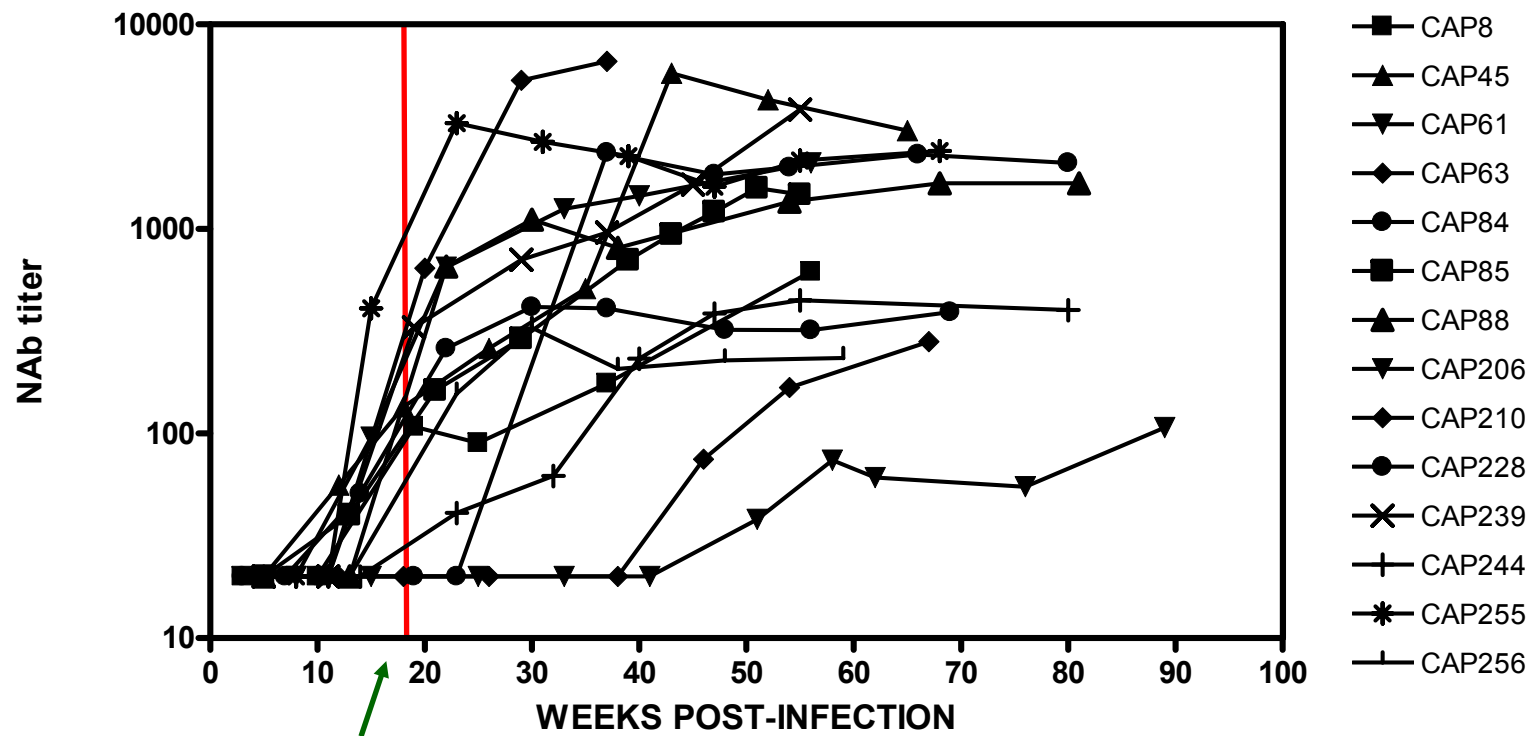


Specificities of Antibodies Mediating Autologous Neutralization of Early HIV-1 subtype C viruses

Penny Moore, Elin Gray, Isaac Choge,
Nthabeleng Ranchobe, Koleka Mlisana, Salim
Abdool Karim, Carolyn Williamson and Lynn Morris
and the CAPRISA 002 Study Team



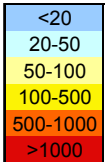
Autologous Neutralizing Antibody Responses in First Year of HIV-1 Subtype C Infection



Median initial autologous response is 19 weeks post-infection

The early neutralizing Ab response at 1 year is highly type-specific

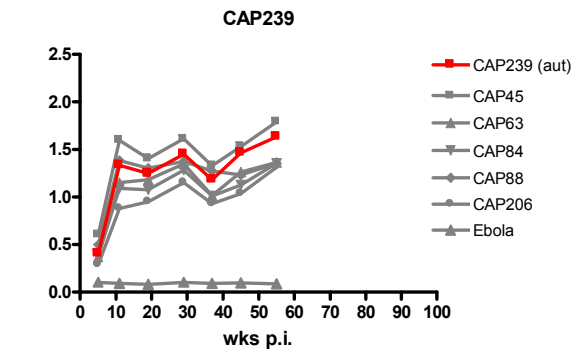
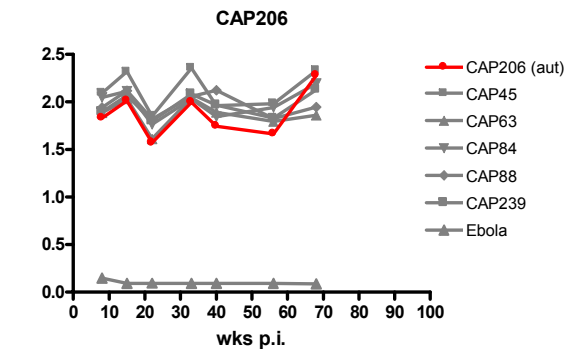
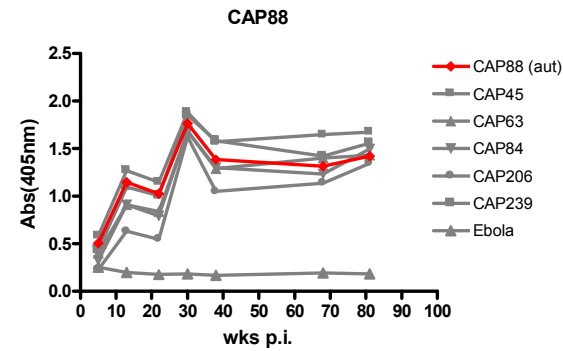
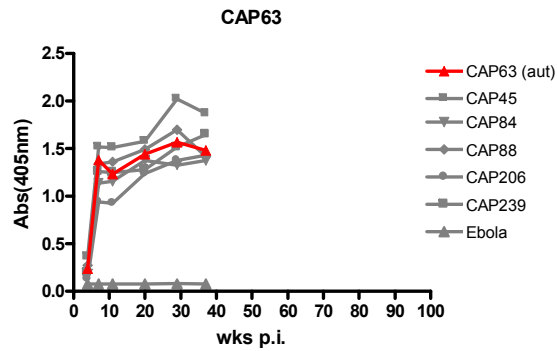
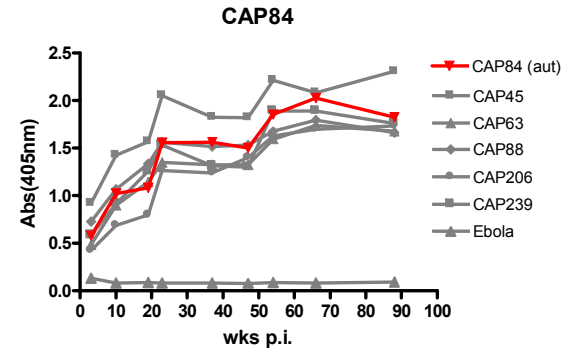
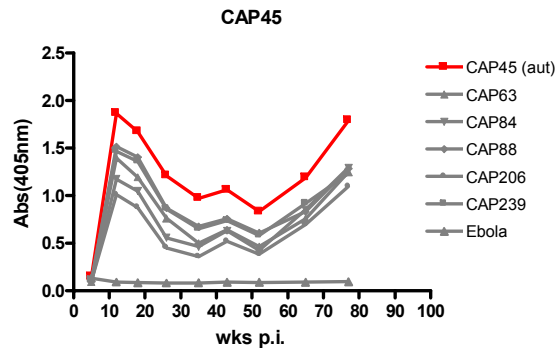
6 th months serum	Enrolment virus													
	CAP 8	CAP 45	CAP 61	CAP 63	CAP 84	CAP 85	CAP 88	CAP 206	CAP 210	CAP 228	CAP 239	CAP 244	CAP 255	CAP 256
CAP 8	155	<20	34	<20	<20	136	<20	37	<20	<20	<20	29	<20	<20
CAP 45	<20	327	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20
CAP 61	<20	<20	<20	<20	27	66	<20	<20	<20	<20	<20	<20	<20	<20
CAP 63	<20	<20	<20	2572	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20
CAP 84	22	<20	<20	<20	2443	21	<20	<20	<20	<20	<20	<20	<20	<20
CAP 85	<20	<20	<20	<20	<20	273	<20	<20	<20	<20	<20	<20	<20	<20
CAP 88	27	<20	<20	<20	<20	<20	257	<20	<20	<20	<20	<20	<20	<20
CAP 206	<20	<20	<20	<20	<20	82	<20	1577	<20	<20	<20	<20	<20	<20
CAP 210	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20
CAP 228	<20	<20	29	<20	27	36	<20	<20	<20	576	<20	<20	<20	<20
CAP 239	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	731	<20	<20	<20
CAP 244	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	103	<20	<20
CAP 255	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	2668	<20
CAP 256	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	272



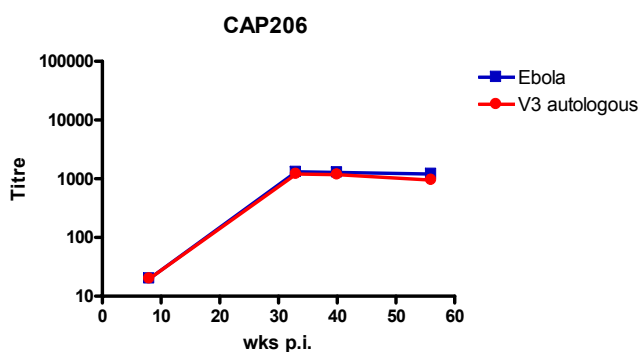
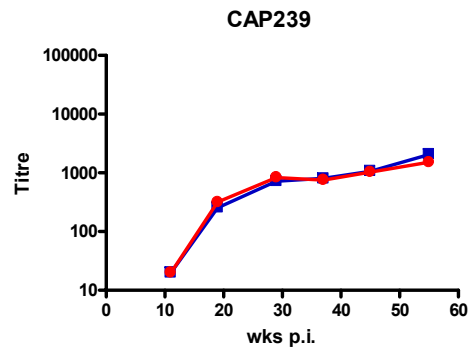
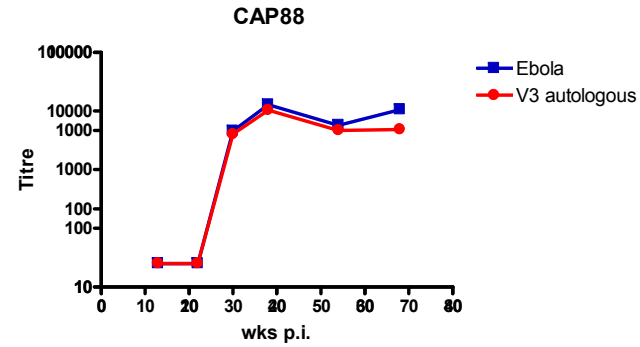
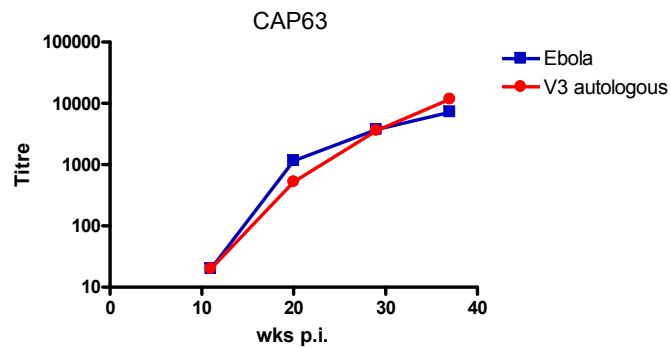
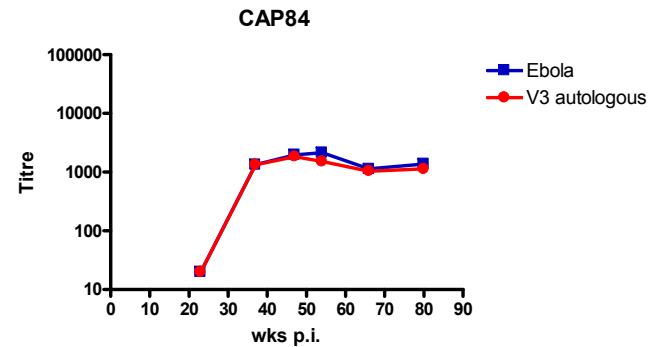
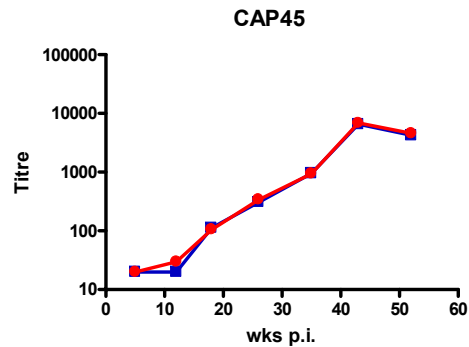
12 th months serum	Enrolment virus													
	CAP 8	CAP 45	CAP 61	CAP 63	CAP 84	CAP 85	CAP 88	CAP 206	CAP 210	CAP 228	CAP 239	CAP 244	CAP 255	CAP 256
CAP 8	733	<20	40	<20	29	248	<20	37	<20	<20	<20	29	23	<20
CAP 45	<20	6199	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20
CAP 61	<20	<20	54	<20	145	84	<20	<20	<20	<20	32	<20	<20	<20
CAP 63	<20	<20	<20	5490	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20
CAP 84	<20	<20	<20	<20	2585	21	<20	<20	<20	<20	<20	<20	<20	<20
CAP 85	29	<20	<20	113	<20	1697	<20	<20	<20	<20	<20	<20	<20	<20
CAP 88	<20	<20	<20	<20	<20	33	1097	<20	<20	<20	<20	<20	<20	<20
CAP 206	<20	<20	<20	<20	<20	236	<20	2425	<20	<20	<20	<20	<20	<20
CAP 210	<20	<20	<20	<20	<20	<20	<20	<20	138	<20	<20	<20	<20	<20
CAP 228	<20	36	<20	<20	27	41	<20	51	<20	405	<20	<20	<20	<20
CAP 239	<20	<20	37	<20	28	<20	<20	<20	<20	<20	3841	<20	<20	<20
CAP 244	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20	416	<20	<20
CAP 255	<20	<20	96	<20	<20	78	<20	<20	<20	<20	67	<20	2163	<20
CAP 256	<20	195	27	<20	<20	<20	<20	<20	<20	<20	85	<20	<20	188

Do anti-V3 antibodies mediate autologous neutralization?

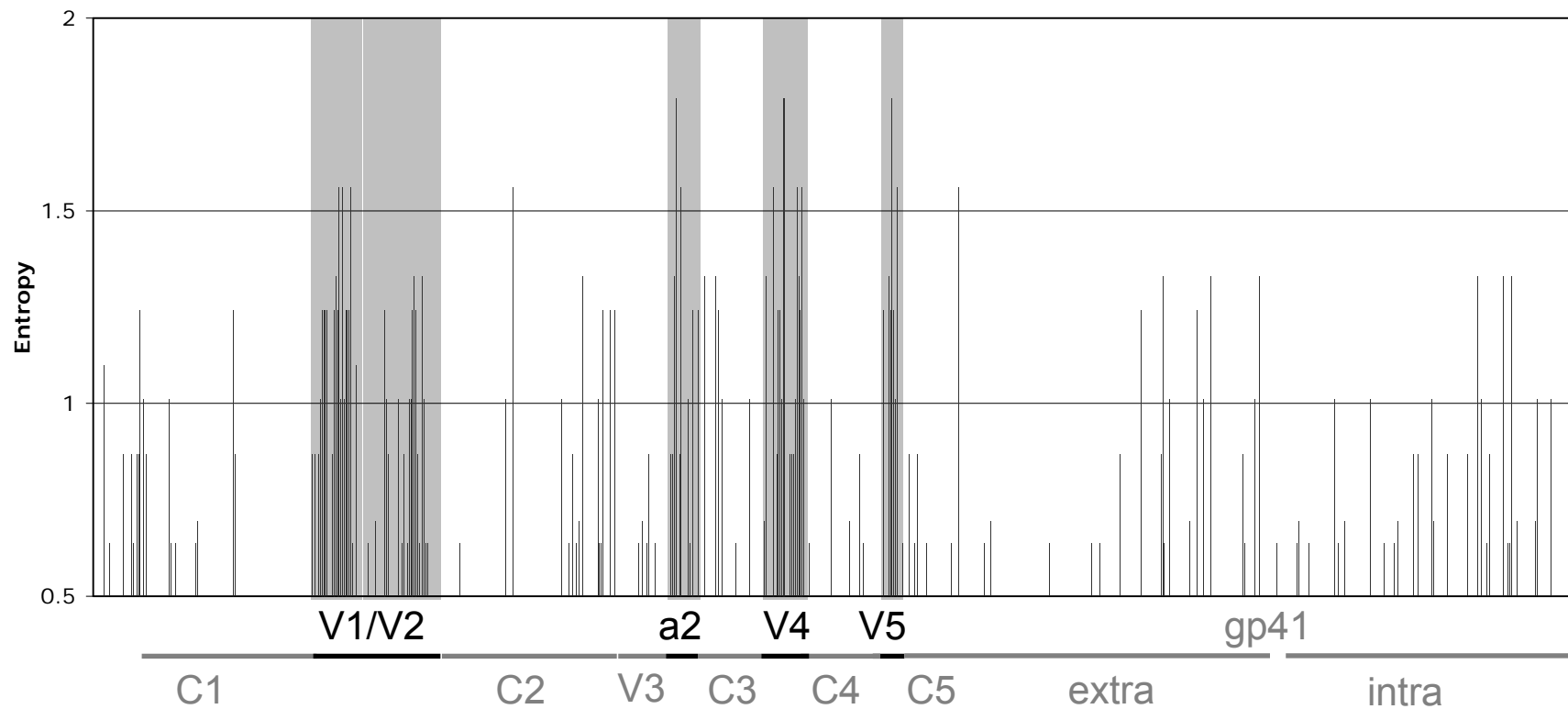
Anti-V3 binding antibodies develop early and are cross-reactive



Anti-V3 antibodies do not mediate autologous neutralization (tested by autologous peptide inhibition)

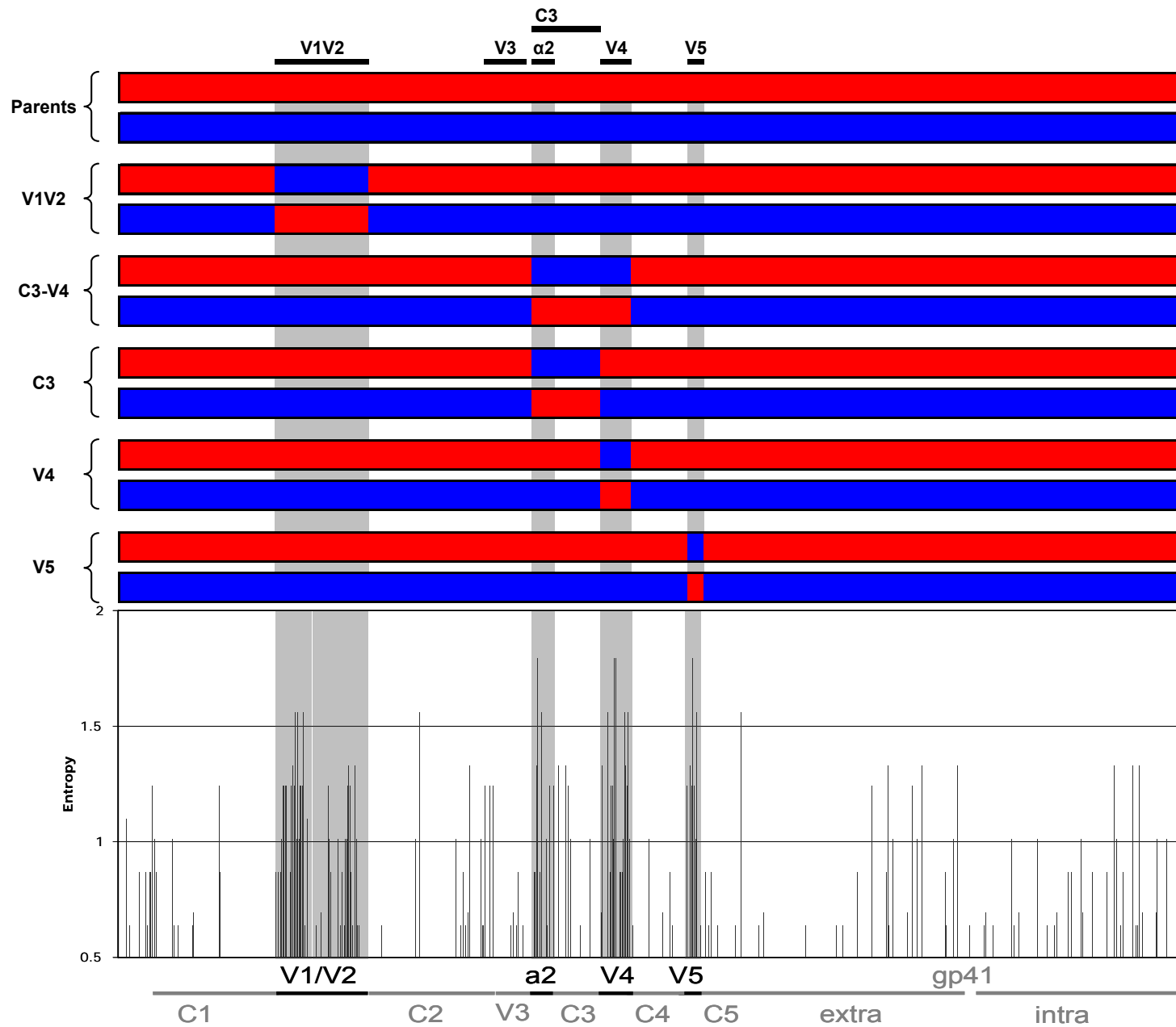


What is the specificity of the early autologous neutralizing antibody response?

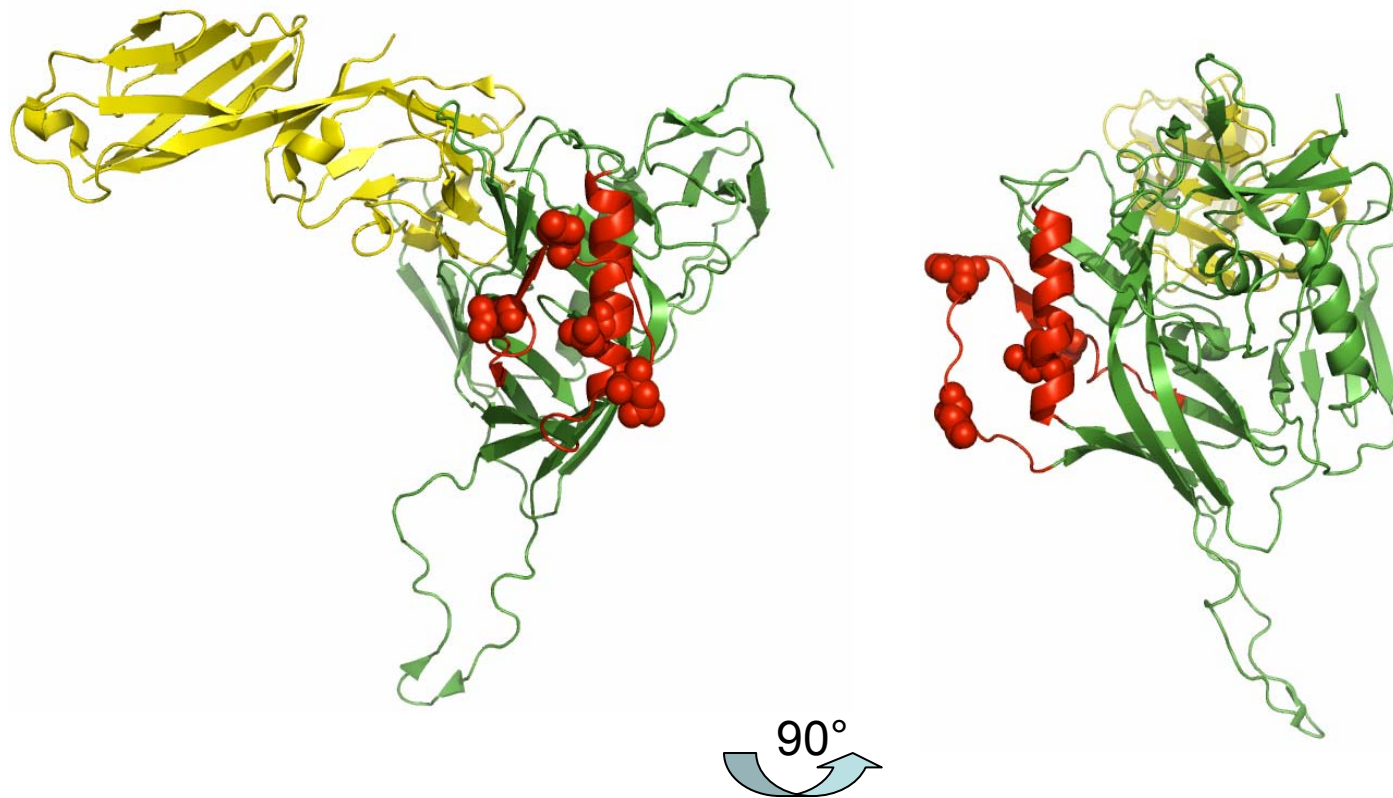


Entropy (variation) along the envelope (n=6 individuals)

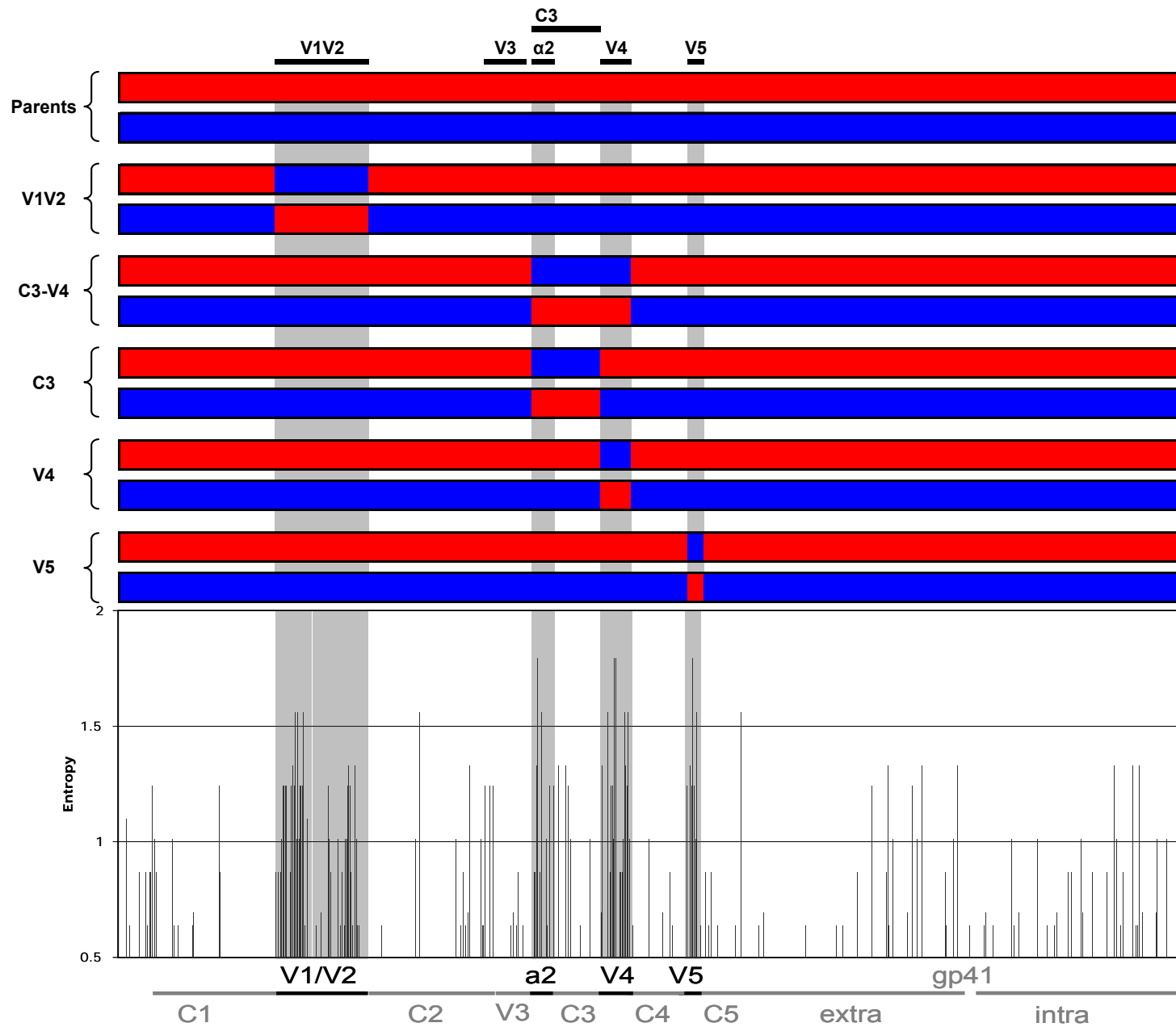
Generation of chimeric viruses







Why C3-V4?



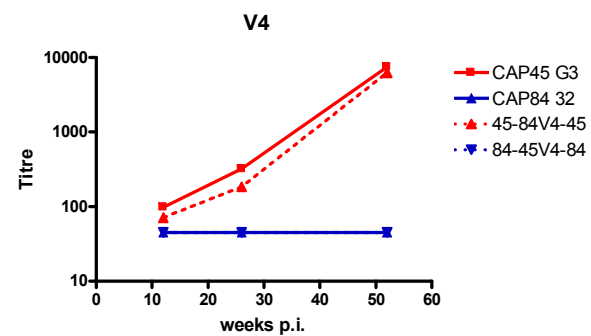
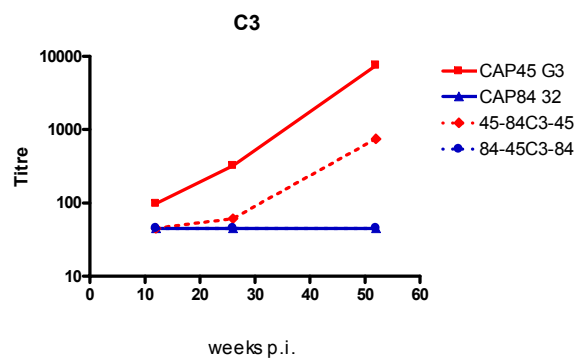
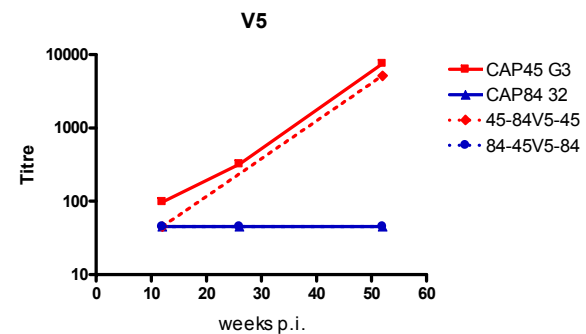
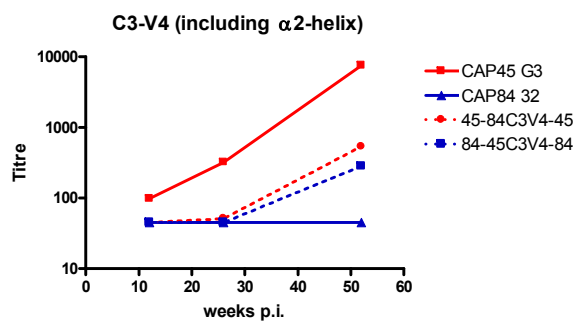
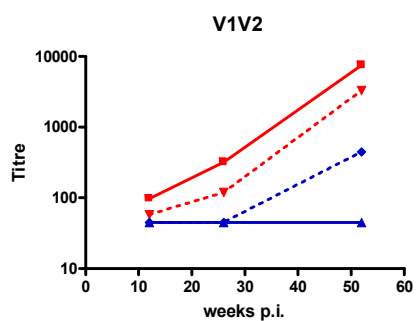
Generation of chimeric viruses



Rationale for neutralization assays

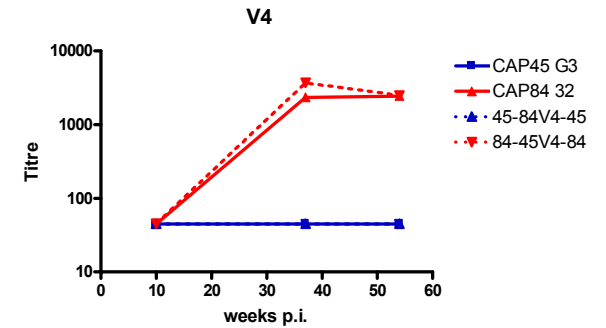
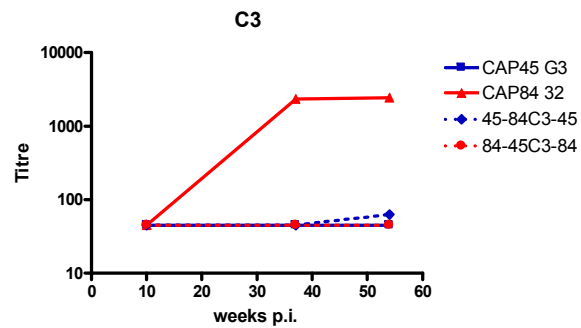
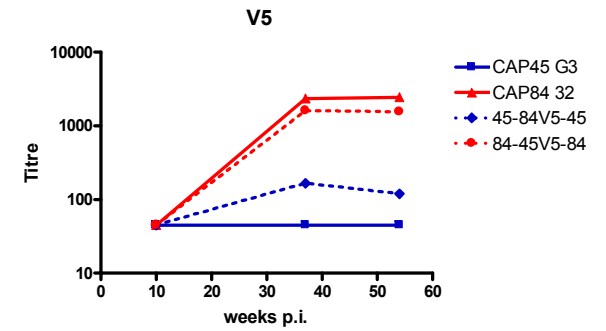
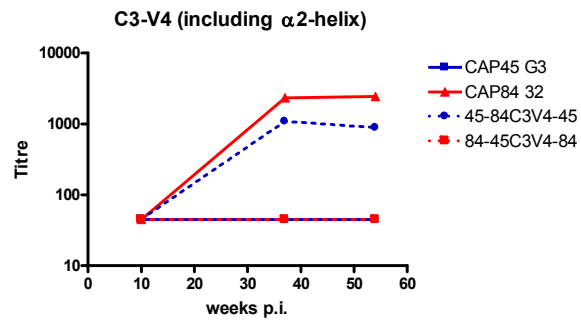
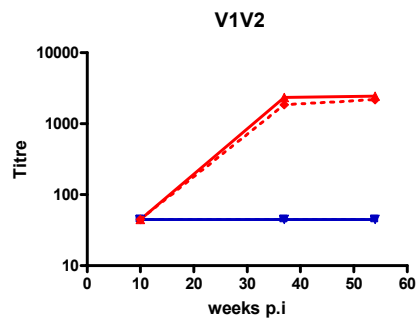
		Sole nAb target		Partial nAb target	
		Serum A	Serum B	Serum A	Serum B
Virus A		+++	-	+++	-
Virus B		-	+++	-	+++
Virus A-B-A		-	+++	+	+
Virus B-A-B	 <u>nAb target</u>	+++	-	+	+

CAP45 serum



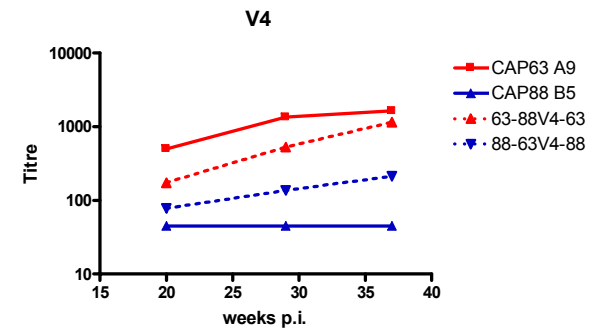
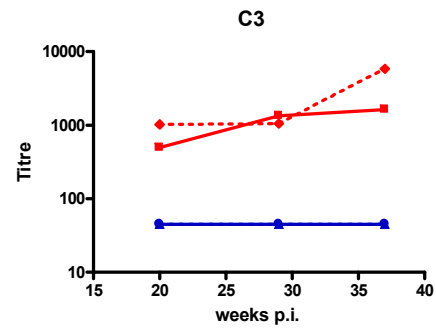
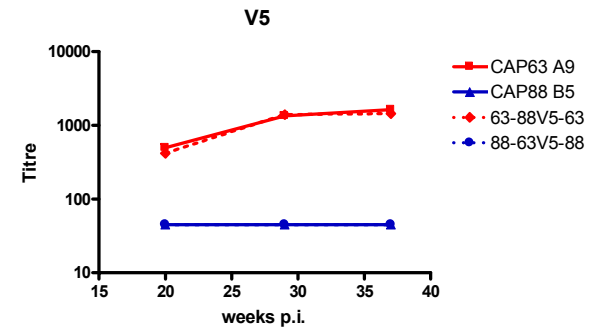
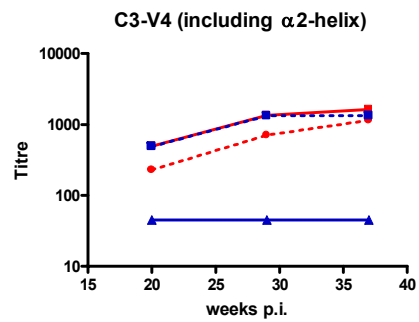
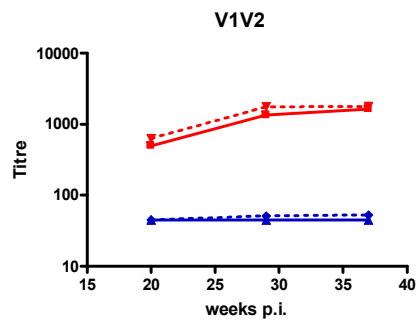
	V1V2	C3-V4	C3	V4	V5
CAP45	++	++	-	-	-

CAP84 serum



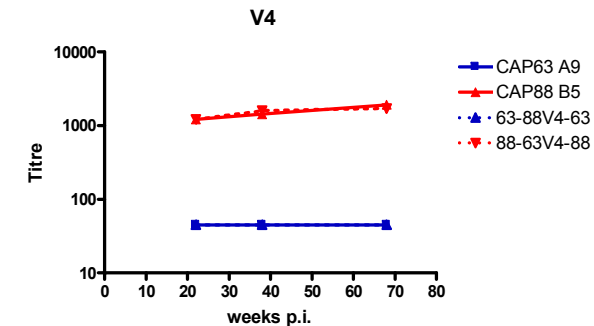
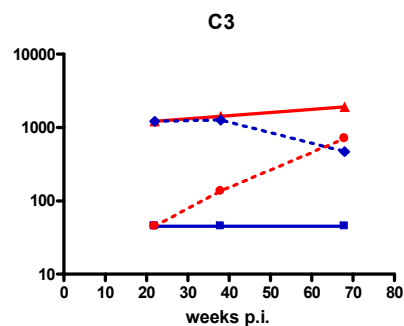
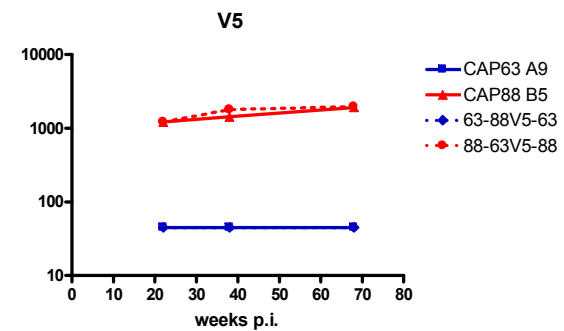
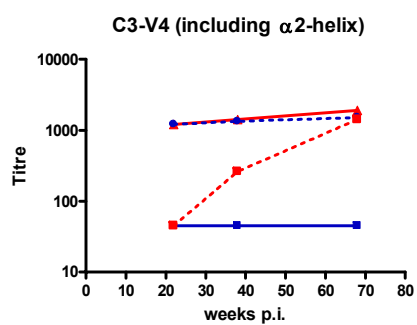
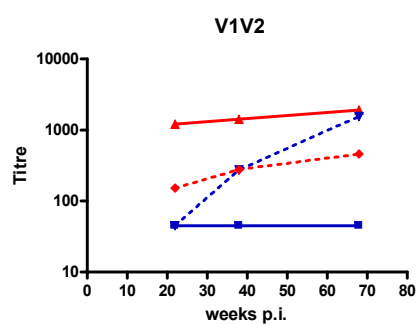
	V1V2	C3-V4	C3	V4	V5
CAP84	-	+++	-	-	+/-

CAP63 serum



	V1V2	C3-V4	C3	V4	V5
CAP63	-	+++	-	+/-	-

CAP88 serum



	V1V2	C3-V4	C3	V4	V5
CAP88	+++	+++	+++	-	-

Summary of Targets of Autologous Neutralization

	V1V2	C3-V4	C3	V4	V5
CAP45	++	++	-	-	-
CAP84	-	+++	-	-	+/-
CAP63	-	+++	-	+/-	-
CAP88	++	+++	+++	-	-

α-2 helix

CD4 bs

V4

```

CAP45.2.00.G3J  NSTWNRTLEQIKKKLREHFLNRT-IEFE-PPSGGDLEVTTHSFNCGGEFFYCNTTRLFKWS-----SNVTNDTITIPC
CAP84.2.00.32J  KTD.EK...KV.E..K..-Y.K.....KQ.V.....R.....N..NLNST.....DGSNITN.....
CAP63.2.00.A9J  KTQ..T...V.....P.K...T.Q..S.....I.....M.....SG..NSTYMS...NGIHIP.GASEV..L..
CAP88.2.00.B5J  KDR.IA...KV....E...P.K.K.K.A..S.....SK..NENETE.....---.T...L..
    
```

	Likely target?
CAP45	V1V2, V4 (with C3)
CAP84	V4 (with C3), V5
CAP63	V4 (with C3)
CAP88	V1V2, Anti-C3 (CD4bs?)

Heterologous neutralization of chimeras and parental viruses

Virus	CAP45 serum	CAP84 serum	CAP63 serum	CAP88 serum	CAP206 serum	CAP239 serum
CAP45	7,499	<45	<45	<45	<45	<45
84/45V1V2/84	447	2177	<45	<45	<45	<45
84/45C3V4/84	282	<45	<45	<45	<45	<45
84/45C3/84	<45	<45	<45	<45	<45	<45
84/45V4/84	<45	2493	<45	<45	<45	<45
84/45V5/84	<45	1551	<45	<45	<45	<45
CAP84	<45	2447	<45	<45	<45	<45
45/84V1V2/45	3,308	<45	<45	<45	<45	<45
45/84C3V4/45	535	890	<45	<45	<45	<45
45/84C3/45	748	63	<45	<45	<45	<45
45/84V4/45	6253	<45	<45	<45	<45	<45
45/84V5/45	4154	120	<45	<45	<45	<45
CAP63	<45	<45	1633	<45	<45	<45
88/63V1V2/88	<45	<45	53	458	<45	<45
88/63C3V4/88	<45	<45	1329	1414	63	<45
88/63C3/88	<45	<45	<45	705	52	45
88/63V4/88	<45	<45	212	1708	53	<45
88/63V5/88	<45	<45	<45	1965	<45	<45
CAP88	<45	<45	<45	1129	53	<45
63/88V1V2/63	<45	<45	1780	2021	<45	<45
63/88C3V4/63	<45	<45	1146	1544	<45	<45
63/88C3/63	<45	<45	5833	468	<45	<45
63/88V4/63	<45	<45	1142	<45	<45	<45
63/88V5/63	<45	<45	1441	<45	<45	<45

What are the targets of autologous neutralization?

- Not the V3 region.
- V1V2 region was a target in 2/4 individuals
- C3-V4 region was a target in 4/4 individuals.
- Separation of C3, which includes the $\alpha 2$ -helix, and V4 resulted in destruction of the epitope in 3/4 individuals, suggesting the possibility that antibodies target V4, but C3 informs the conformation of V4.
- C3 was itself a target in CAP88 – CD4bs?
- V5 region a minor target in 1/4 individual

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Katie Davis

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