

Table S1.

Neutralizing activity of PGT MAbs against a cross-clade 141-pseudovirus panel.

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Isolate	NCBI Accession	Subtype*	IC ₅₀ / µg/ml										
			PGT 121	PGT 123	PGT 125	PGT 126	PGT 127	PGT 128	PGT 130	PGT 135	PGT 143	PGT 145	
92RW009	AY669700	A	1.739	15.680	0.144	>50	>50	0.812	1.274	>50	0.010	0.026	†
92RW008	AY669703	A	0.003	0.003	0.004	0.008	0.012	0.003	0.089	1.417	0.385	0.400	†
92RW020	AY669706	A	0.004	0.002	0.004	0.006	0.010	0.005	0.039	0.067	>50	0.997	†
92RW024	AY669699	A	>50	>50	35.530	41.995	>50	>50	>50	>50	0.122	0.069	†
92RW026	AY669702	A	0.014	0.012	0.007	0.008	0.024	0.010	0.037	0.068	5.364	1.453	†
92UG031	AY669701	A	>50	>50	>50	>50	>50	>50	>50	>50	0.095	3.220	†
92UG037	AY494974	A	0.031	0.023	0.005	0.011	0.014	0.006	0.061	3.672	0.854	3.148	†
93RW029	AY669697	A	>50	>50	>50	>50	>50	>50	34.264	>50	0.053	>50	†
93UG077	AY669704	A	0.019	0.028	0.012	0.020	0.055	0.014	21.392	>50	>50	>50	†
94UG103	AY669705	A	2.518	0.678	0.008	0.008	0.017	0.011	1.402	>50	>50	0.331	†
Q23.17	AF004885	A	<0.001	<0.001	0.003	0.009	0.006	0.009	0.118	41.647	0.308	1.317	†
Q259.d2.17	AF407152	A	15.379	>50	>50	>50	>50	>50	0.320	>50	>50	44.232	†
Q461.e2	AF407156	A	>50	>50	>50	>50	>50	>50	3.007	>50	35.248	7.801	†
Q769.d22	AF407158	A	>50	>50	>50	>50	>50	>50	1.234	>50	>50	0.260	†
Q842.d12	AF407160	A	0.005	0.017	0.001	0.287	1.000	0.008	0.003	>50	0.028	0.032	†
MS208.A1	DQ187010	A	>50	>50	>50	>50	>50	>50	>50	0.403	0.183	0.334	†
0260.v5.c36	HM215256	A	0.053	0.036	0.053	0.093	0.083	0.058	1.319	0.792	>50	>50	†
0330.v4.c3	HM215257	A	0.050	0.052	>50	16.952	>50	1.604	>50	>50	0.021	0.990	†
191084 B7-19	HM215266	A (T/F)	0.011	0.008	4.725	1.218	0.497	0.022	>50	0.058	0.023	0.028	†
191955 A11	HM215272	A (T/F)	>50	>50	>50	>50	>50	14.195	1.082	>50	0.002	<0.001	†
9004SS A3 4	HM215350	A (T/F)	<0.001	<0.001	<0.001	<0.001	0.006	0.002	0.078	>50	0.320	0.018	†
94KE105	AY669768	AC	0.029	0.024	0.004	0.006	0.023	0.007	0.004	0.063	0.368	1.317	†
3301.v1.c24	HM215294	AC	0.008	0.005	11.393	0.446	0.262	0.067	0.458	>50	0.102	0.219	†
6041.v3.c23	HM215321	AC	>50	>50	>50	>50	>50	>50	>50	>50	>50	0.964	†
6540.v4.c1	HM215330	AC	>50	>50	>50	>50	>50	11.798	1.025	>50	0.032	0.080	†
6545.v4.c1	HM215332	AC	>50	>50	>50	>50	>50	>50	15.991	>50	0.032	0.114	†
0815.v3.c3	HM215260	ACD	0.025	0.012	0.029	0.068	0.116	0.030	0.560	>50	>50	>50	†
3103.v3.c10	HM215288	ACD	0.009	0.009	0.020	0.030	0.031	0.014	0.148	2.002	5.755	0.043	†
92TH021	AY669775	AE	>50	>50	0.006	0.197	>50	0.010	0.009	>50	0.003	0.013	†
CMU02	AY669779	AE	>50	>50	>50	>50	>50	>50	>50	>50	>50	1.425	†
92BR020	AY669718	B	0.014	0.008	0.016	0.015	0.059	0.009	1.395	0.073	25.892	1.051	†
93TH305	AY669729	B	0.007	0.008	0.008	0.013	0.017	0.006	0.021	>50	17.270	0.032	†
APV-13	DQ869019	B	0.251	0.138	0.007	0.012	0.026	0.008	0.052	0.716	>50	0.337	†
APV-17	DQ869023	B	0.066	0.114	8.063	0.353	10.378	0.016	10.661	>50	1.108	0.488	†
APV-6	DQ869030	B	0.018	0.023	0.021	0.007	0.040	0.007	>50	>50	13.968	0.104	†
JR-FL	U63632	B	0.021	0.014	0.009	0.014	0.029	0.007	0.046	>50	>50	30.401	†
NL4-3	AF324493	B	>50	>50	>50	>50	>50	>50	8.034	>50	>50	0.006	†
QH0692	AF277065	B	0.823	0.158	0.048	0.048	0.129	0.029	>50	>50	>50	>50	†
SF162env	EU123924	B	0.005	0.005	0.004	0.003	0.019	0.007	0.007	0.023	>50	>50	†
6535.3	AY835438	B	0.002	0.001	0.007	0.008	0.011	0.004	0.025	>50	>50	>50	†
QH0692.42	AY835439	B	0.302	0.092	0.025	0.023	0.098	0.029	1.121	>50	>50	>50	†
SC422661.8	AY835441	B	0.038	0.027	>50	0.097	>50	1.078	>50	0.477	3.799	0.024	†
PVO.4	AY835444	B	0.098	0.061	0.021	0.020	0.081	0.011	2.364	>50	0.111	0.192	†
TRO.11	AY835445	B	0.005	0.006	0.124	0.051	0.096	0.019	0.172	0.030	0.996	0.040	†
AC10.0.29	AY835446	B	0.024	0.016	>50	0.317	>50	0.008	0.245	>50	0.042	0.010	†
RHPA4259.7	AY835447	B	0.015	0.013	0.027	0.025	1.242	0.026	0.198	>50	0.054	0.029	†
THRO4156.18	AY835448	B	>50	>50	>50	>50	>50	>50	>50	>50	0.011	0.010	†
REJO4541.67	AY835449	B	4.774	>50	>50	>50	>50	>50	4.092	>50	9.157	<0.001	†
TRJO4551.58	AY835450	B	1.314	1.023	0.015	0.027	0.051	0.018	0.038	>50	>50	>50	†
WITO4160.33	AY835451	B	0.334	0.429	>50	6.108	>50	>50	1.797	5.842	<0.001	<0.001	†
CAAN5342.A2	AY835452	B	0.007	0.008	2.236	0.096	0.244	0.514	17.497	2.561	>50	6.675	†
1006_11_C3_1601	EU289183	B (T/F)	0.002	0.004	3.502	0.021	0.079	0.011	1.190	>50	>50	>50	†

1012_11_TC21_3257	EU289184	B (T/F)	0.003	0.002	6.354	0.014	0.482	0.011	7.830	34.894	0.008	0.009
1054_07_TC4_1499	EU289185	B (T/F)	0.064	0.051	>50	21.351	>50	0.035	0.012	>50	>50	>50
1056_10_TA11_1826	EU289186	B (T/F)	0.004	<0.001	<0.001	<0.001	0.004	<0.001	<0.001	>50	0.289	0.230
62357_14_D3_4589	EU289189	B (T/F)	2.597	1.190	>50	22.492	>50	1.144	0.783	>50	>50	>50
6240_08_TA5_4622	EU289190	B (T/F)	0.033	0.015	0.354	0.098	0.061	0.019	>50	22.623	>50	>50
6244_13_B5_4576	EU289191	B (T/F)	0.061	0.068	0.011	0.033	0.050	0.020	0.141	0.112	>50	7.266
SC05_8C11_2344	EU289200	B (T/F)	0.019	0.015	0.193	0.026	0.057	0.017	2.099	7.940	0.540	0.093
WEAU_d15_410_5017	EU289202	B (T/F)	0.026	0.022	0.209	0.029	0.098	0.032	0.824	0.237	>50	1.951
CNE17	HM215403	BC	7.600	25.119	38.130	5.588	13.532	0.432	>50	>50	0.005	0.091
CNE19	HM215405	BC	0.008	0.833	>50	>50	>50	>50	>50	0.008	>50	0.103
CNE20	HM215406	BC	<0.001	0.002	0.010	0.003	0.002	0.001	0.002	0.003	>50	0.318
CNE21	HM215407	BC	0.007	0.004	0.010	0.013	0.017	0.010	0.024	0.035	0.003	<0.001
CNE30	HM215411	BC	>50	>50	>50	>50	>50	>50	6.221	>50	5.399	4.660
CNE52	HM215416	BC	2.045	1.095	>50	>50	>50	>50	>50	43.687	>50	0.020
CNE53	HM215417	BC	0.007	0.003	1.213	0.065	0.094	0.010	21.555	0.033	0.002	0.006
CNE58	HM215421	BC	>50	>50	>50	1.591	>50	13.768	>50	>50	0.014	0.183
93IN905	AY669742	C	0.005	0.004	0.009	0.015	0.024	0.009	0.020	0.011	0.002	0.002
93MW959	AY669739	C	0.013	0.011	37.481	9.441	6.951	0.045	8.548	>50	0.002	1.203
97ZA012	AY669741	C	0.002	0.002	2.465	0.042	>50	0.019	1.318	>50	>50	0.915
98IN022	AY669748	C	0.007	0.011	22.057	0.279	19.189	0.014	>50	0.014	0.001	0.005
ZM53M.PB12	AY423984	C	<0.001	0.406	>50	>50	>50	>50	>50	>50	0.011	0.367
ZM135M.PL10a	AY424079	C	0.716	1.185	>50	>50	>50	>50	>50	>50	>50	>50
ZM109F.PB4	AY424138	C	8.639	>50	>50	>50	>50	>50	>50	>50	>50	0.042
ZM249M.PL1	DQ388514	C	>50	>50	>50	>50	>50	39.657	>50	>50	0.411	1.442
ZM197M.PB7	DQ388515	C	>50	>50	>50	>50	>50	>50	>50	>50	0.242	0.628
ZM214M.PL15	DQ388516	C	0.460	0.180	>50	2.075	>50	1.498	2.500	>50	>50	>50
ZM233M.PB6	DQ388517	C	3.689	6.541	>50	>50	>50	>50	>50	0.377	0.139	0.025
Du156.12	DQ411852	C	0.004	0.004	0.218	0.068	0.047	0.017	0.121	20.357	0.023	0.001
Du172.17	DQ411853	C	0.033	0.013	0.026	0.052	0.815	0.028	0.049	>50	>50	>50
Du422.1	DQ411854	C	0.039	0.035	0.056	0.091	0.083	0.039	0.085	>50	>50	22.564
CAP45.2.00.G3	DQ435682	C	1.634	>50	>50	>50	>50	>50	>50	>50	1.335	0.001
CAP210.2.00.E8	DQ435683	C	26.301	43.636	>50	41.472	>50	>50	>50	45.003	0.570	37.807
HIV-001428-2.42	EF117266	C	0.014	0.006	>50	0.508	2.041	0.026	0.510	0.025	>50	0.001
HIV-0013095-2.11	EF117267	C	>50	>50	>50	>50	>50	>50	>50	>50	>50	9.271
HIV-16055-2.3	EF117268	C	0.153	>50	>50	>50	>50	>50	>50	>50	0.001	0.003
HIV-16845-2.22	EF117269	C	3.969	1.255	>50	>50	>50	0.181	>50	4.966	>50	>50
249M B10	EU166866	C (T/F)	>50	>50	>50	>50	>50	7.868	>50	>50	0.302	0.947
Ce703010054_2A2	FJ443808	C (T/F)	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
7030102001E5(Rev-)	FJ443999	C (T/F)	0.009	0.009	0.008	0.008	0.190	0.007	0.289	>50	>50	>50
Ce704809221_1B3	FJ444103	C (T/F)	0.025	0.127	0.362	0.129	0.128	0.026	0.408	>50	0.124	0.102
Ce0393_C3	FJ444215	C (T/F)	>50	>50	>50	>50	>50	>50	>50	>50	>50	0.112
Ce0682_E4	FJ444325	C (T/F)	>50	>50	>50	>50	>50	>50	>50	>50	0.256	33.578
Ce1086_B2	FJ444395	C (T/F)	<0.001	0.092	>50	>50	>50	>50	>50	>50	>50	>50
Ce1172_H1	FJ444421	C (T/F)	0.011	0.008	0.014	0.020	0.024	0.013	0.056	>50	22.295	0.260
Ce1176_A3	FJ444437	C (T/F)	0.013	0.010	0.022	0.045	0.035	0.009	0.041	25.597	>50	>50
1394C9G1(Rev-)	FJ444529	C (T/F)	0.264	2.201	0.280	0.049	0.043	0.011	0.041	0.072	0.010	0.001
Ce2010_F5	FJ444561	C (T/F)	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
Ce2060_G9	FJ444600	C (T/F)	>50	>50	>50	>50	>50	>50	>50	>50	0.216	0.016
246F_C1G	FJ496194	C (T/F)	0.041	0.044	>50	31.534	>50	0.005	>50	>50	>50	>50
ZM247v1(Rev-)	FJ496204	C (T/F)	0.028	0.021	0.267	0.171	0.069	0.021	0.030	>50	8.567	7.190
BF1266.431a	HM215360	C (T/F)	>50	>50	>50	>50	>50	>50	0.408	>50	>50	1.345
3817.v2.c59	HM215310	CD	18.888	>50	1.472	0.479	0.972	0.003	3.192	>50	>50	>50
6480.v4.c25	HM215329	CD	<0.001	<0.001	0.063	0.035	0.047	0.003	0.392	0.577	>50	>50
6811.v7.c18	HM215340	CD	<0.001	<0.001	4.105	0.323	0.229	0.003	0.156	0.052	>50	>50
6952.v1.c20	HM215343	CD	0.056	0.025	>50	>50	>50	>50	>50	0.017	>50	3.120
C3347.c11	AF259954	CRF01_AE	>50	>50	2.204	38.418	>50	0.001	0.002	>50	>50	0.005
BJOX009000.02.4	HM215372	CRF01_AE	2.858	>50	<0.001	0.012	0.143	<0.001	0.006	>50	0.070	0.117

CNE5	HM215415	CRF01 AE	>50	>50	0.005	0.777	>50	0.018	0.008	>50	0.011	0.001
CNE8	HM215427	CRF01 AE	>50	>50	0.016	0.056	0.397	0.019	0.030	>50	4.031	0.272
BJOX010000.06.2	HM215373	CRF01 AE (T/F)	>50	>50	>50	>50	>50	4.817	0.031	>50	>50	>50
BJOX015000.11.5	HM215377	CRF01 AE (T/F)	>50	>50	0.001	0.473	4.062	0.001	0.003	0.489	>50	>50
BJOX025000.01.1	HM215386	CRF01 AE (T/F)	>50	>50	>50	>50	>50	>50	>50	>50	>50	6.632
BJOX028000.10.3	HM215389	CRF01 AE (T/F)	>50	>50	0.015	0.018	0.058	0.024	0.025	>50	>50	>50
263-8	EU513182	CRF02 AG	0.648	0.416	>50	3.143	>50	0.342	>50	>50	3.340	32.071
T255-34	EU513184	CRF02 AG	18.695	>50	>50	>50	>50	>50	>50	>50	45.292	>50
T257-31	EU513185	CRF02 AG	>50	>50	>50	>50	>50	>50	0.041	>50	4.002	5.177
211-9	EU513187	CRF02 AG	0.852	0.931	7.670	0.046	4.480	0.062	>50	>50	0.043	0.129
T250-4	EU513189	CRF02 AG	<0.001	0.003	0.005	0.007	0.007	<0.001	0.004	>50	0.022	0.002
235-47	EU513195	CRF02 AG	0.137	0.555	>50	>50	>50	>50	>50	3.580	>50	3.212
T251-18	EU513196	CRF02 AG	29.016	14.316	>50	>50	>50	>50	>50	>50	>50	0.351
T278-50	EU513198	CRF02 AG	>50	>50	>50	>50	>50	0.031	0.142	>50	>50	10.324
928-28	EU513199	CRF02 AG	44.189	>50	>50	>50	>50	>50	>50	>50	>50	>50
98CN009	AY669747	CRF07 BC	0.009	0.007	0.030	0.019	0.090	0.025	0.136	0.071	10.206	0.136 †
98CN006	AY669745	CRF08 BC	0.010	0.008	0.201	0.046	0.067	0.015	0.258	0.429	>50	>50 †
92UG001	AY669754	D	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50 †
92UG005	AY669758	D	18.292	9.794	>50	0.037	1.107	0.018	0.959	>50	>50	>50 †
92UG024	AY669760	D	>50	>50	>50	>50	>50	>50	>50	0.010	>50	1.600 †
92UG046	AY669757	D	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50 †
94UG114	AY494966	D	0.004	0.005	0.349	0.038	7.091	0.083	>50	1.289	>50	20.113 †
3016.v5.c45	HM215283	D	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
A07412M1.vrc12	HM215357	D	0.009	0.194	>50	>50	>50	>50	>50	6.791	7.260	0.002
191821 E6 1	HM215270	D (T/F)	>50	>50	0.393	0.006	21.783	0.010	0.010	0.035	>50	0.186
P0402 c2 11	EU885759	G	0.005	0.004	>50	0.169	>50	0.007	0.116	>50	0.022	0.009
X1193 c1	EU885761	G	0.016	0.011	0.002	0.014	0.010	>50	0.011	0.017	0.053	0.013
X1254 c3	EU885762	G	0.014	0.002	0.004	0.009	0.014	>50	0.042	1.912	>50	5.597
X2088 c9	EU885764	G	0.003	0.011	>50	>50	>50	>50	>50	0.007	>50	>50
X2131 C1 B5	FJ817368	G	0.004	0.005	0.214	0.059	0.190	>50	0.094	0.007	0.186	0.018
P1981 C5 3	FJ817369	G	<0.001	<0.001	<0.001	<0.001	<0.001	0.019	2.630	>50	24.661	5.413
X1632 S2 B10	FJ817370	G	>50	>50	>50	>50	>50	>50	0.293	>50	17.761	0.012

* (T/F): Transmitted / Founder Virus

† Neutralization data taken from Ref. [5]

Table S2.

Ensemble classifier predictions of positions of HIV-1 Env positions constituting bnMAb epitopes using randomly and independently selected subsets of the 141-strain pseudovirus panel. Predictions generated using 35, 70, 105, and 126 viral strains, respectively constituting 25%, 50%, 75%, and 90% of the 141-strain pseudovirus panel are reported to assess the robustness of our predictions to the size and composition of the panel. We also list the experimentally identified positions reported in [Tables 1–3](#).
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bnMAb	Positions					Experiment
	Ensemble classifier					
	25%	50%	75%	90%	100%	
PGT 121	-	332	332	332	332	332
		580		843		334
		592				
PGT 123	-	332	330	330	330	325
		334	332	332	332	332
			334	334	334	334
PGT 125	-	-	332	-	-	301
						303
PGT 126	588	-	297	332	297	301
				334	332	303
					334	332
						334
PGT 127	588	-	332	332	332	301
				334	334	303
						332
						334
PGT 128	-	-	332	332	332	303
					334	
PGT 130	-	373	-	-	792	301
		793				303
						307
						309
						324
						325
						423
PGT 135	-	-	-	-	334	297
						330
						332
						334
						392
						394
PGT 143	-	166	166	166	166	160
						166
PGT 145	-	-	160	166	160	160
			166		166	

Table S3.

Comparison of the ensemble classifier predictions of HIV-1 Env positions constituting bnMAb epitopes (cf. [Tables 1–3](#)), to those identified by application of Fisher’s exact test to detect positions with statistically significant differences in the observed distribution of amino acid residues in the neutralized ($IC_{50} \leq 10 \mu\text{g/ml}$) and non-neutralized ($IC_{50} > 10 \mu\text{g/ml}$) strains in the pseudovirus panel. Results for Fisher’s exact test are reported at 5%, 1% and 0.1% significance; p-values were corrected for multiple comparisons using the Benjamini–Hochberg procedure [63]. We also list the experimentally identified positions reported in [Tables 1–3](#).

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bnMAb	Positions				
	Fisher's Exact Test			Ensemble Classifier	Experiment
	$\alpha=0.05$	$\alpha=0.01$	$\alpha=0.001$		
PGT 121	147	330	332	332	332
	152	332	334		334
	277	334			
	307	429			
	323	442			
	330	452			
	332	475			
	334	602			
	346	619			
	362	720			
	363				
	372				
	375				
	429				
	442				
	452				
	475				
	507				
	519				
	591				
	592				
	602				
	613				
	619				
	629				
	641				
	645				
	647				
	720				
	736				
	742				
	796				
	837				
	843				
PGT 123	8	330	330	330	325
	136	332	332	332	332
	147	334	334	334	334
	151	372			
	152	375			
	277	429			
	292	452			
	315	475			
	330	507			
	332	519			
	334	591			
	346	592			
	352	602			
	362	619			
	372	629			
	375	720			
	429				
	442				

	446				
	452				
	475				
	507				
	519				
	591				
	592				
	602				
	612				
	613				
	619				
	629				
	647				
	720				
	740				
	746				
	796				
	797				
	843				
PGT 125	-	-	-	-	301
					303
PGT 126	332	332	332	297	301
	334	334	334	332	303
				334	332
					334
PGT 127	330	332	-	332	301
	332	334		334	303
	334				332
					334
PGT 128	332	332	-	332	303
	334	334		334	
PGT 130	471	-	-	792	301
	500				303
	792				307
					309
					324
					325
					423
PGT 135	334	-	-	334	297
					330
					332
					334
					392
					394
PGT 143	166	166	166	166	160
					166
PGT 145	160	-	-	160	160
	166			166	

Table S4.

Ensemble classifier predictions of HIV-1 Env positions constituting bnMAb epitopes as a function of the MI classifier IC₅₀ cutoff.

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bnMAb	MI IC ₅₀ cutoff / µg/ml					
	<i>0.1</i>	<i>1</i>	<i>5</i>	<i>10</i>	<i>20</i>	<i>50</i>
PGT 121	330	330	332	332	332	330
	332	332				332
	843					
PGT 123	330	330	330	330	330	330
	332	332	332	332	332	332
	334	334	334	334	334	334
	843					
PGT 125	-	-	-	-	82	-
PGT 126	332	332	332	297	297	297
	334	334	334	332	332	332
				334	334	334
PGT 127	332	332	332	332	330	332
	334	334	334	334	332	334
					334	
PGT 128	332	332	153	332	332	332
		334	332	334		
			334			
PGT 130	-	-	792	792	-	-
PGT 135	-	-	-	334	334	334
PGT 143	-	166	166	166	166	166
PGT 145	-	166	160	160	160	160
			166	166	166	166