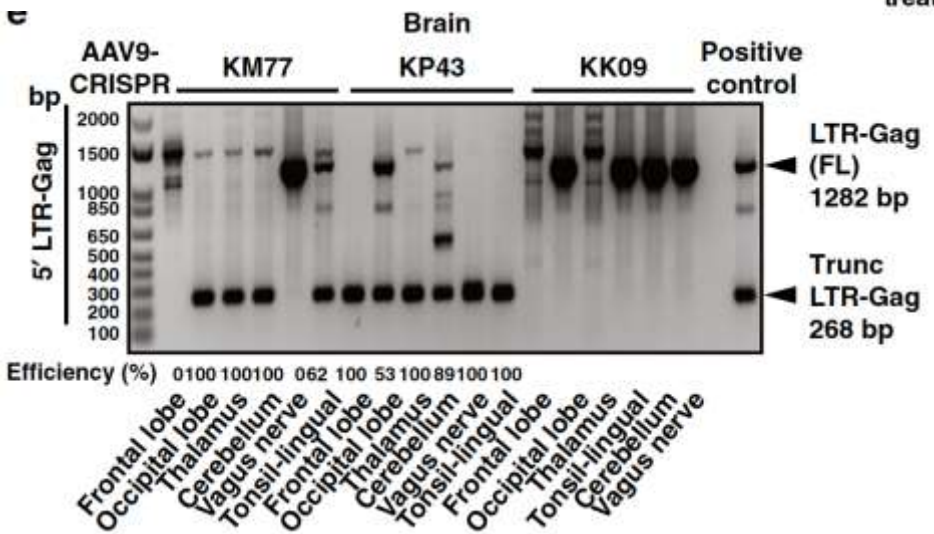
CRISPR-Based Editing of SIV Proviral DNA in NHPs

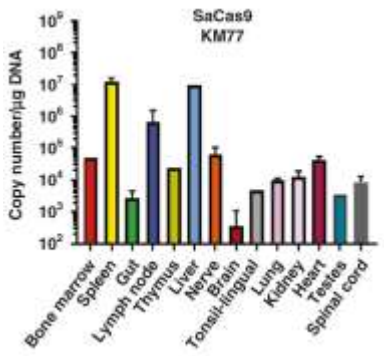


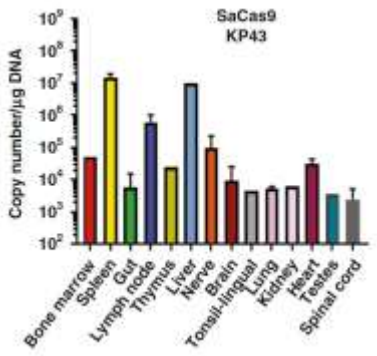


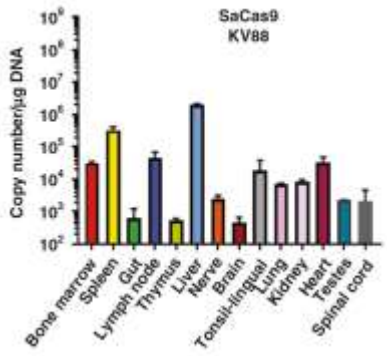












Mancuso et al, Nature Comm 2020, doi.org/10.1038/s41467-020-19821-7

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