Vaccinal effect of anti-HIV-1 antibodies

Ole Schmeltz Søgaard, Professor and MD

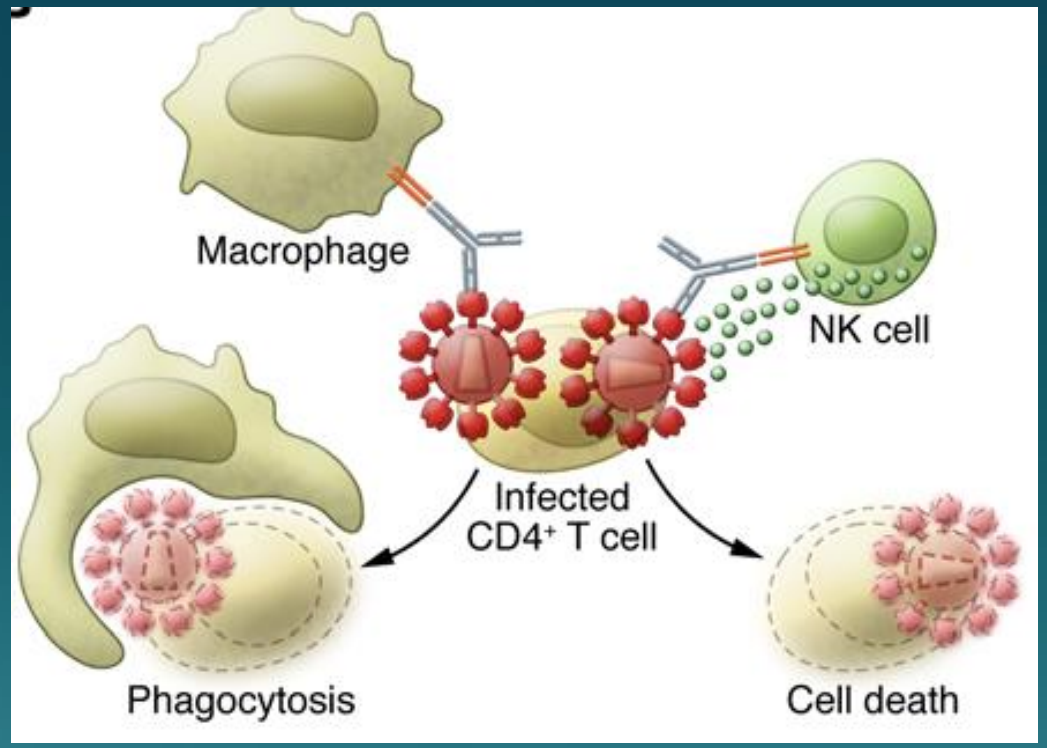
Dept of Infectious Diseases, Aarhus University Hospital, Denmark

AARHUS UNIVERSITY

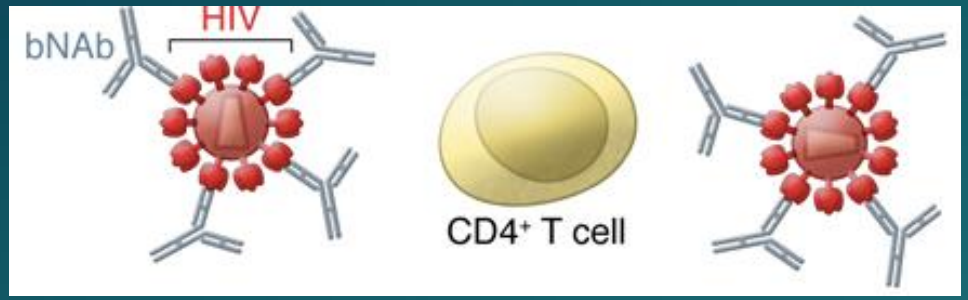
midt Central Denmark Region

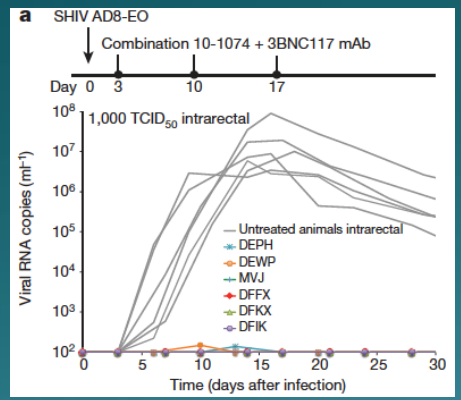
Can bNAbs do more than ART?

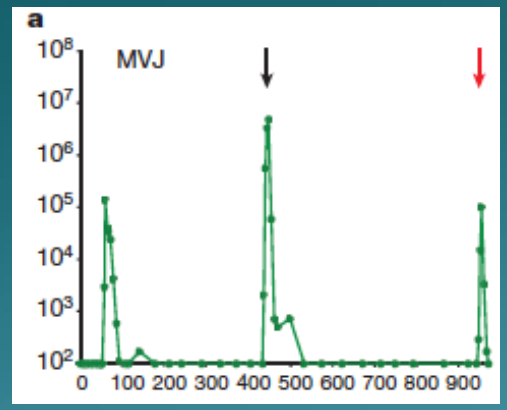
bNAbs can engage innate immune effector cells and facilitate killing of infected cells



bNAb mediated enhancement of HIV-specific adaptive immunity?

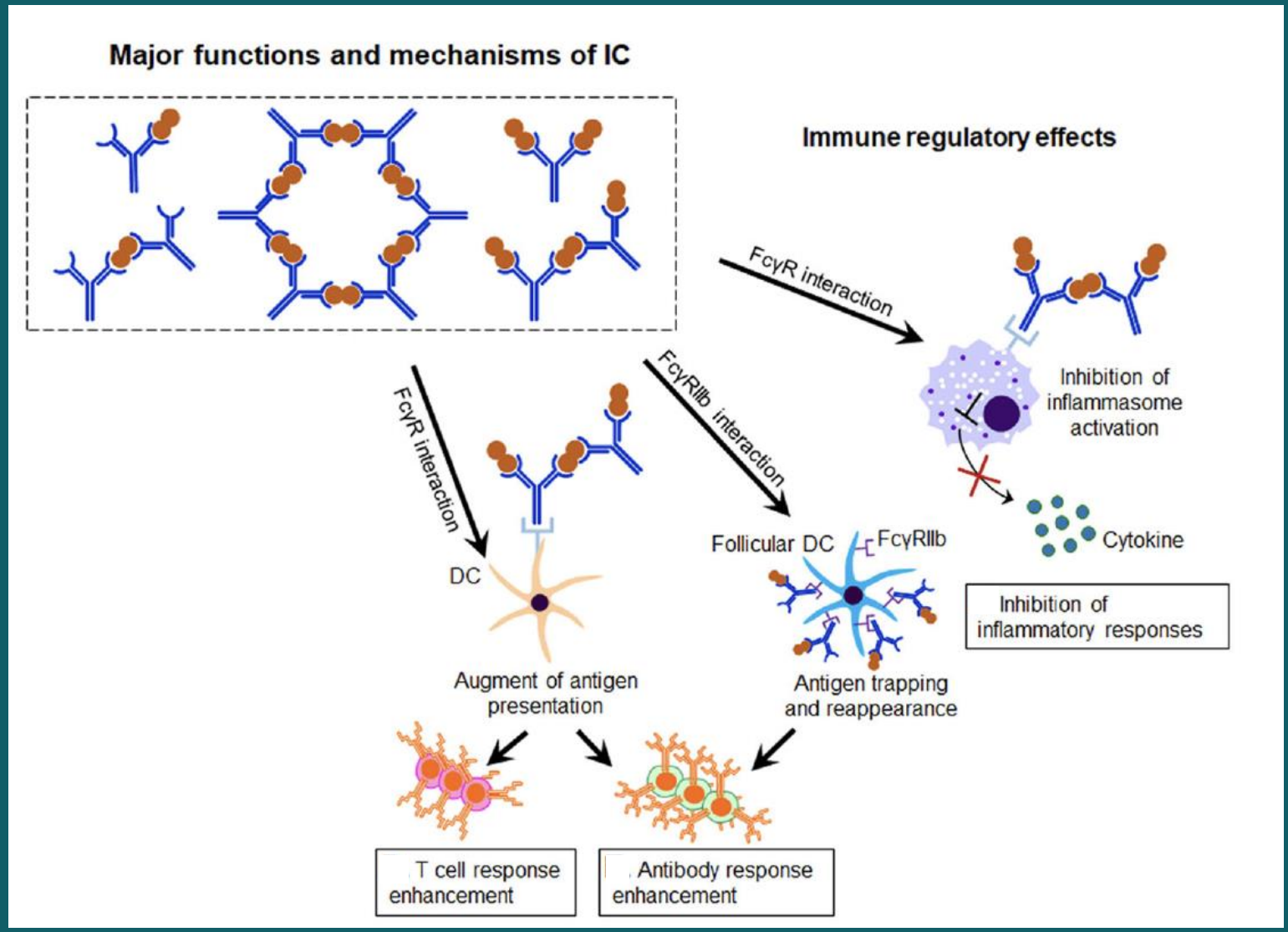






Caskey et al. Nature, 2015; Halper-Stromberg and Nussenzweig JCI 2016; Nishimura et al Nature 2017

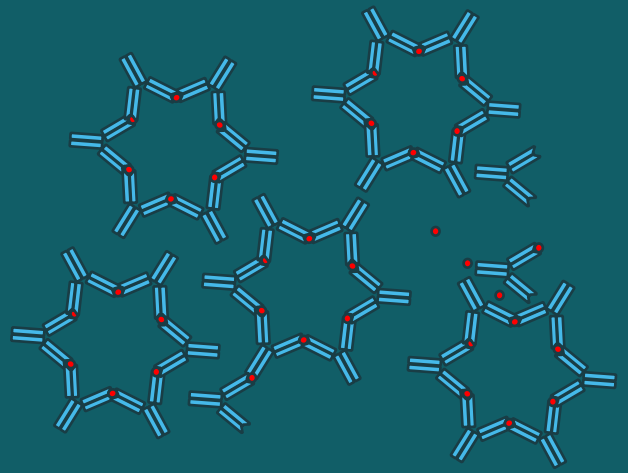
Antibody:antigen immune complexes



Adapted from Wen et al. NPJ 2019

Impact of antibody:antigen ratio

	HIGH ANTIGEN LOAD	LOW ANTIGEN LOAD
bNAb administration	E.g. at ART initiation	E.g. during ART or into ATI
Plasma viremia	High (10^4-10^7 c/mL)	< 50 c/mL
HIV antigen in blood and tissue	Abundent	Very low
Opportunity for antibody:antigen immune complex formation	High	Low to modest
Risk of resistance development to bNAbs	No	Yes



Studies of nAbs/bNAbs administration in a high antigen load setting

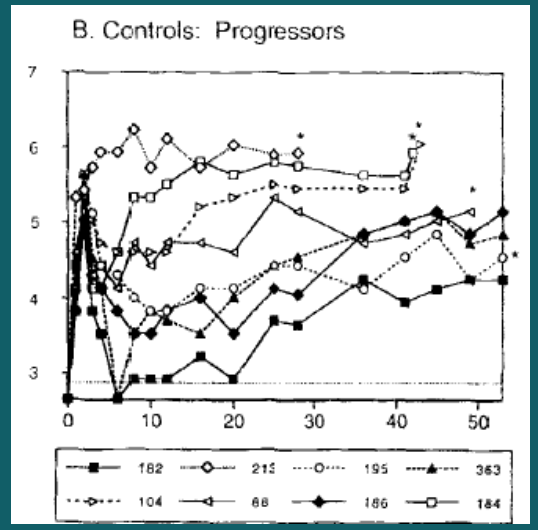
Investigations into HIV/SIV antibodies as treatment for almost 30 years

Passive immune globulin therapy in the SIV/macaque model: early intervention can alter disease profile

Nancy L. Haigwood[a,*], Andrew Watson[a], William F. Sutton[a], Jan McClure[a], Anne Lewis[b], Jane Ranchalis[a], Bruce Travis[a], Gerald Voss[c], Norman L. Letvin[c], Shiu-Lok Hu[a], Vanessa M. Hirsch[d], Philip R. Johnson[b]

[a]*Department of Immunodeficiency and Immunosuppression, Bristol-Myers Squibb Pharmaceutical Research Institute, 3005 First Avenue, Seattle, Washington 98121, USA*
[b]*Children's Hospital Research Foundation, Columbus, Ohio 43205, USA*
[c]*Harvard Medical School, Beth Israel Hospital, Boston, Massachusetts 02215, USA*
[d]*Laboratory of Infectious Disease, NIAID, NIH, Rockville, Maryland 20852, USA*

Accepted 15 March 1996



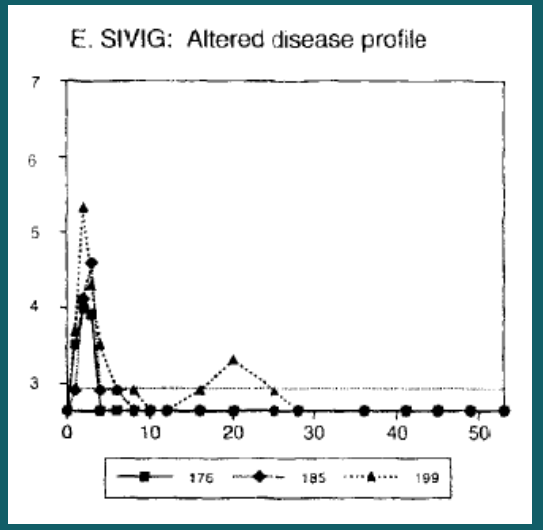


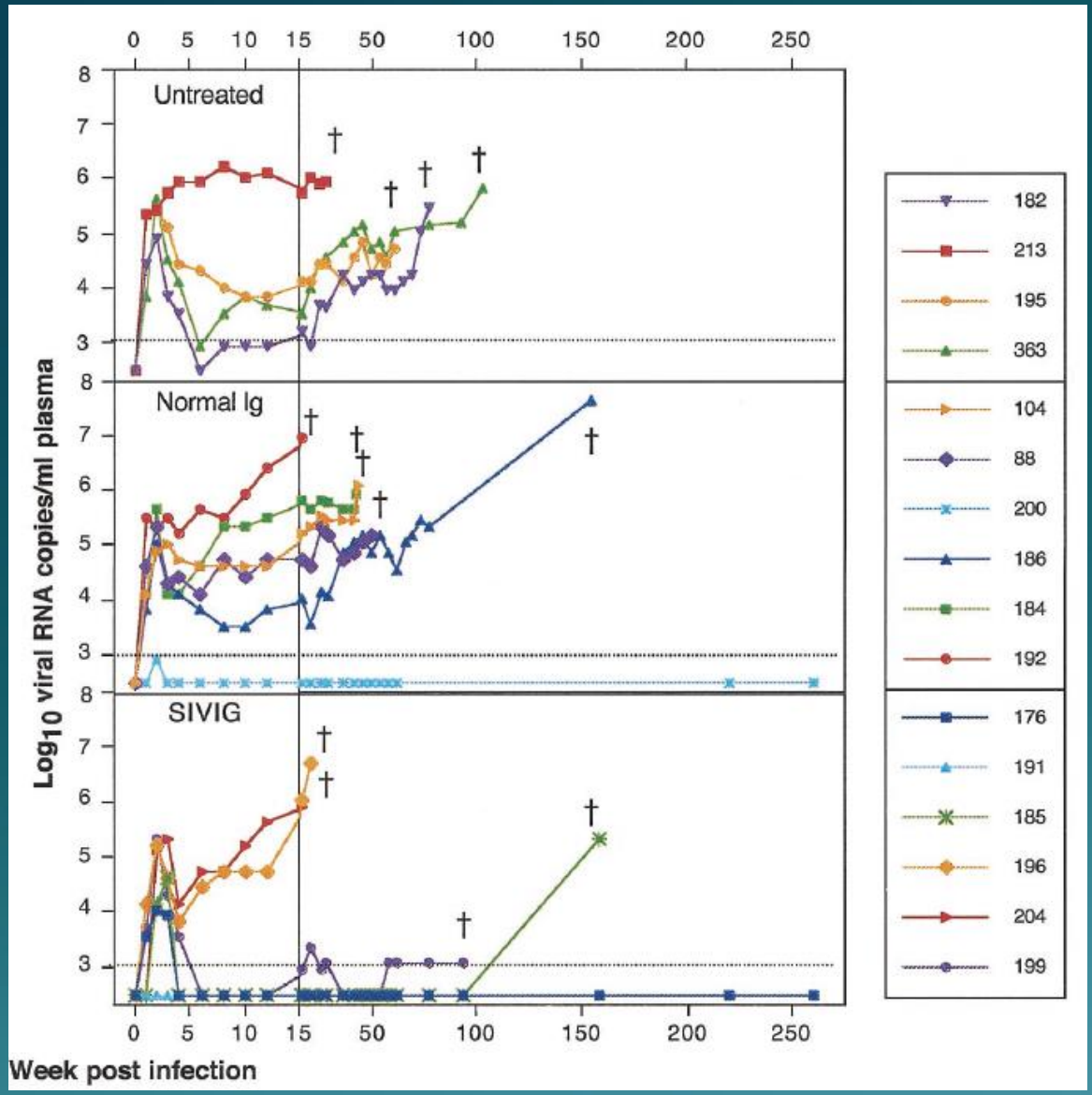
Table 1
Summary of clinical status at 67 weeks post infection

Group	Animal	Clinical signs	Week of euthanasia
SIVIG	196	CD4 decline; wasting	18
	204	Wasting and diarrhea	20
	176	Healthy	—
	185	Healthy	—
	191	Healthy	—
	199	Healthy	—
Normal IG	192	Wasting and diarrhea	20
	184	Wasting and diarrhea; CD4 decline; ataxia	42
	104	Lymphadenopathy; pneumonia	43
	88	Wasting and diarrhea; CD4 decline	52
	186	Persistent (>40 week) rash; secondary infections	—
	200	Healthy	—
Untreated	213	Wasting and diarrhea; involution of lymphoid tissue	36
	195	CD4 decline; pulmonary thromboembolism	67
	182	CD4 decline; respiratory distress	—
	363	CD4 decline; diarrhea	—

Neutralizing anti-SIV-Abs during primary infection

Total IgG was purified from the plasma of a single animal infected with SIV and surviving more than 6 years without signs of AIDS.

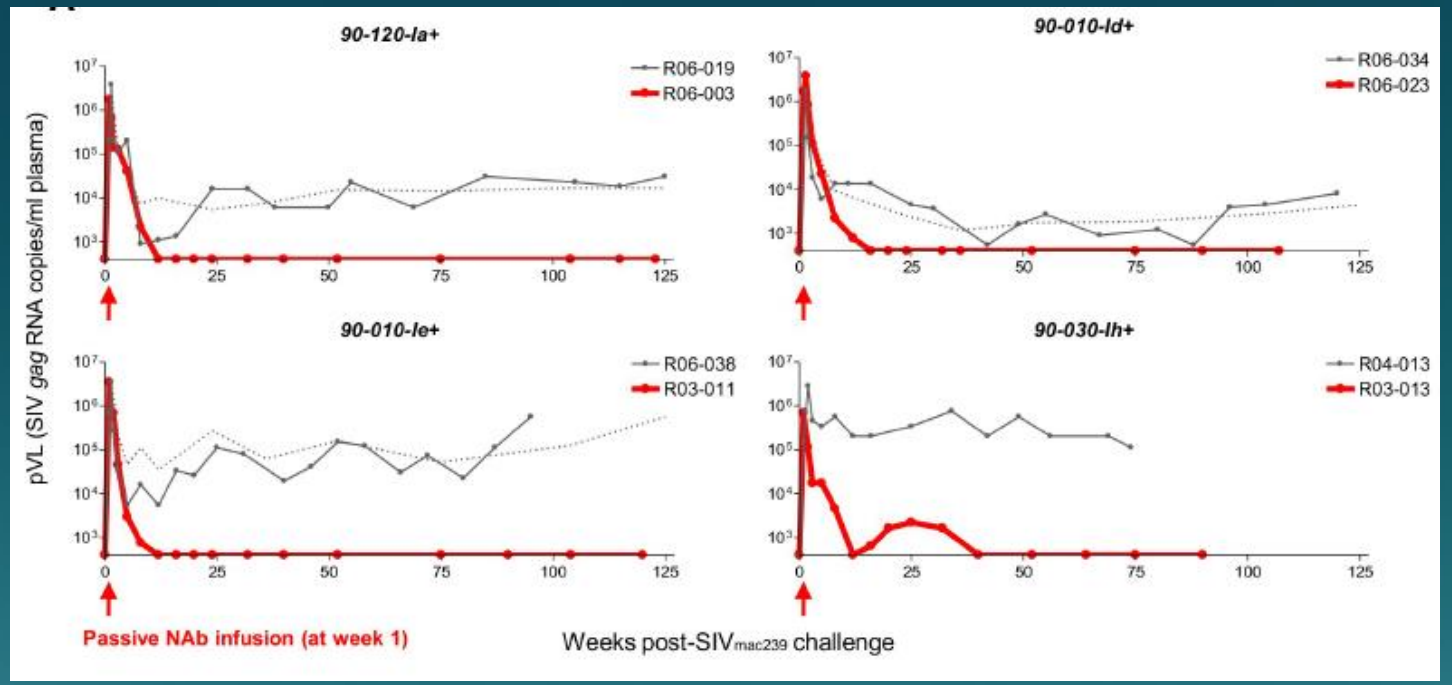
Infused IgG delayed binding antibody and accelerated Nab production.



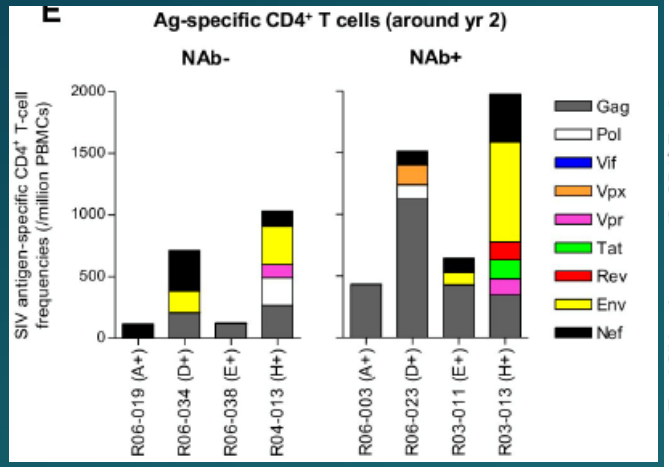
Haigwood et al. JVI 2004

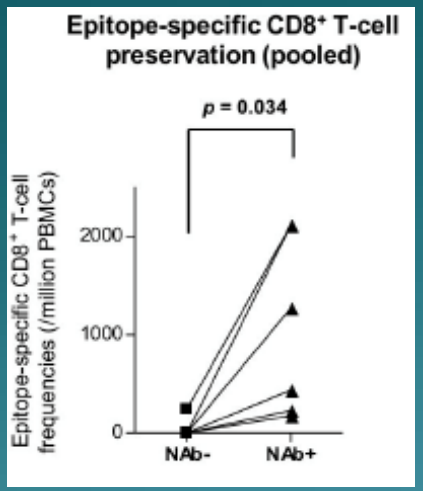
Neutralizing antibodies

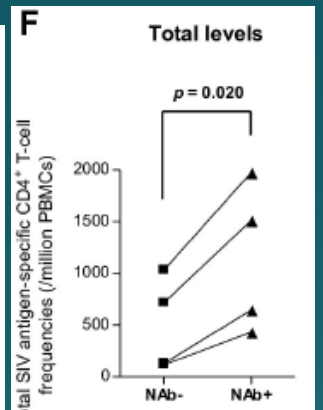
Passive iv infusion with 300 mg of polyclonal anti-SIV neutralizing IgG at day 7 post-infection with mac239.

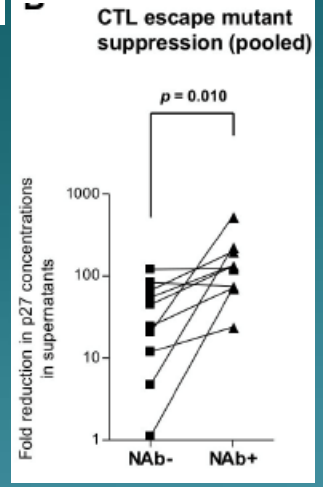


Enhanced SIV-specific T cell responses









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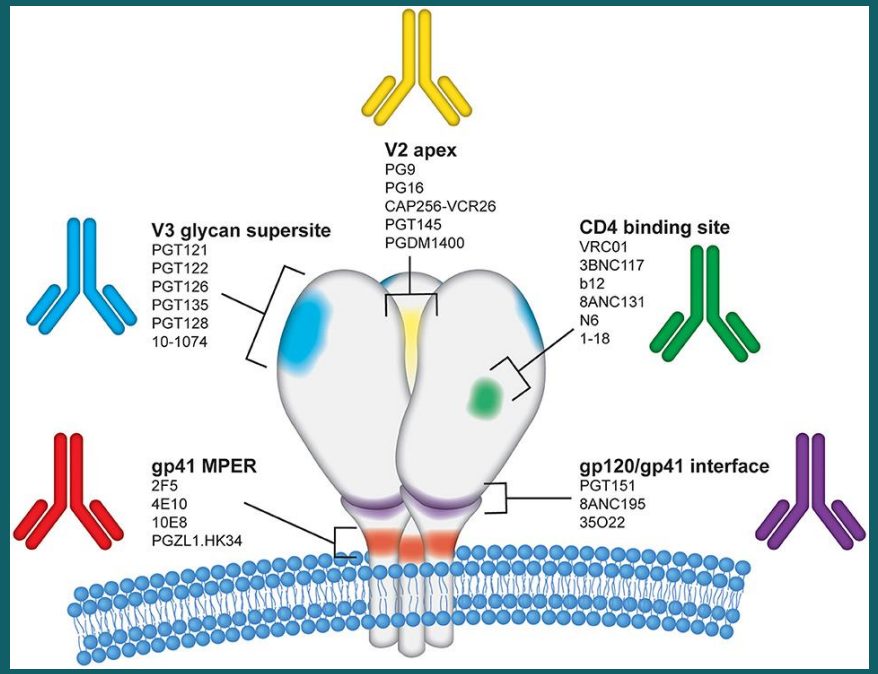
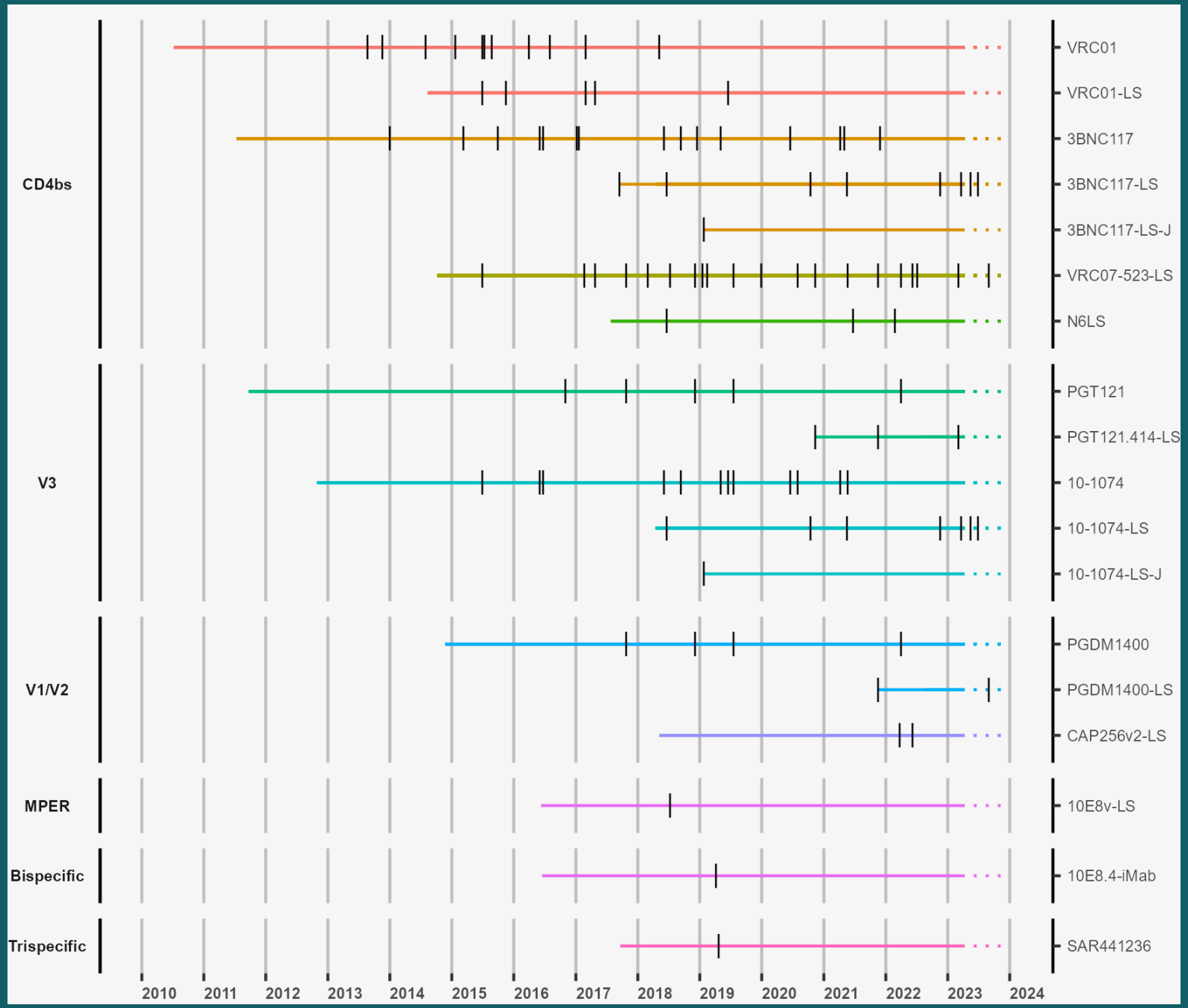
Iseda et al. JVI, 2016, Yamamoto et al. JVI 2009

Development of bNAbs against HIV-1



Spencer et al, Frontiers Public Health 2021



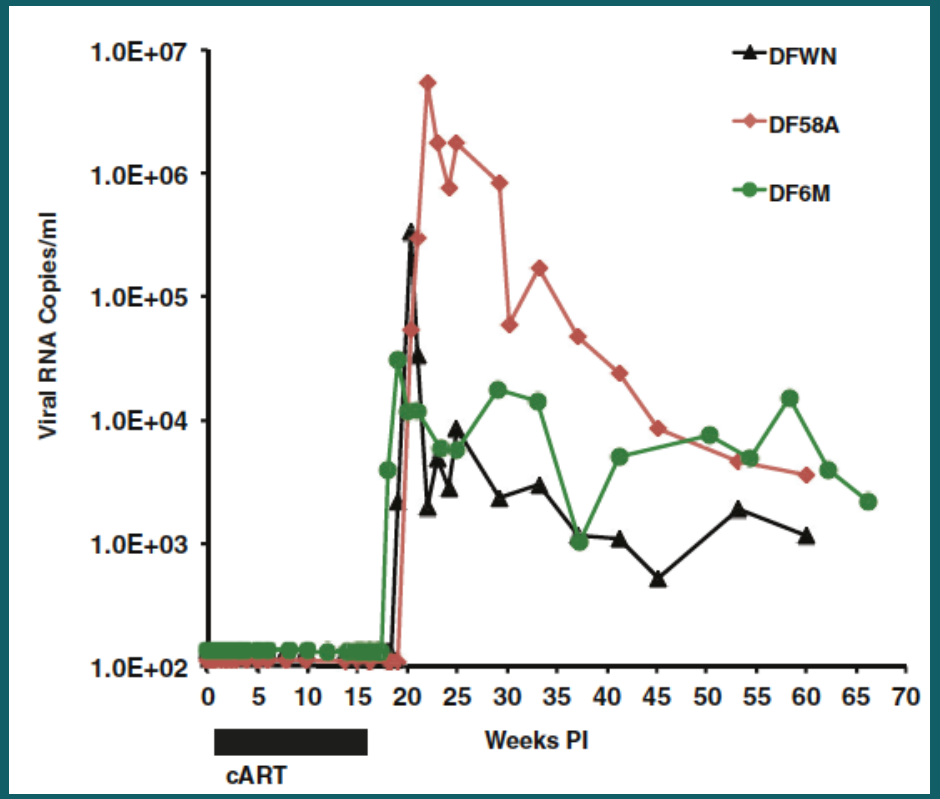
Frattari et al. Current Opi HIV/AIDS 2023

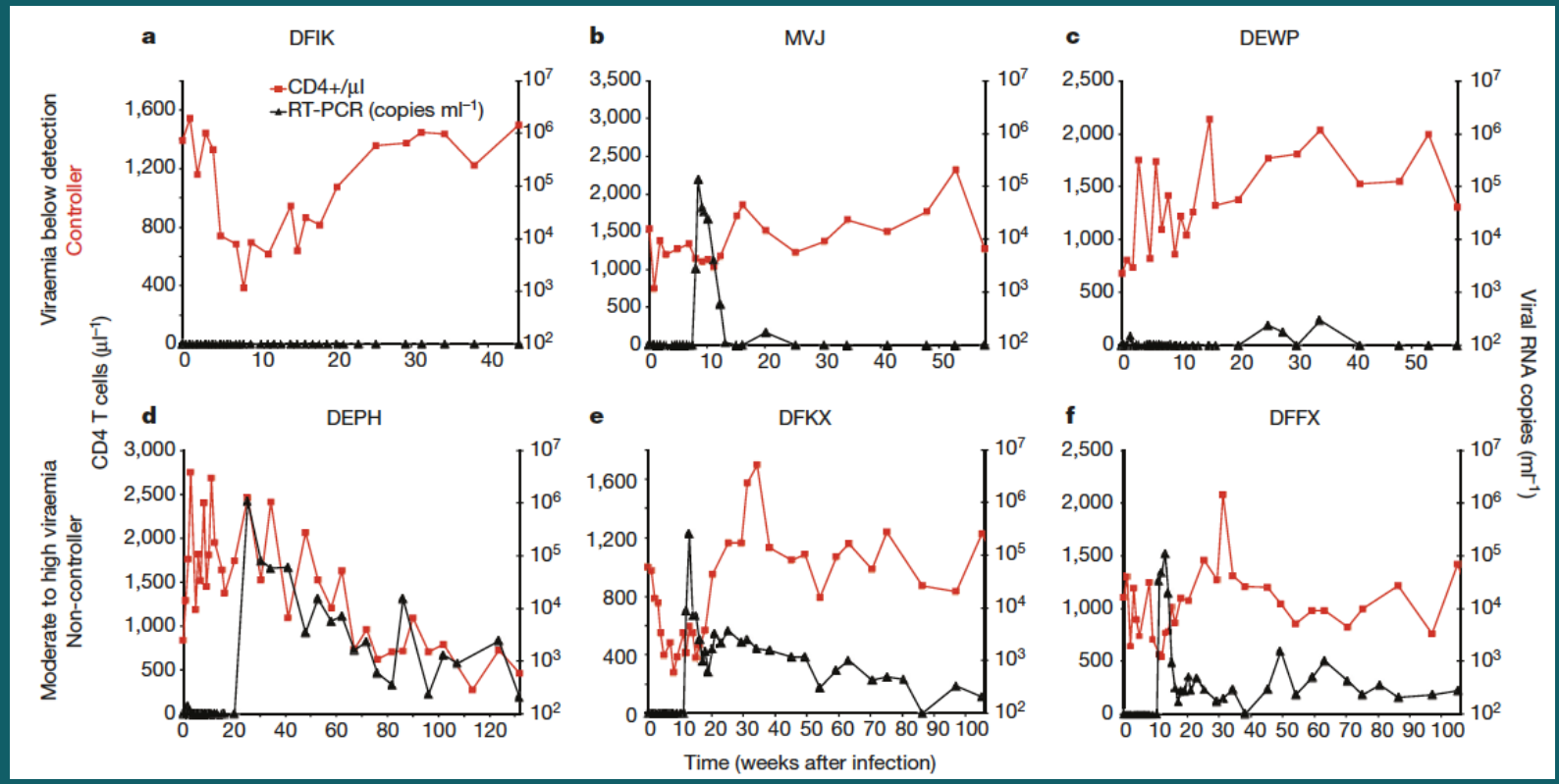
ART or bNAbs dosed in acute $SHIV_{ad08}$ infection

Early bNAbs suppress VL

15 weeks of early ART

And leads to longterm control in some animals

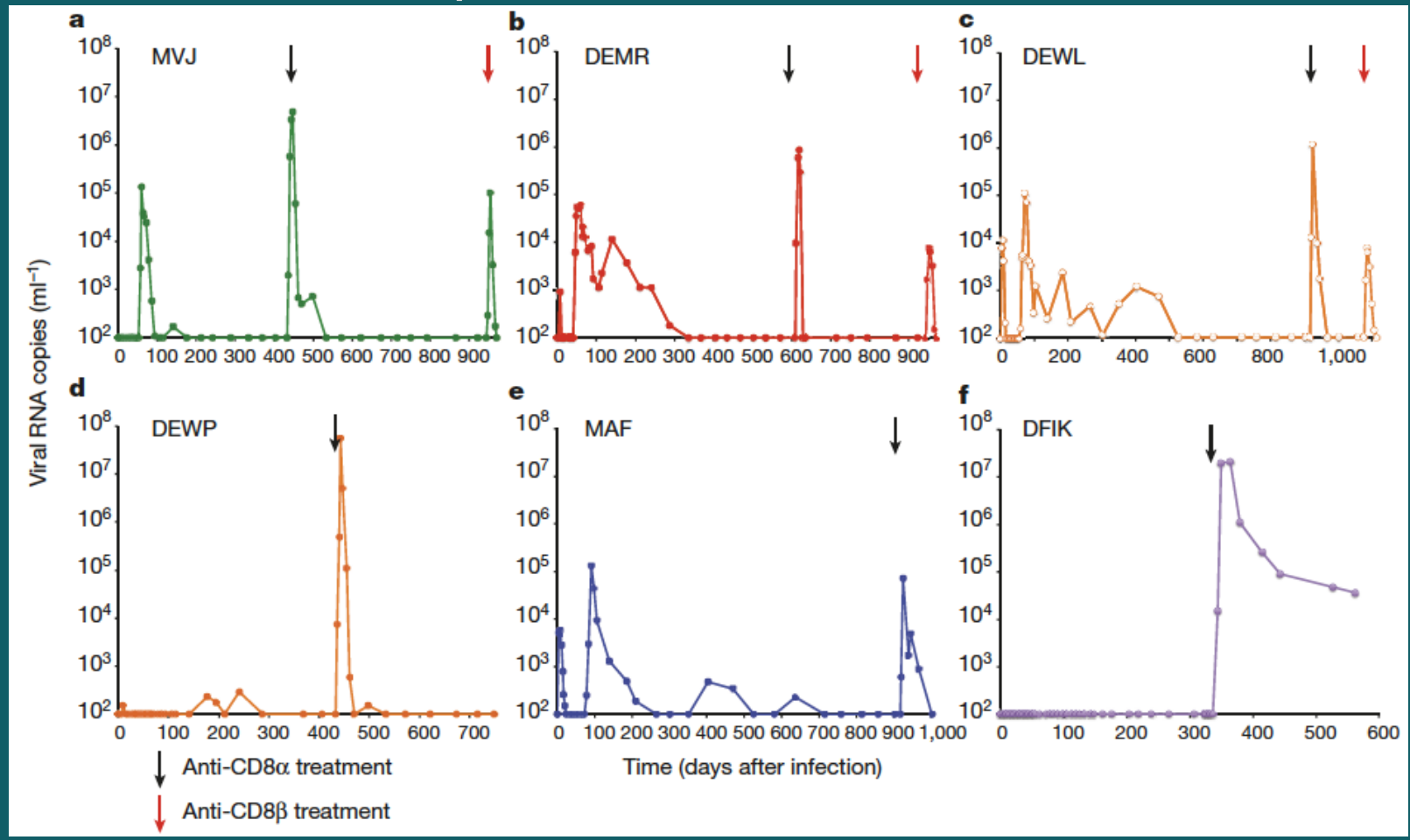




Nishimura et al. Nature 2017

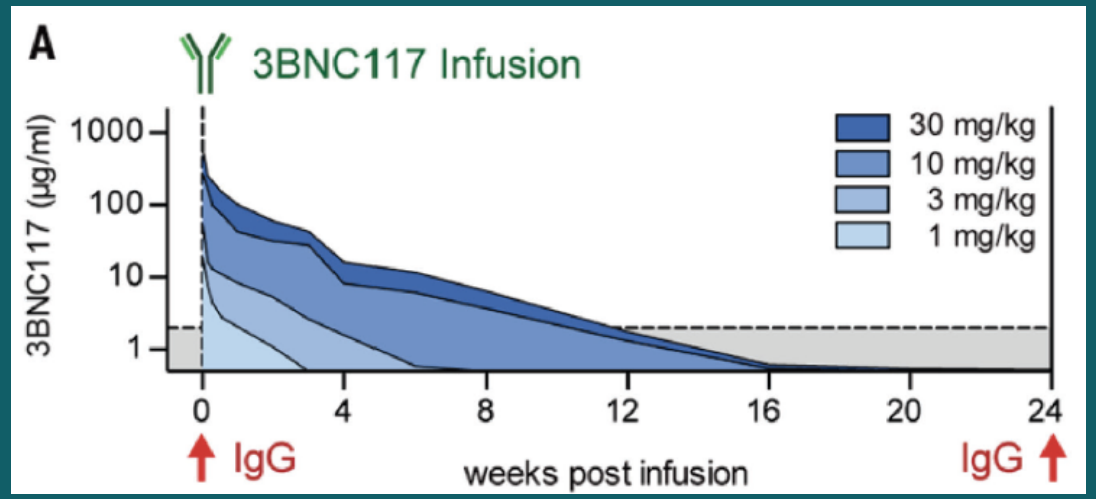
bNAbs dosed in acute $SHIV_{ad08}$ infection

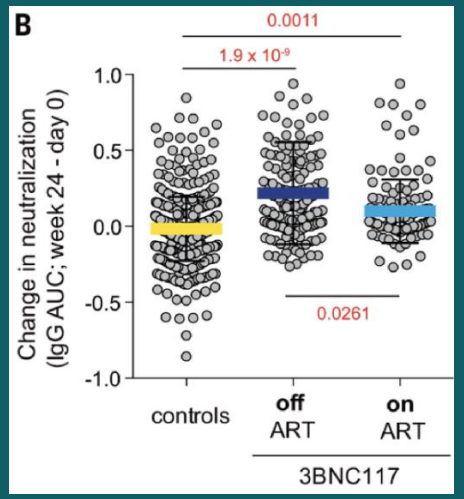
CD8 T cell depletion leads to viral rebound

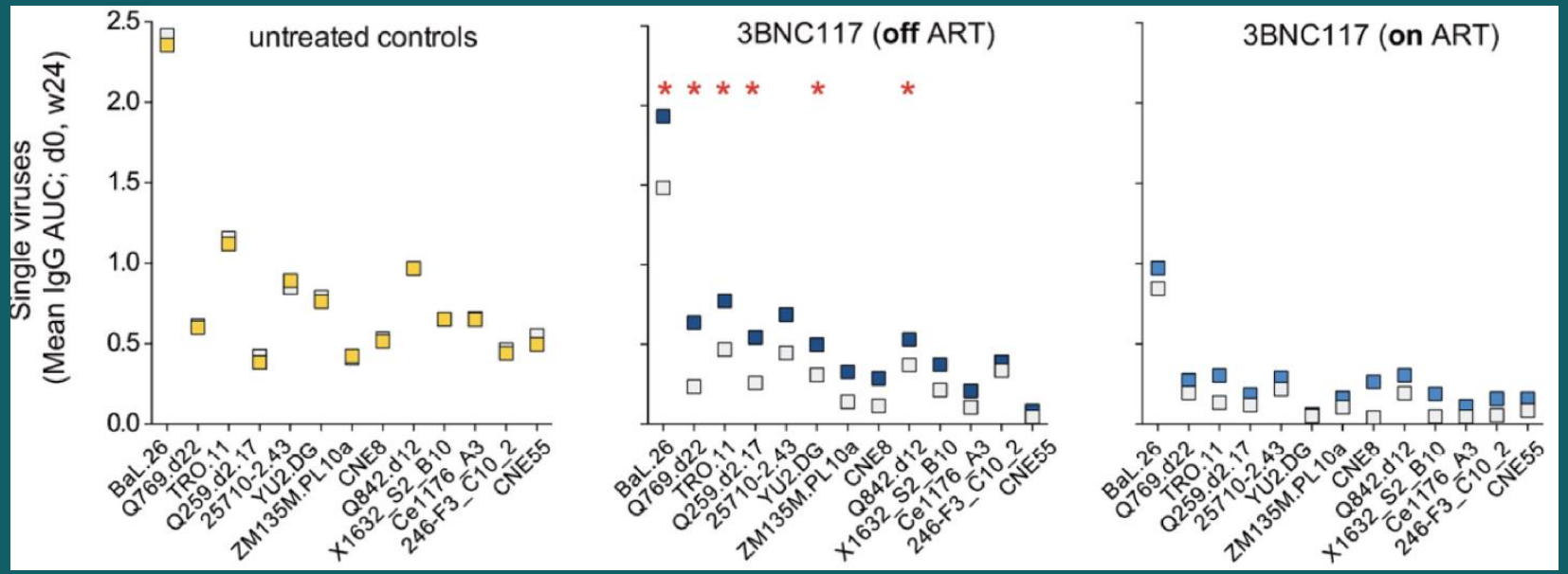


Nishimura et al. Nature 2017

Induction of autologous tier-2 nAbs



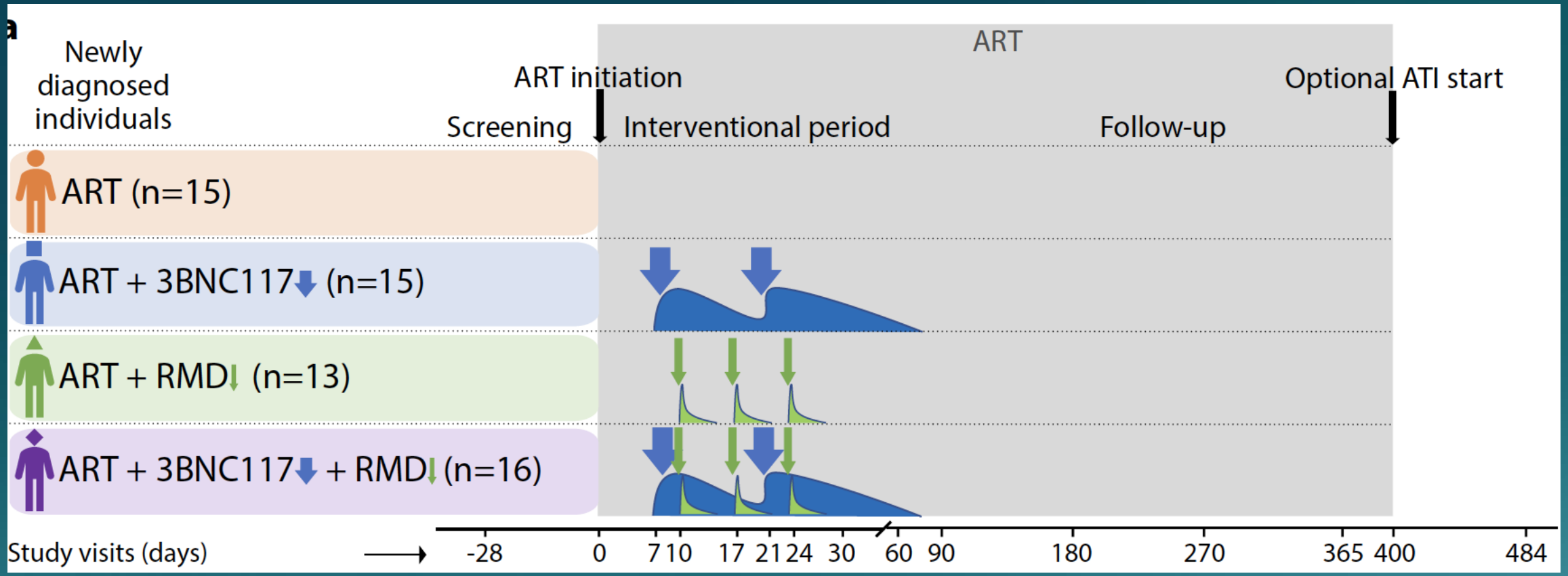




The absolute change in neutralizing activity varied between viruses and individuals, ranging from small effects to dramatic increases

Schoofs et al. Science 2016

eCLEAR trial design (open label RCT)



Gunst et al., 2022 Nature Medicine

Pre-ART sensitivity to 3BNC117 (plasma)

3BNC group: 8/15 (53%) sensitive

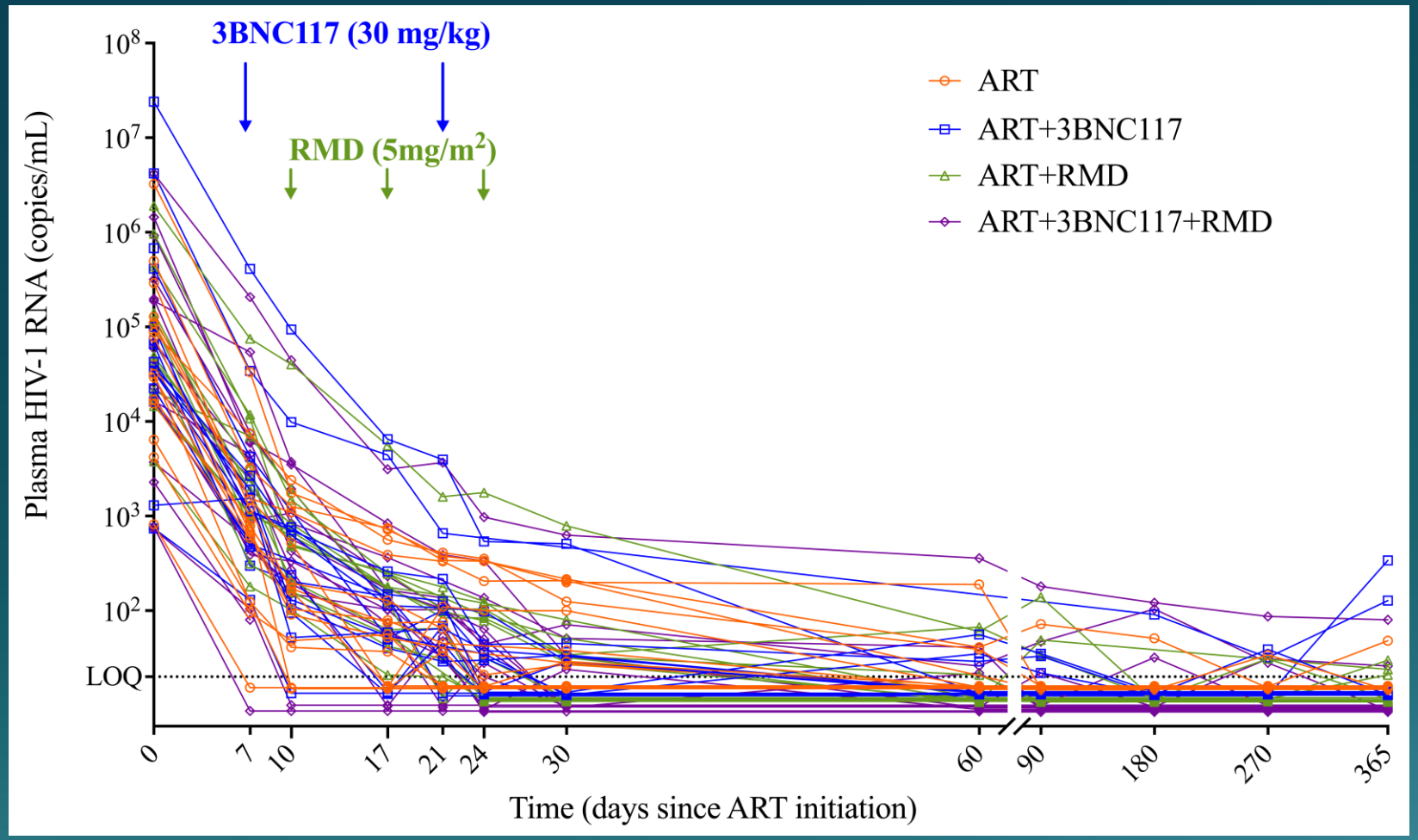
		Monogram PhenoSense		*env* sequencing	
	Participant ID	IC90	MPI	Sensitive/ total	Assessment
ART+3BNC117 (n=15)	109	-	-	33/33	Sensitive
	135	-	-	31/31	Sensitive
	210	0.62	98.0	-	Sensitive
	211	-	-	30/31	Sensitive
	302	0.66	99.8	-	Sensitive
	412	0.18	99.5	-	Sensitive
	701	0.92	99.7	-	Sensitive
	703	0.30	99.9	-	Sensitive
	106	2.48	99.1	-	Resistant
	125	1.63	97.2	-	Resistant
	126	2.10	97.8	-	Resistant
	205	3.41	97.0	-	Resistant
	401	4.15	98.2	-	Resistant
	404	1.88	99.0	-	Resistant
	704	>50	44.2	-	Resistant

3BNC/RMD group: 10/16 (63%) sensitive

		Monogram PhenoSense		*env* sequencing	
	Participant ID	IC90	MPI	Sensitive/ total	Assessment
ART+3BNC117+RMD (n=16)	103	0.96	99.2	-	Sensitive
	107	0.25	99.9	-	Sensitive
	116	0.34	99.9	-	Sensitive
	130	-	-	33/33	Sensitive
	203	1.22	99.6	-	Sensitive
	212	0.67	99.9	-	Sensitive
	303	0.20	99.6	-	Sensitive
	304	0.74	99.9	-	Sensitive
	408	0.15	99.5	-	Sensitive
	706	0.80	99.7	-	Sensitive
	112	>50	08.6	-	Resistant
	301	4.51	98.8	-	Resistant
	308	3.09	94.6	-	Resistant
	402	-	-	7/35	Resistant
	411	3.22	99.3	-	Resistant
	709	7.44	96.3	-	Resistant

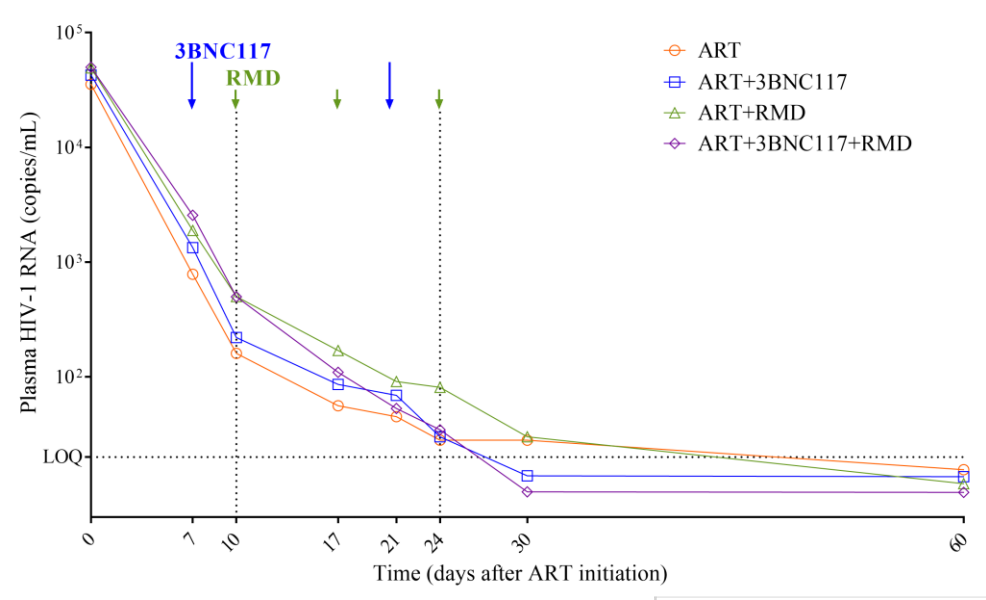
Monogram Phenosense 3BNC117 sensitivity. Sensitive defined IC90<1.5 ug/mL AND MPI≥98 as agreed on consensus meeting in Nov 2019 In case of ”Inconlusive” Phenosense result, SGA was performed to obtain ≥30 individual full length Env sequences. Follow sequincing, sensitivity was predicted using the Nussenzweig Lab machine learning algorithm,

Plasma HIV RNA kinetics



Gunst et al. Nature Med 2022

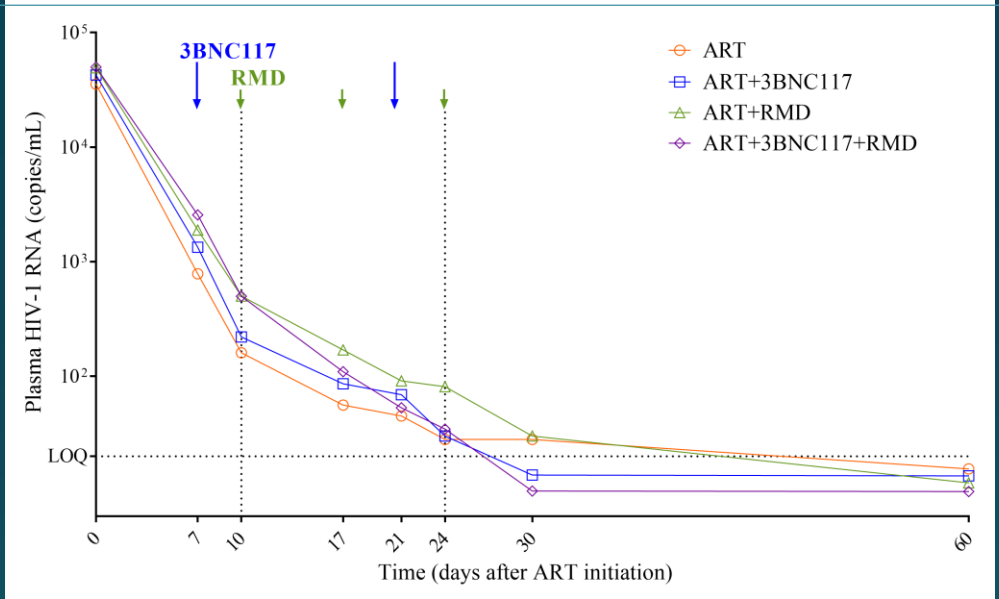
3 phase pVL decay mixed-effects model



3 phase pVL decay mixed-effects model

	Phase (days)	1 (0-10)	95%-CI	*P*	2 (10-24)	95%-CI	*P*	3 (24-90)	95%-CI	*P*
Overall	ART	-41.1	(-55.2;-22,7)	ref	-10.0	(-14.9;-4.86)	ref	-3.19	(-4.75;-1.61)	ref
	ART+3BNC117	-43.7	(-71.1;9.66)	0.823	-16.4	(-27.0;-4.29)	0.070	-3.09	(-6.54;0.49)	0.918
	ART+RMD	-36.2	(-67.5;25.2)	0.694	-18.5	(-29.0;-6.51)	0.017	-3.03	(-6.54;0.61)	0.875
	ART+3BNC117+RMD	-36.5	(-67.3;23.2)	0.706	-16.9	(-27.3;-4.93)	0.048	-2.70	(-6.19;0.92)	0.622

Pre-ART bNAb sensitivity impacts pVL



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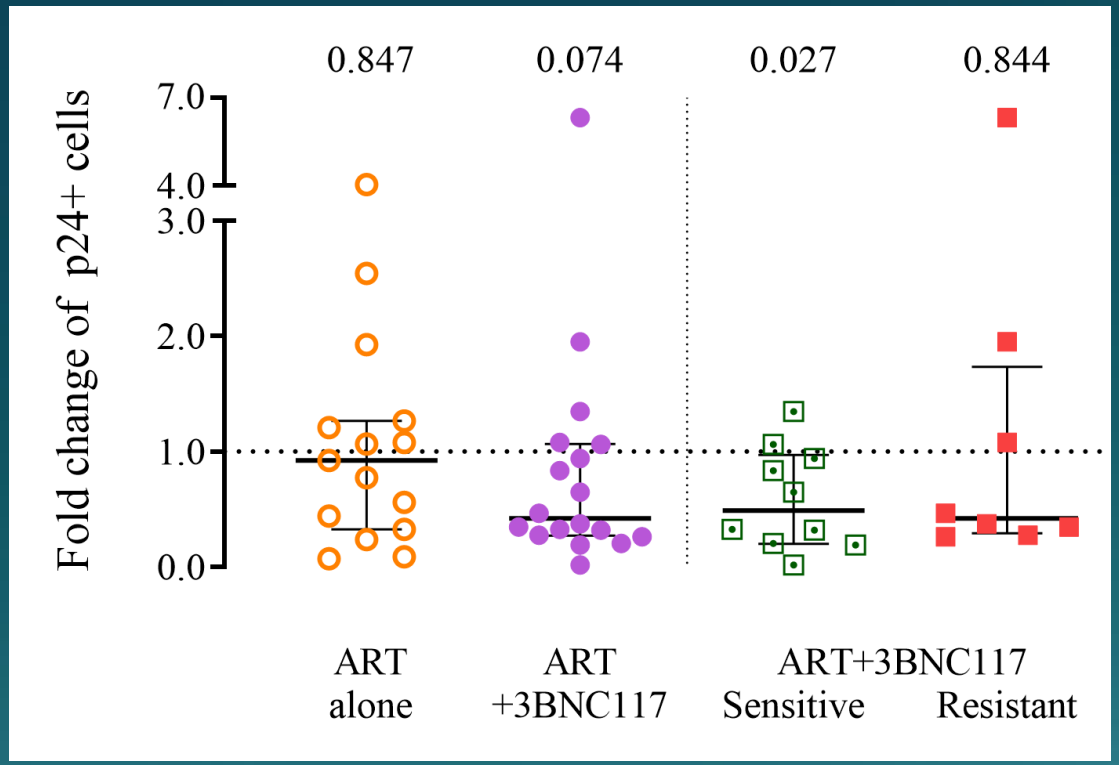
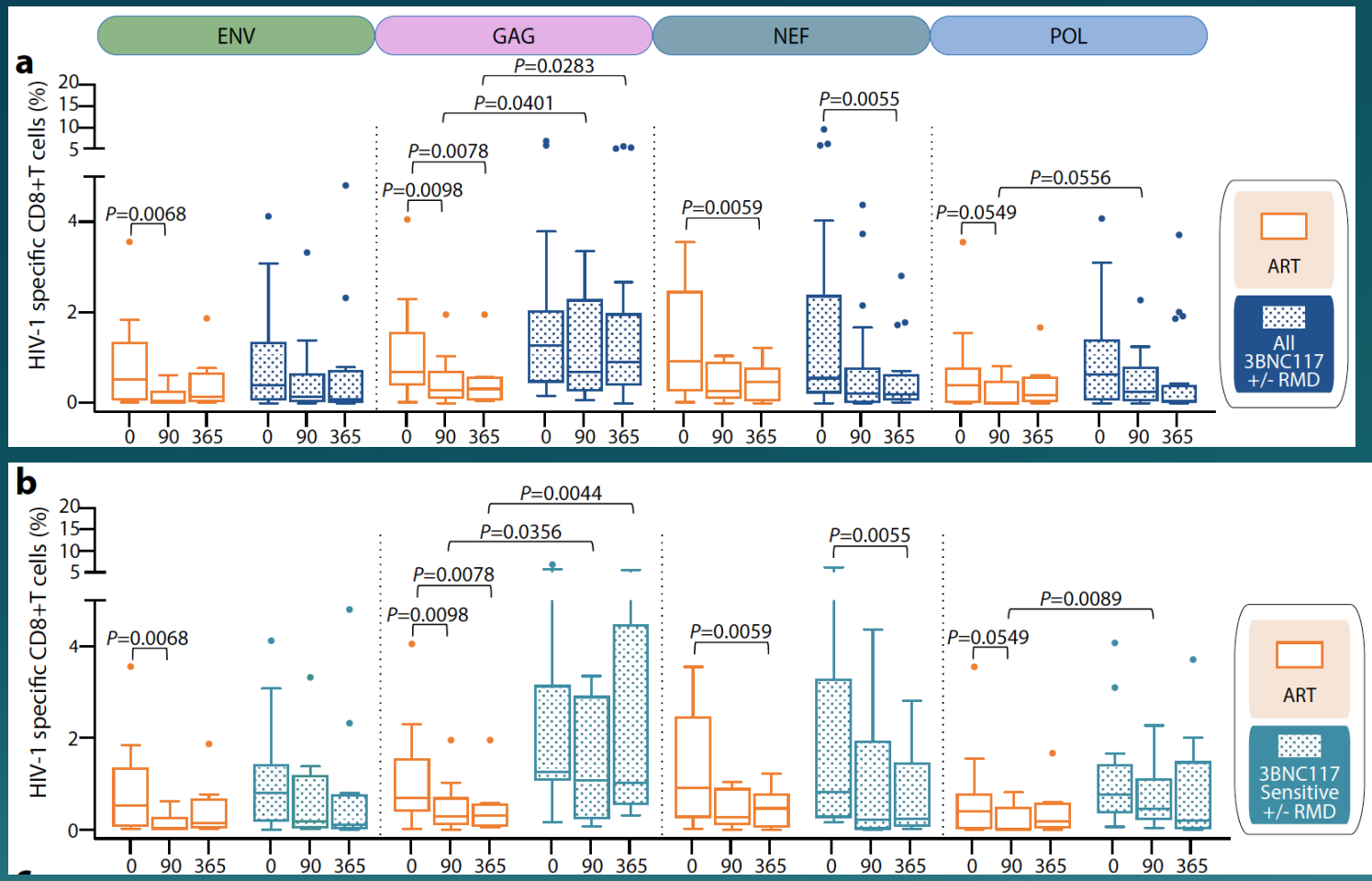
	ART+3BNC117+RMD	-36.5	(-67.3;23.2)	0.706	-16.9	(-27.3;-4.93)	0.048	-2.70	(-6.19;0.92)	0.622
Sensitive	ART+3BNC117	-38.9	(-62.1;-1.41)	0.714	-17.9	(-28.8;-5.16)	0.045	-4.02	(-7.80;-0.07)	0.488
	ART+3BNC117+RMD	-36.2	(-60.1;1.91)	0.556	-17.9	(-28.8;-5.28)	0.042	-2.81	(-6.64;1.17)	0.739
Resistant	ART+3BNC117	-48.8	(-69.0;-15.5)	0.629	-14.7	(-26.0;-1.58)	0.247	-2.02	(-5.87;1.98)	0.327
	ART+3BNC117+RMD	-37.0	(-61.7;3.39)	0.631	-15.1	(-26.2;-2.28)	0.198	-2.51	(-6.48;1.64)	0.568

Effect of 3BNC on HIV^{p24+} CD4 T cells

Fold change in HIV^{p24+} cells day 0 to day 10



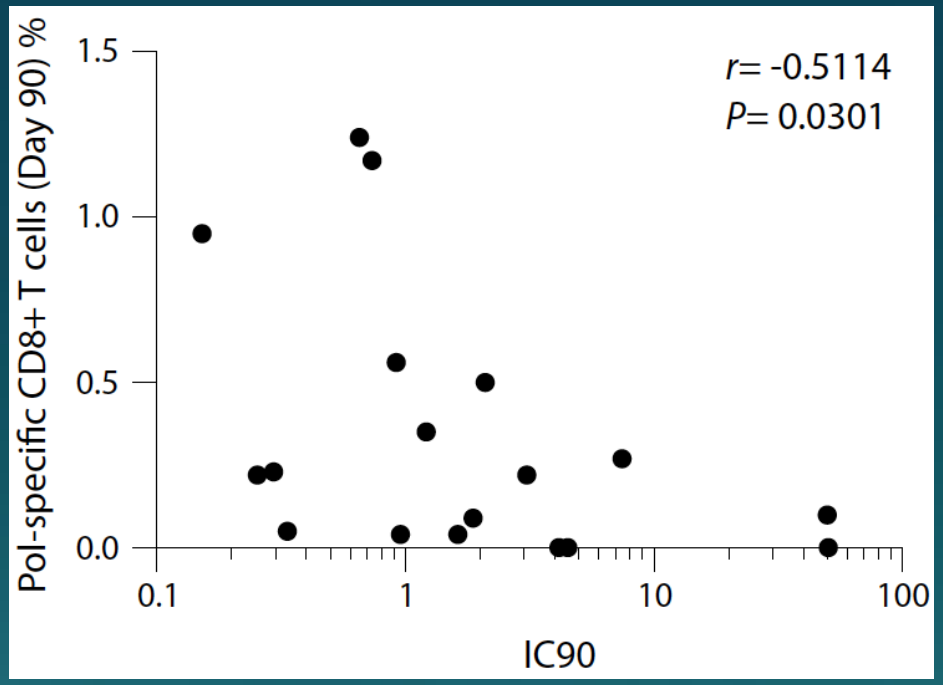
The frequency of Gag-specific CD8+ T cells was significantly higher in individuals receiving 3BNC117



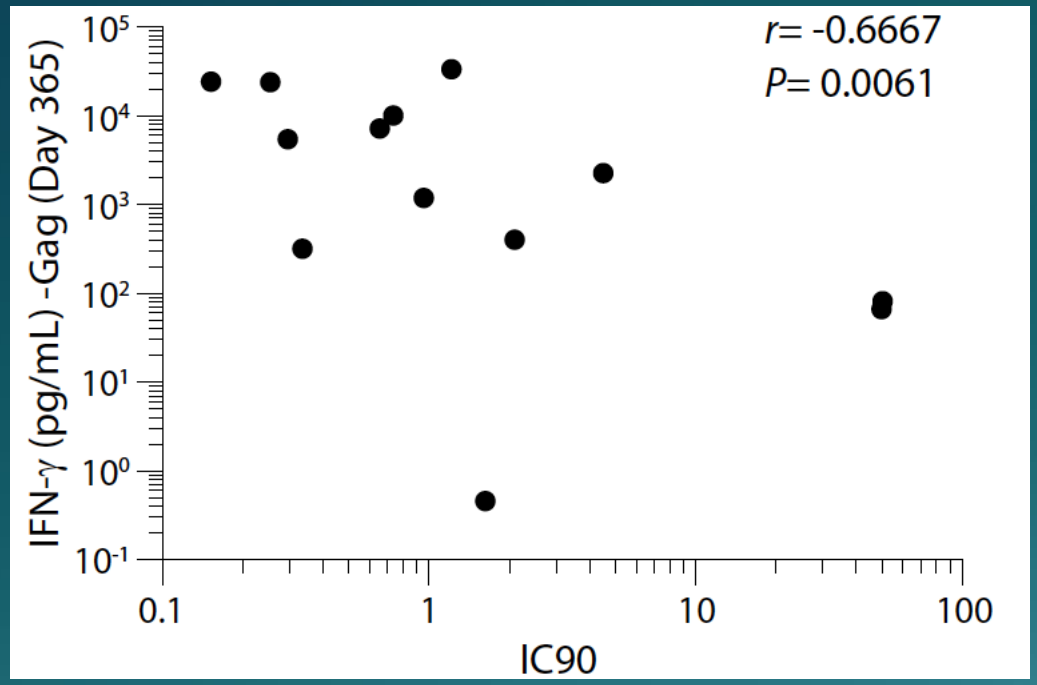
Rosas-Umbert et al., 2022 Nature Comm

HIV-specific CD8+ T cell responses at 3 and 12 months correlated with baseline 3BNC117 sensitivity

Pol-specific CD8 responses at 3 m

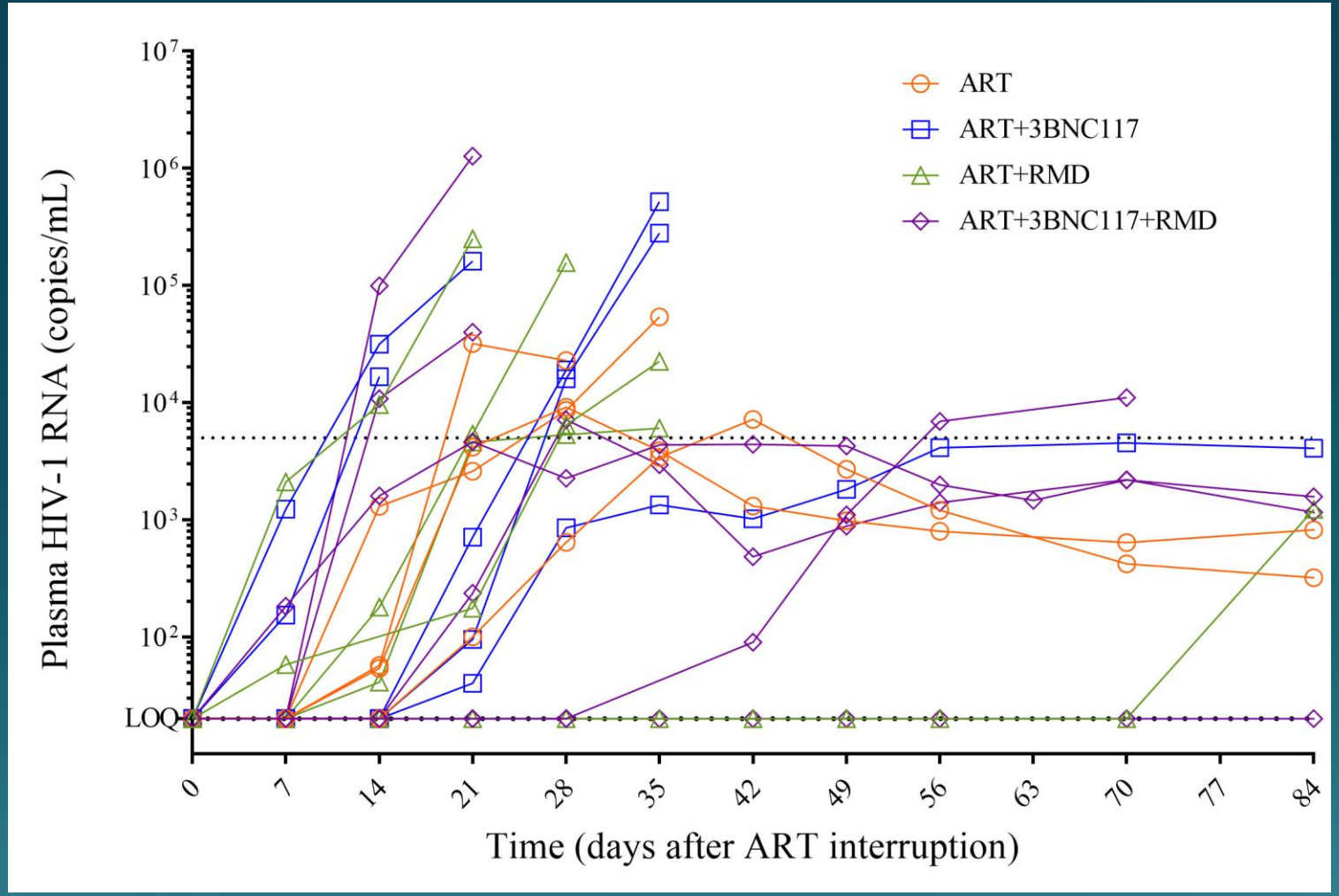


Gag-specific INF-g responses at 12 m



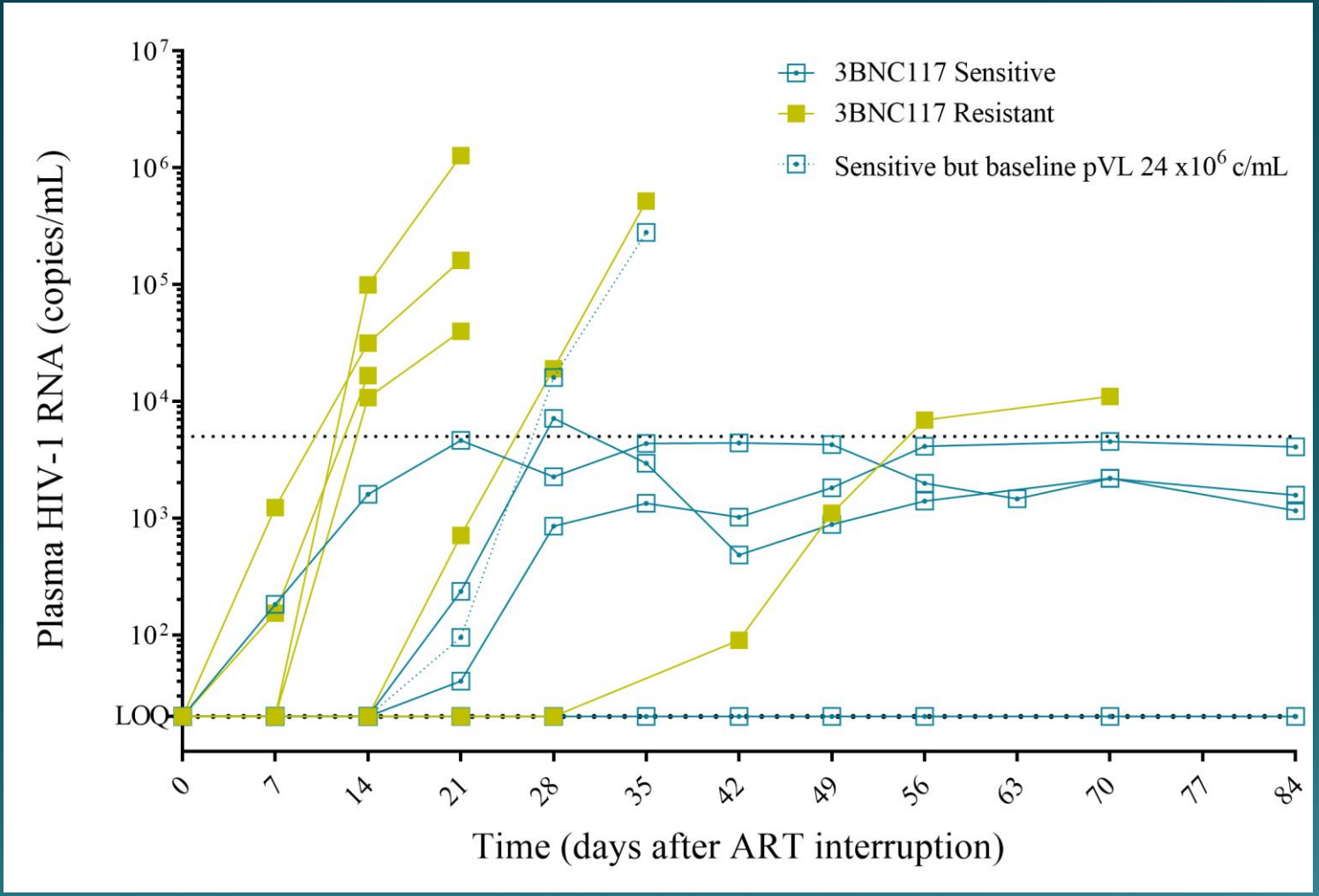
Rosas-Umbert et al., 2022 Nature Comm

Analytical treatment interruption (12 weeks)



- 20 participants consented to interrupt ART
- Start of ATI ≥400 days after starting ART
- Weekly pVL and CD4 count
- Viral rebound defined as two consecutively pVLs >5,000 c/mL

ATI: 3BNC-treated individuals only (+/-RMD)

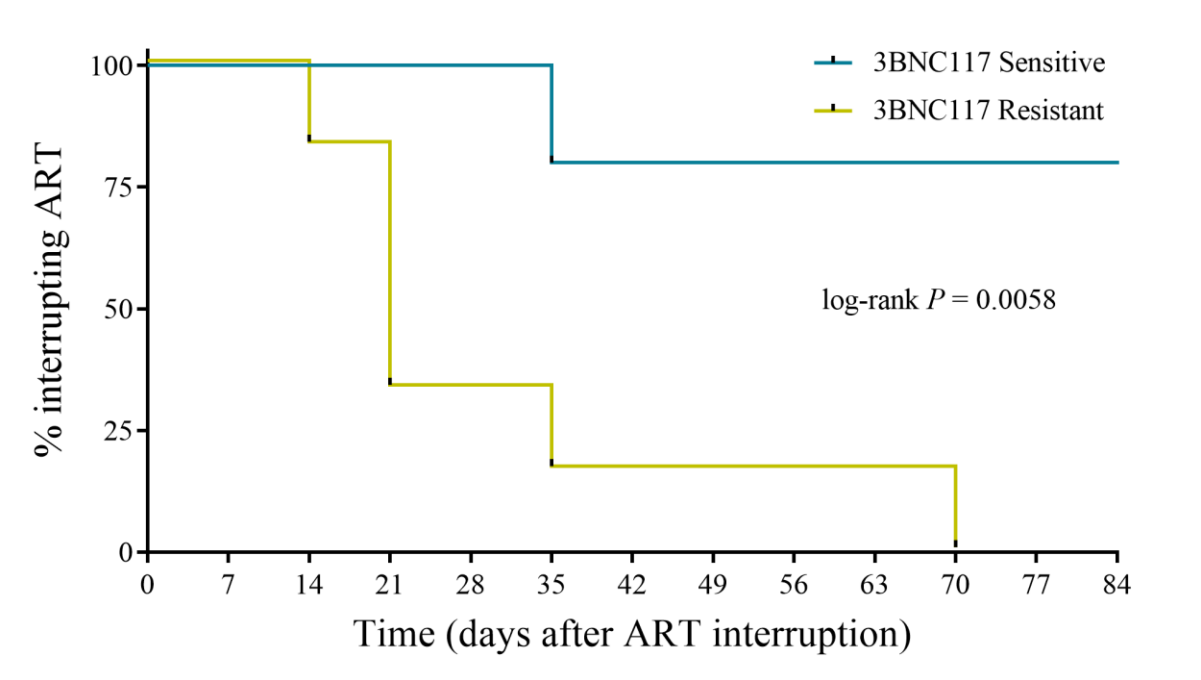


ID107 remains off treatment with undetectable pVL 5 years after stopping ART

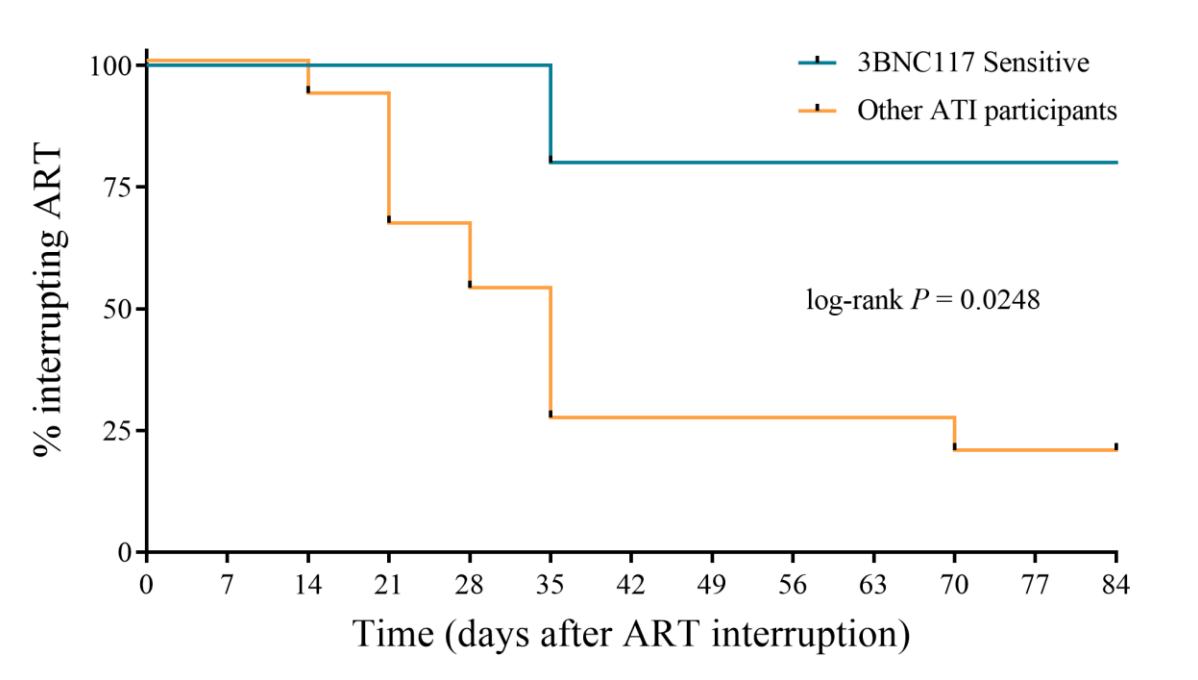
Gunst et al., 2022 Nature Medicine

ATI – 3BNC sensitive (+/-RMD) vs others

3BNC sensitive vs resistant

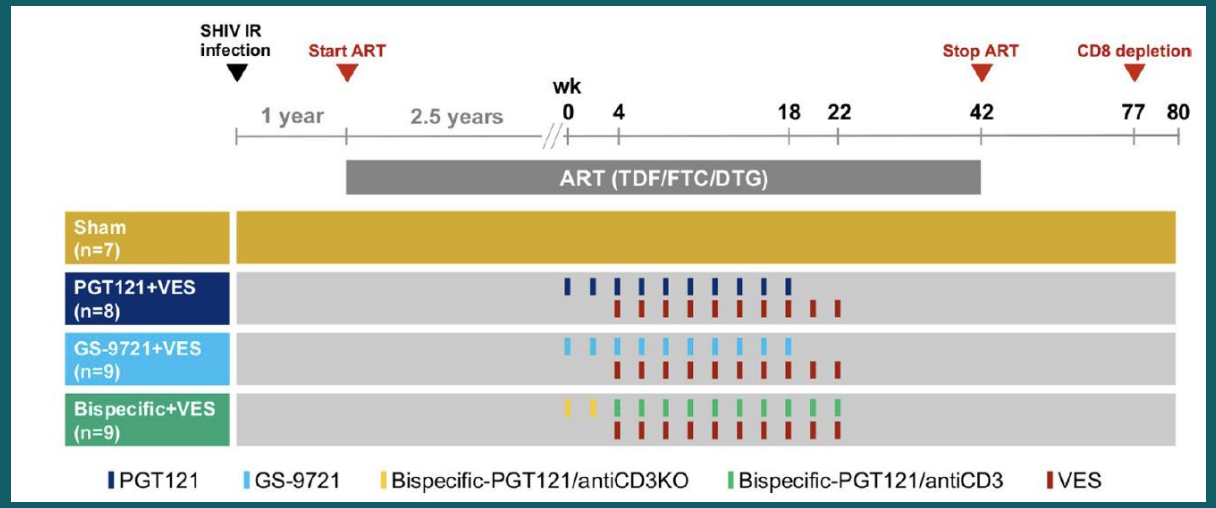


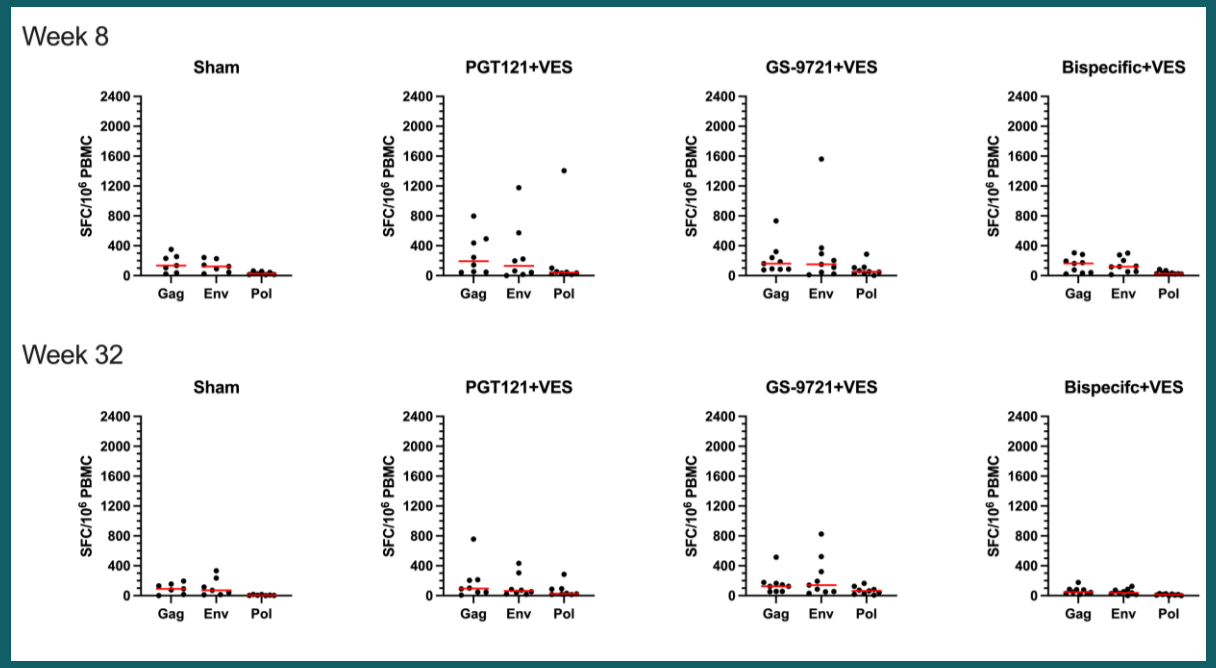
3BNC sensitive vs all other ATI participants

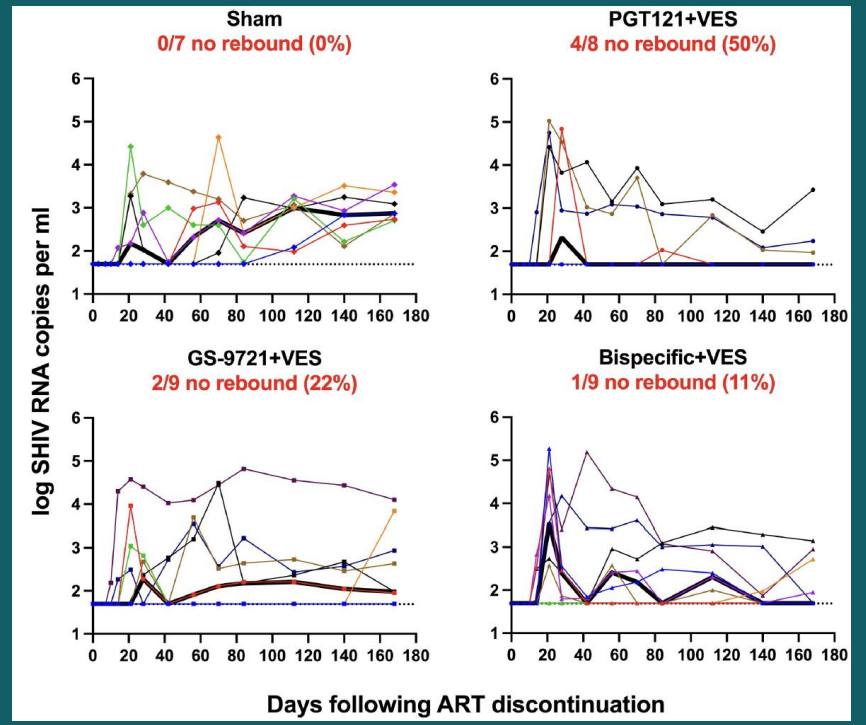


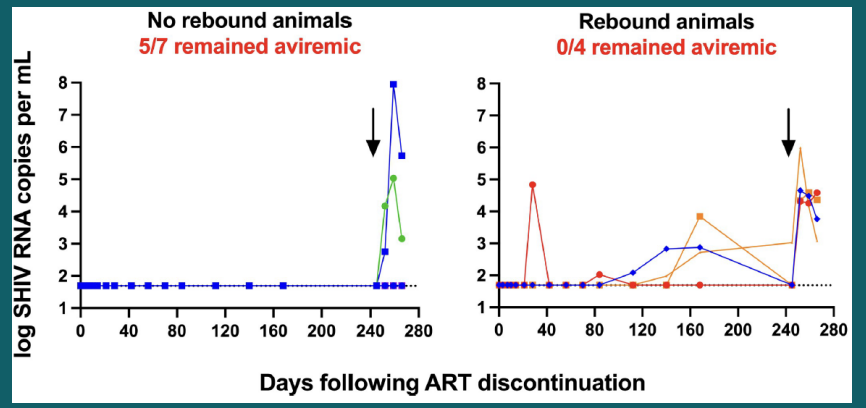
Studies of nAbs/bNAbs administration in a low antigen load setting

bNAbs in ART-suppressed NHPs with SHIV



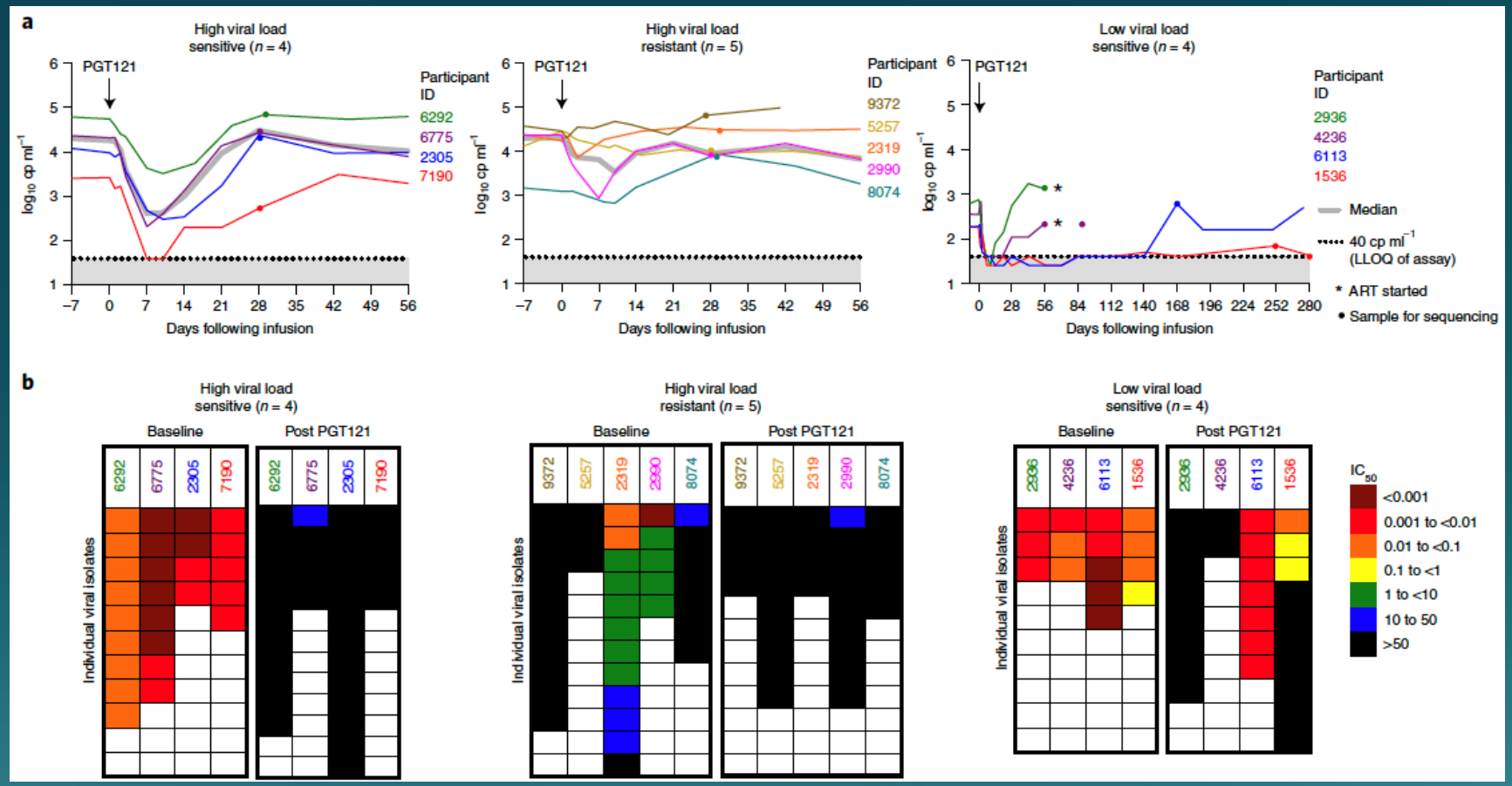




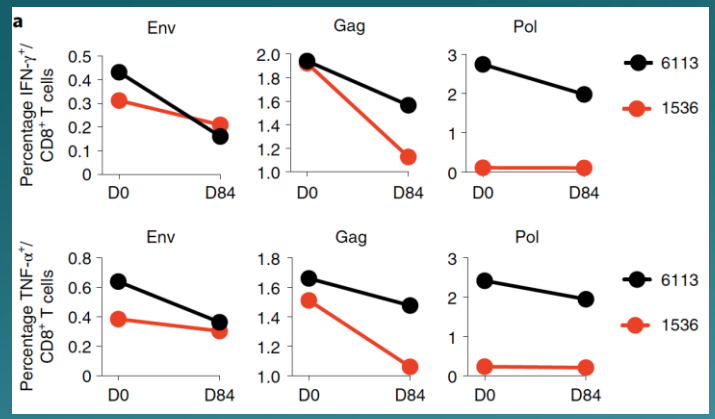


Moldt et al, Plos Path 2022

A phase 1 trial of PGT121 in viremic individuals



CD8 responses in 2 controllers at day 84



Stephenson et al, Nature Med 2021

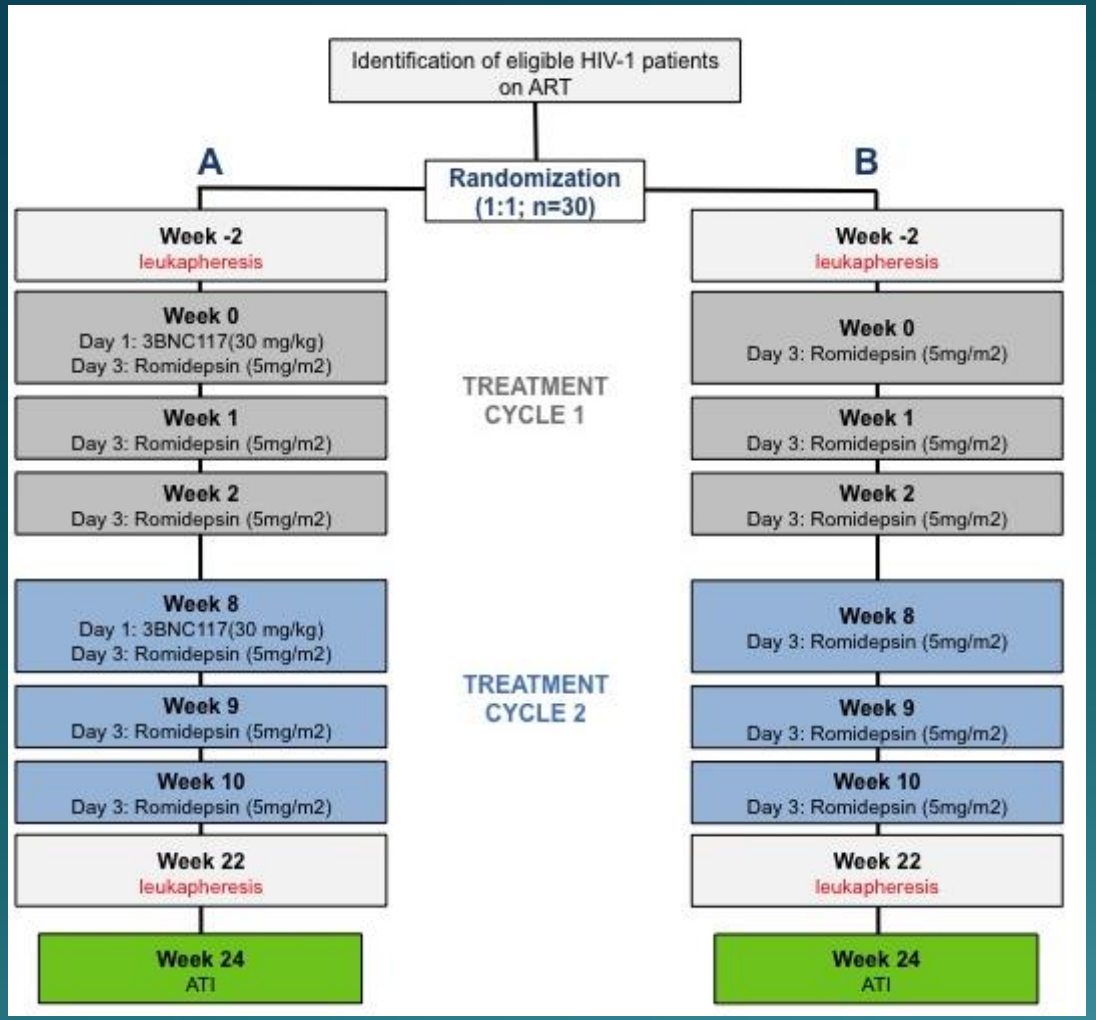
AARHUS UNIVERSITY

Effect of 3BNC117 and romidepsin on the HIV-1 reservoir in people taking suppressive antiretroviral therapy (ROADMAP): a randomised, open-label, phase 2A trial

Henning Gruell, Jesper D Gunst*, Yehuda Z Cohen*, Marie H Pahus, Jakob J Malin, Martin Platten, Katrina G Millard, Martin Tolstrup, R Brad Jones, Winnifer D Conce Alberto, Julio C C Lorenzi, Thiago Y Oliveira, Tim Kümmerle, Isabelle Suárez, Cecilia Unson-O'Brien, Lilian Nogueira, Rikke Olesen, Lars Østergaard, Henrik Nielsen, Clara Lehmann, Michel C Nussenzweig, Gerd Fätkenheuer, Florian Klein, Marina Caskey, Ole S Søgaard*

ROADMAP study (Romidepsin +/- 3BNC117)

- Collaboration between The Rockefeller University, Aarhus and Cologne University hospitals
- Study population (n=22): (Chronically infected) persons on stable long-cART
- Primary endpoint: Time to rebound

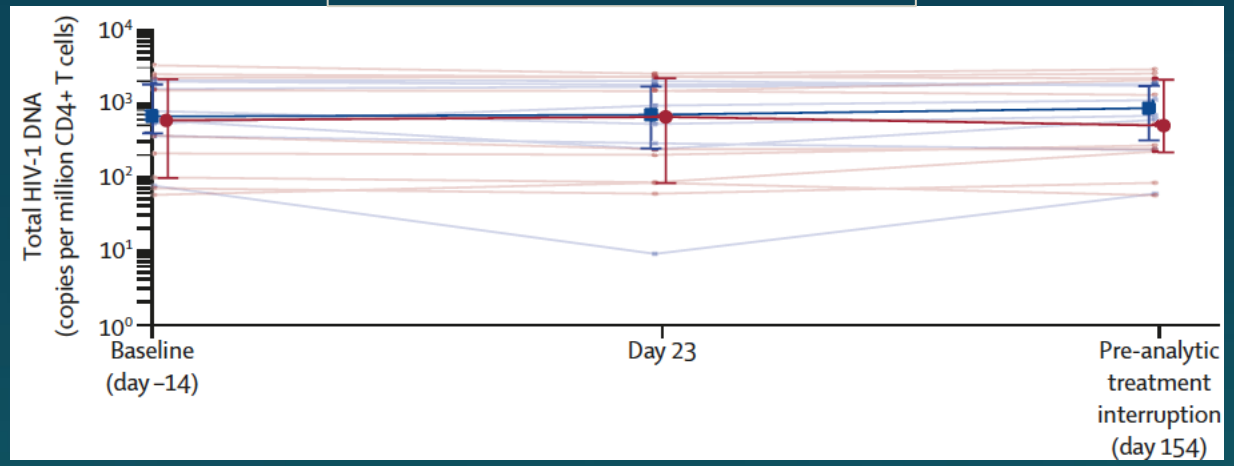


amfAR MAKING AIDS HISTORY

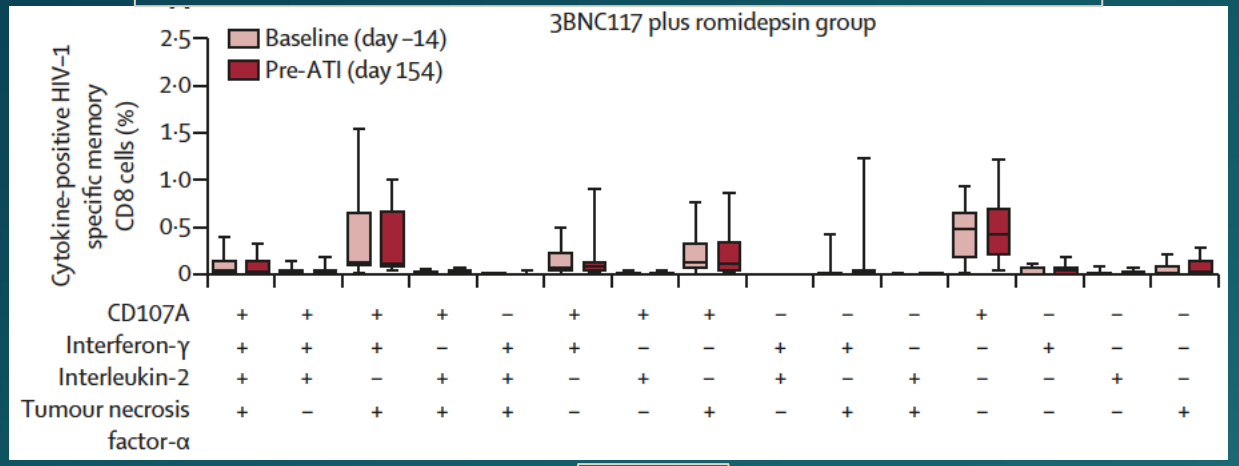
Gruell et al., 2022 Lancet Microbe

Reservoir size, CTLs and viral rebound

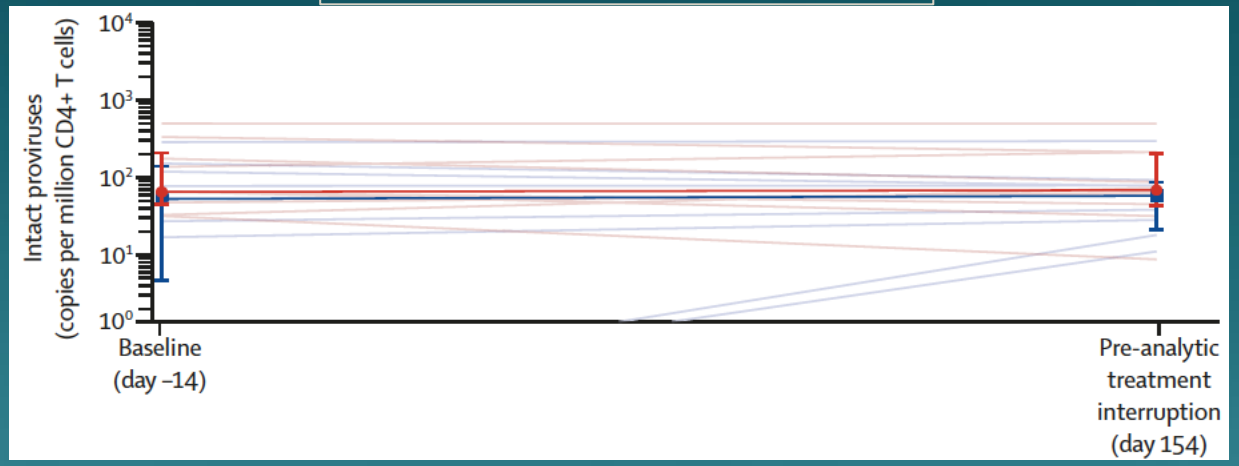
Total HIV-1 DNA



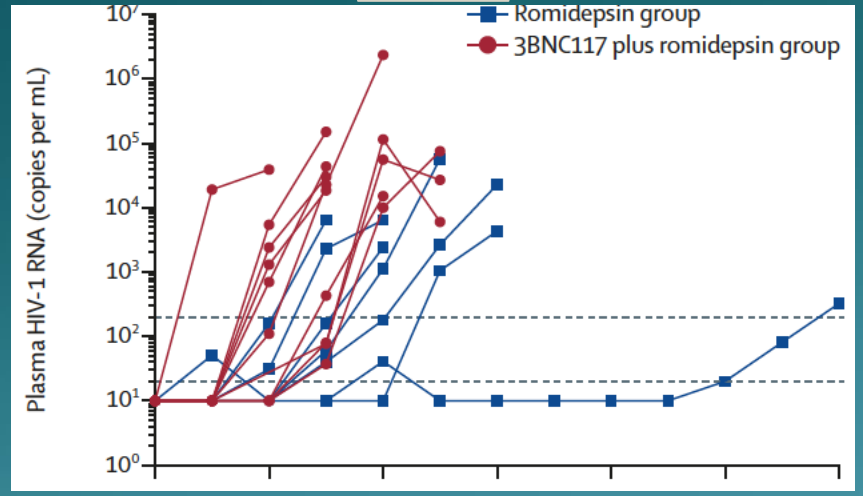
HIV-specific CTL responses



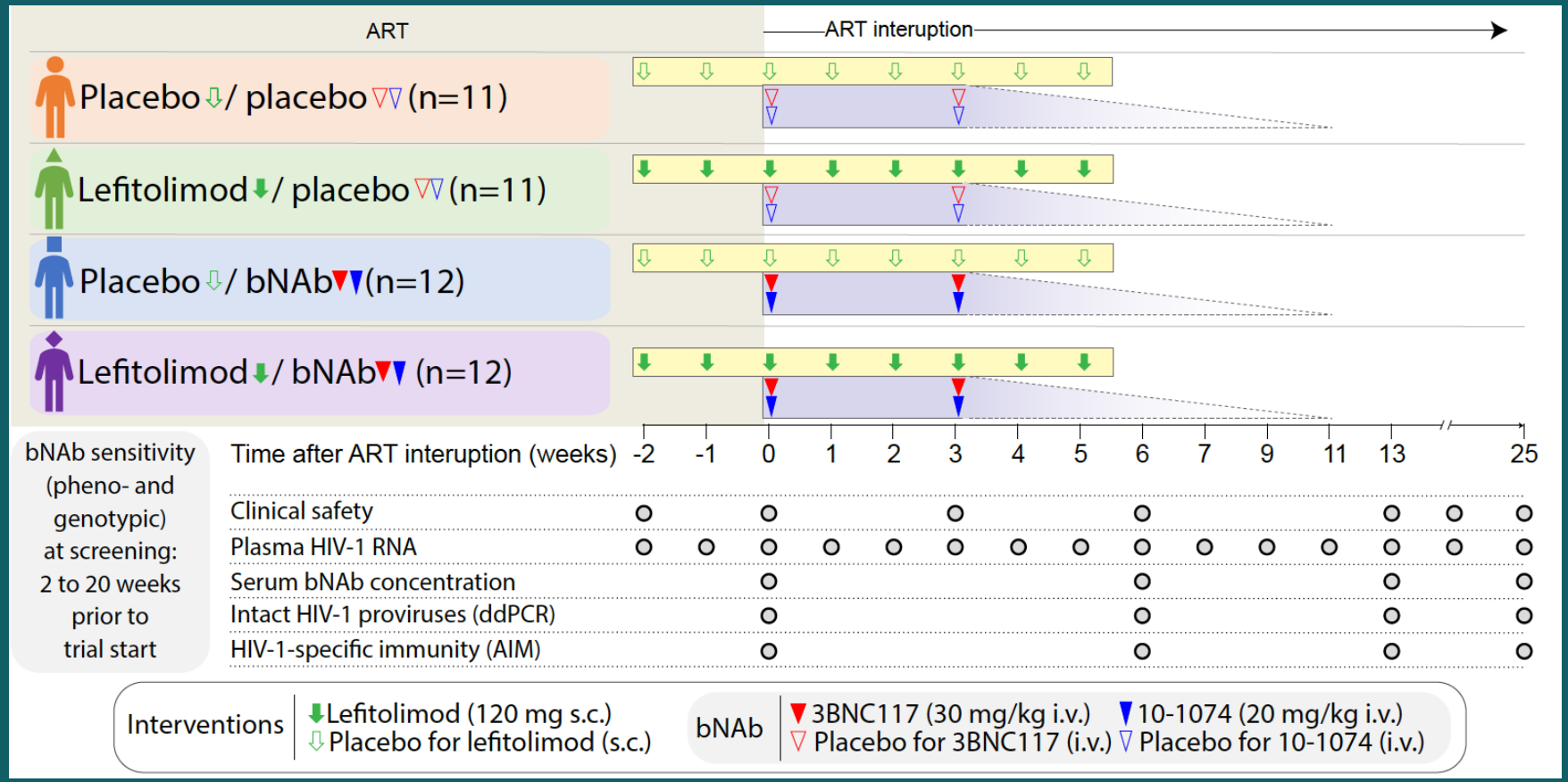
Intact HIV-1 DNA



ATI



Study design: Randomized, double-blinded, placebo-controlled trial



- Primary endpoint: Time to viral rebound (>1,000 c/mL for 4 weeks or x2 >100,000 c/mL)

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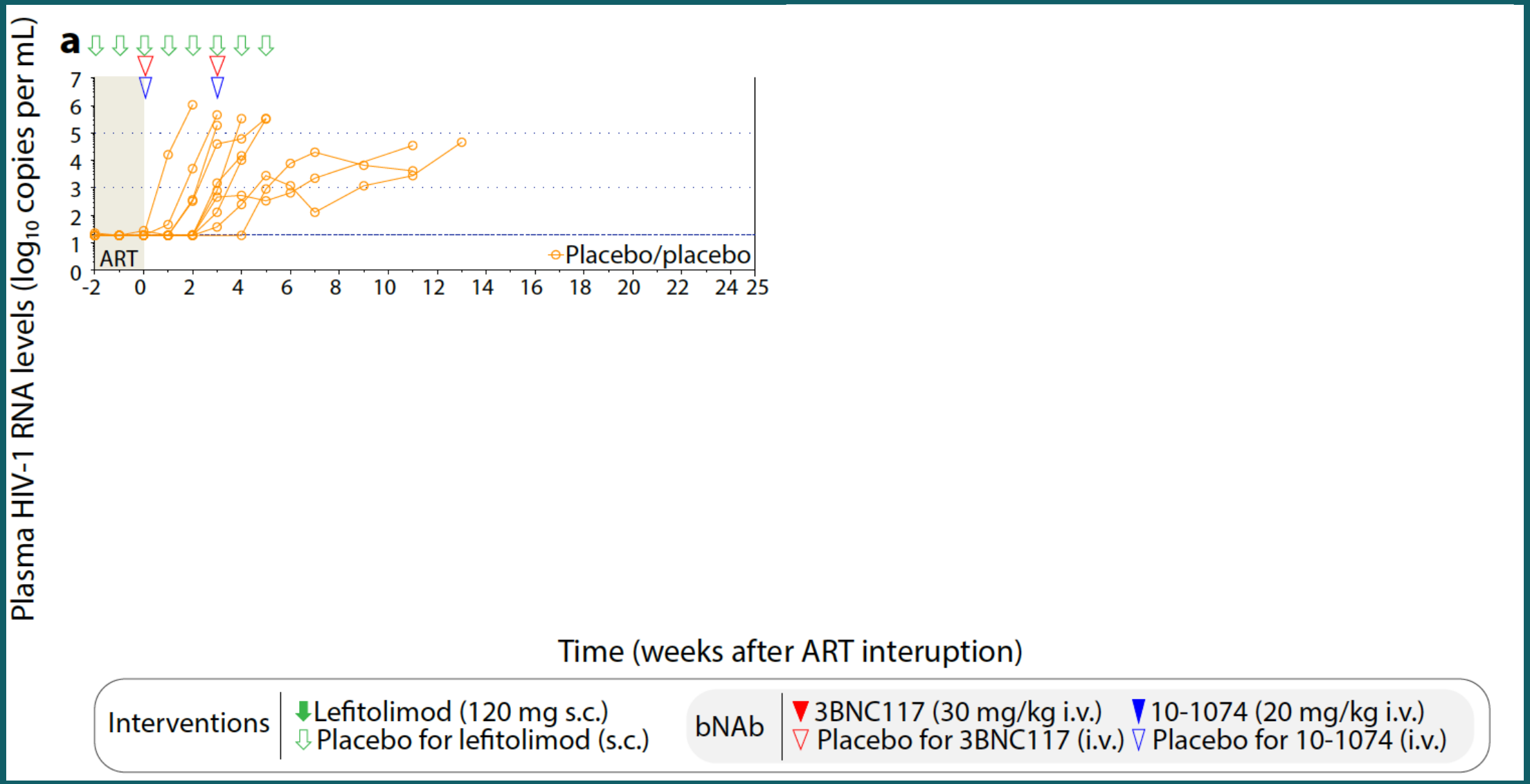
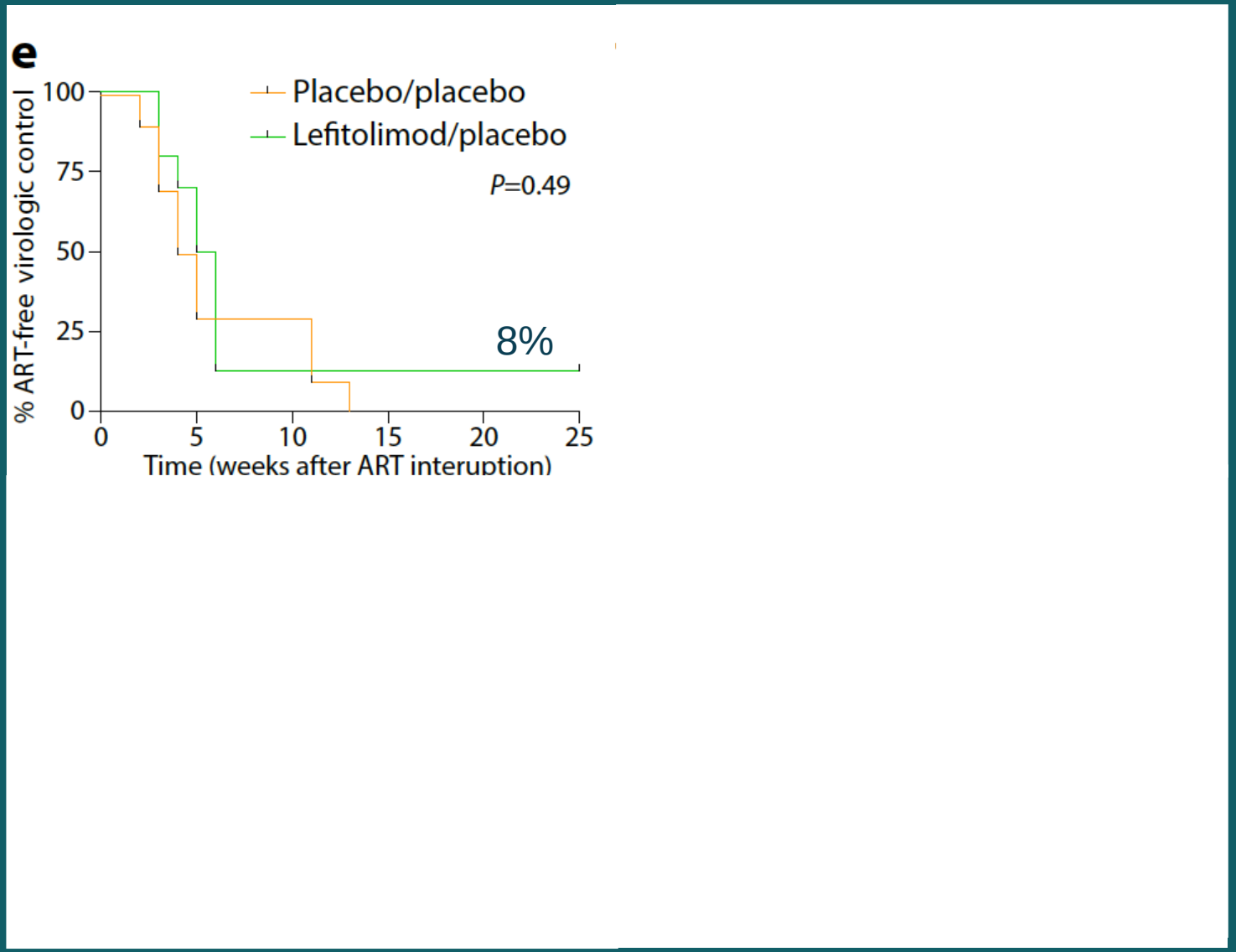
Gunst et al., 2023 Nature Medicine

Time to viral rebound



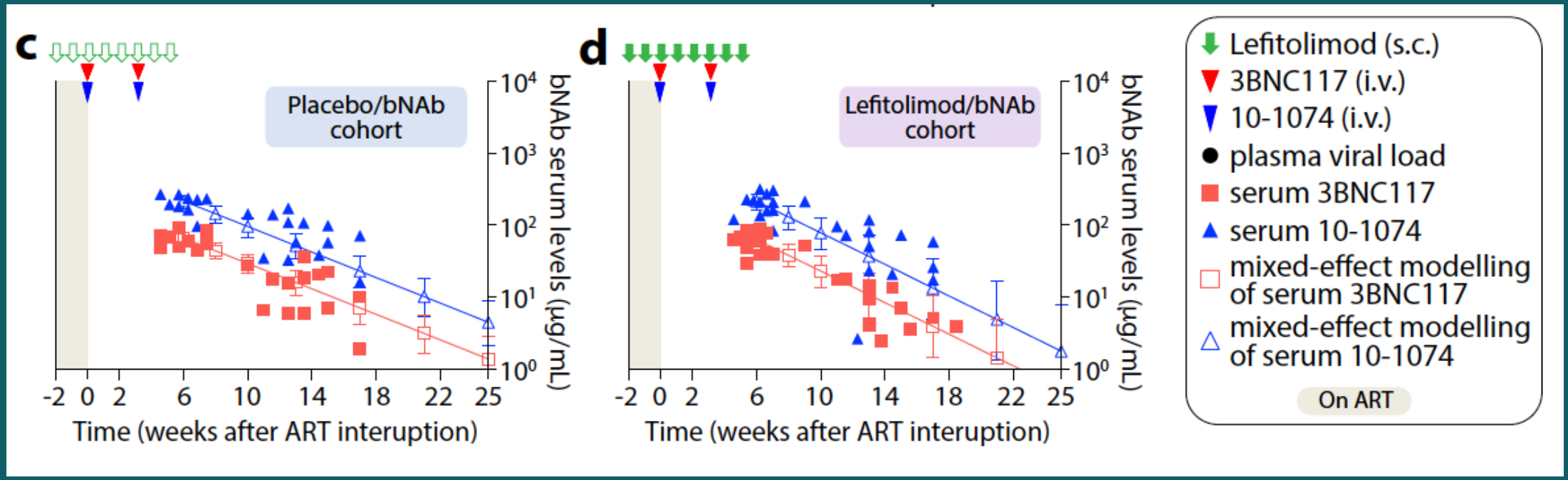
Gunst et al., 2023 Nature Medicine

Time to viral rebound



Gunst et al., 2023 Nature Medicine

Impact of TLR9a on bNAb concentrations



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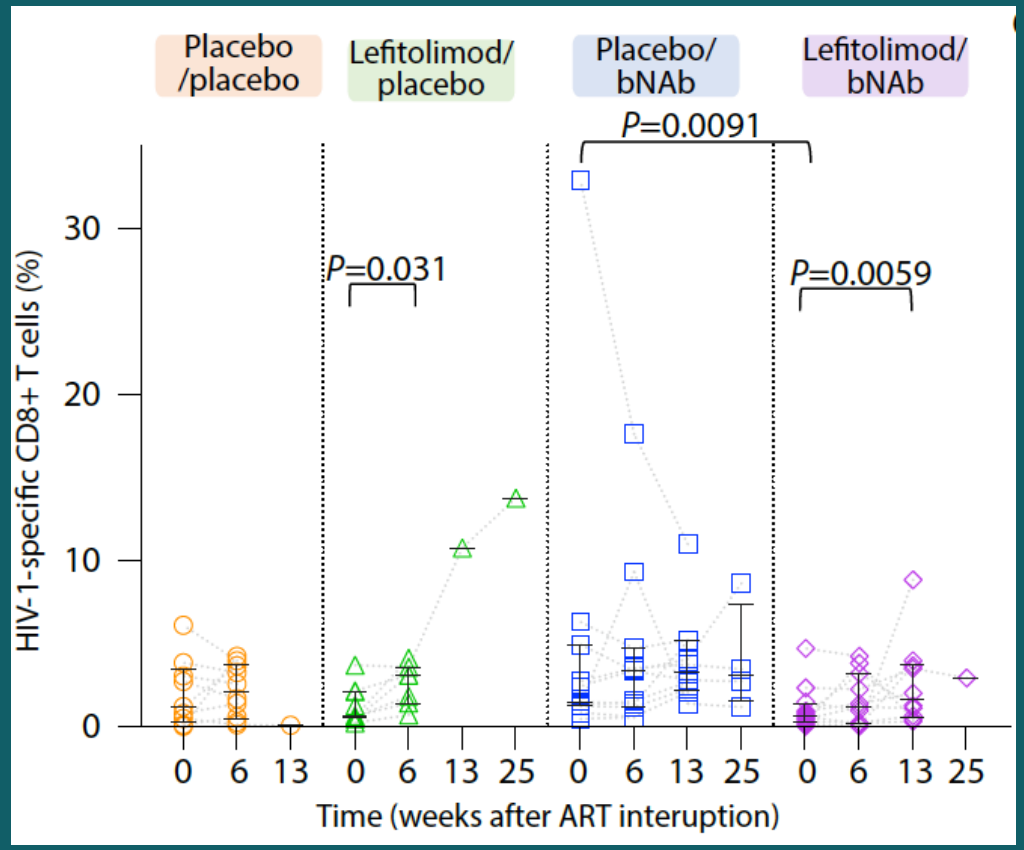
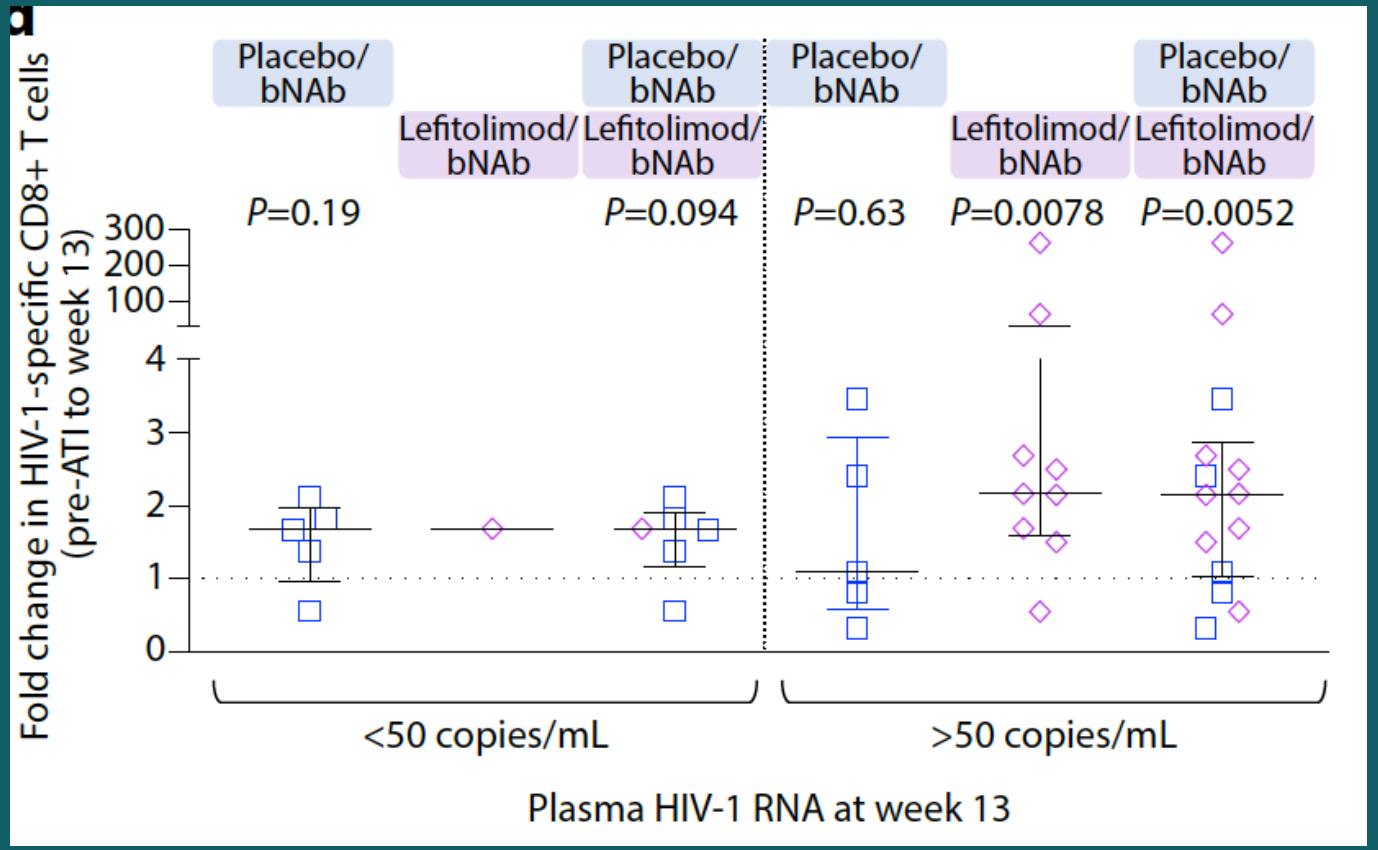
Gunst et al., 2023 Nature Medicine

HIV specific T cell immunity - AIM





Gunst et al., 2023 Nature Medicine

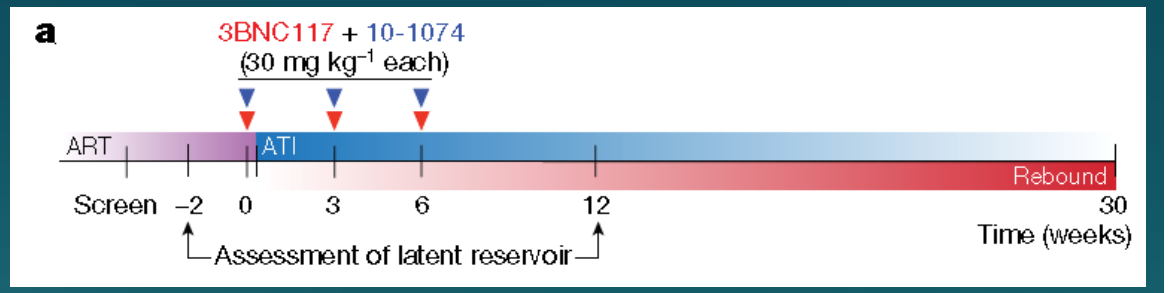
Combining two bNAbs

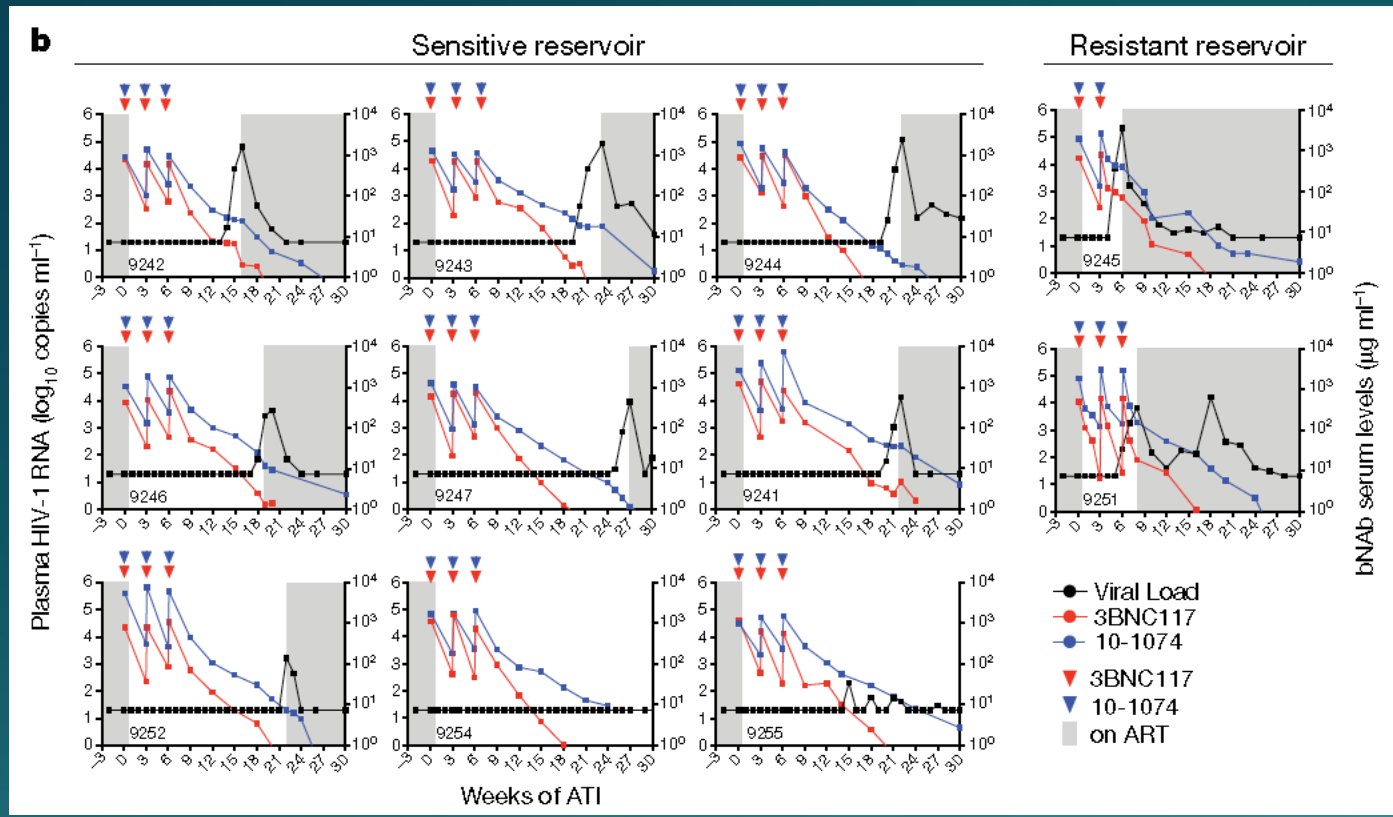
ARTICLE

https://doi.org/10.1038/s41586-018-0531-2

Combination therapy with anti-HIV-1 antibodies maintains viral suppression

Pilar Mendoza[1,19], Henning Gruell[2,3,4,19], Lilian Nogueira[1], Joy A. Pai[1], Allison L. Butler[1], Katrina Millard[1], Clara Lehmann[3,4,5], Isabelle Suárez[3,4,5], Thiago Y. Oliveira[1], Julio C. C. Lorenzi[1], Yehuda Z. Cohen[1], Christoph Wyen[3,6], Tim Kümmerle[3,6], Theodora Karagounis[1], Ching-Lan Lu[1], Lisa Handl[7], Cecilia Unson-O'Brien[1], Roshni Patel[1], Carola Ruping[2], Maike Schlotz[2], Maggi Witmer-Pack[1], Irina Shimeliovich[1], Gisela Kremer[3], Eleonore Thomas[3], Kelly E. Seaton[8], Jill Horowitz[1], Anthony P. West Jr[9], Pamela J. Bjorkman[9], Georgia D. Tomaras[8,10,11,12], Roy M. Gulick[13], Nico Pfeifer[7,14,15,16], Gerd Fätkenheuer[3,4], Michael S. Seaman[17], Florian Klein[2,4,5,20]*, Marina Caskey[1,20]* & Michel C. Nussenzweig[1,18,20]*



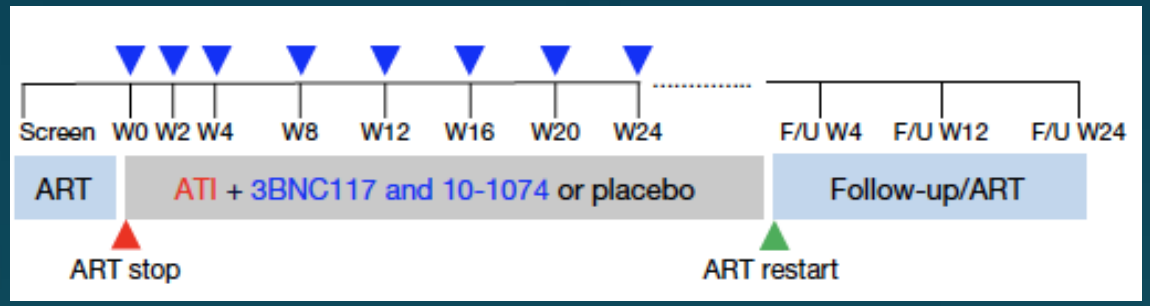


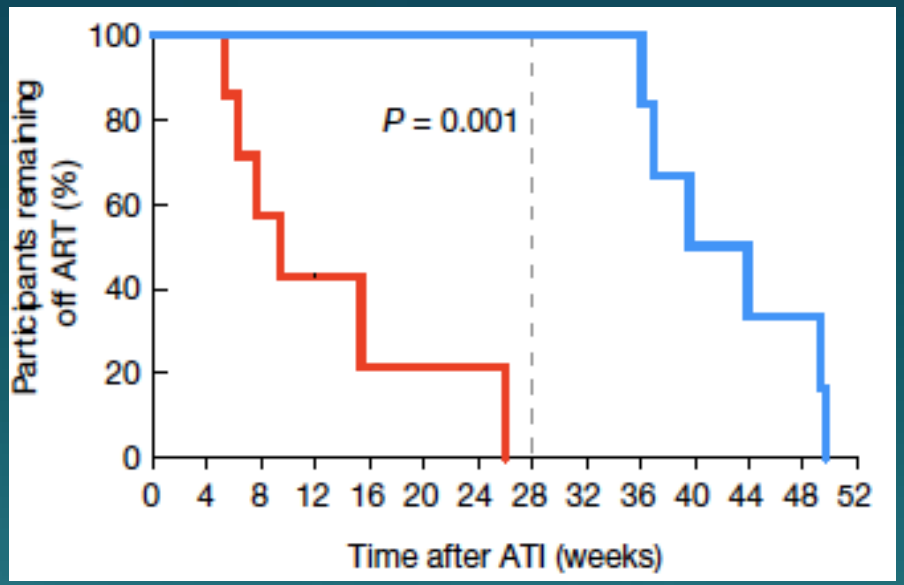
Median time to viral rebound: 21 Weeks (i.e. 15 weeks from last bNAb infusion)

Mendoza et al. Nature 2018

Article

Combination anti-HIV antibodies provide sustained virological suppression

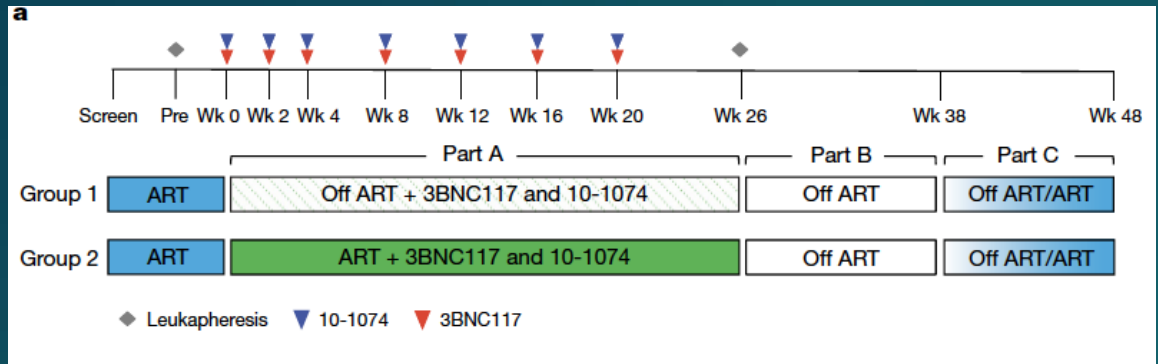


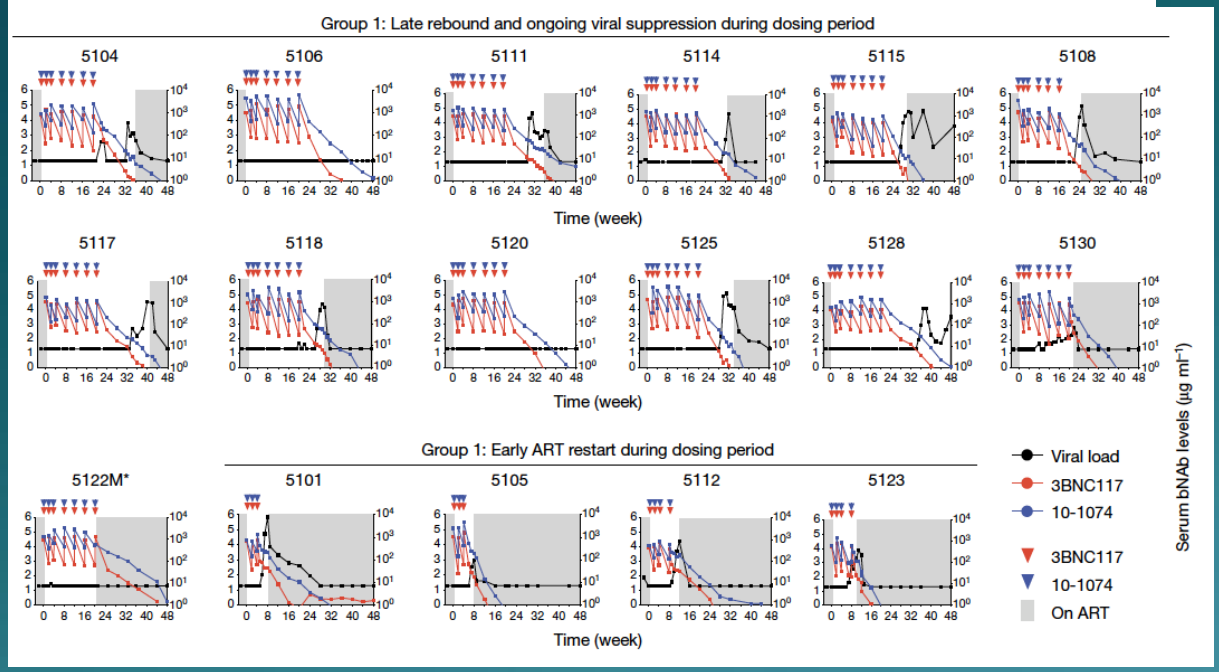


Sneller et al. Nature 2022

Article

Prolonged viral suppression with anti-HIV-1 antibody therapy





Gaebler et al. Nature 2022

Conclusions

- Some evidence of a HIV-1 bNAb-induced vaccinal effect

- HIGH antigen load setting:
  - Studies generally show FcγR-mediated boosting of adaptive immune responses
  - But magnitude of effect varies between individuals

- LOW antigen load setting:
  - Studies generally show limited or no FcγR-mediated boosting of adaptive immune responses
  - But some individuals might have some beneficial effects