V1V2 neutralizing epitopes are conserved within divergent groups of HIV-1.

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The aim of this study was to analyze the cross-group neutralization potency of 23 broadly neutralizing antibodies (bNabs) using a large panel of sixteen non-M primary isolates (PI) (12 group O PI, 2 group N PI, 1 group P PI and 1 recombinant M/O PI).
The bNabs targeted all the major neutralizing epitopes: the CD4 binding site (CD4bs), the N160-dependant V1/V2 epitopes, the N332-dependant V3 epitopes, the membrane proximal external domain of gp41 (MPER), and conformational epitopes involving different regions of either gp120 (JM4) or gp120 and gp41 (8ANC195). The bispecific antibodies PG9-iMab and PG16-iMab combine the HIV-1 inhibitory activity of an anti-human CD4 with that of the anti-V1/V2 PG9/PG16 antibodies.

	Primary Isolate / Group	BCF02 O	BCF03 O	BCF108 O	RBF125 O	RBF189 O	YBF16 O	YBF26 O	YBF32 O	YBF35 O	YBF37 O	YBF38 O	YBF39 O	RBF208 M/O	YBF30 N	N1.FR.2011 N	RBF168 P
NAb																	
Anti-CD4bs	VRC01	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	3.64	> 10	> 10	> 10
	VRC03	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10
	NIH45-46^{G54W}	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	1.50	> 10	> 10	> 10
	45-46 m2	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	0.23	> 1	> 1	> 1
	45-46 m7	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	0.31	> 1	> 1	> 1
	45-46 m25	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	0.36	> 1	> 1	> 1
	45-46 m28	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	> 1	0.19	> 1	> 1	> 1
	3BNC117	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	0.63	> 10	> 10	> 10
Anti-V1/V2	PGT145	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	0.13
	PG9	0.23	9.39	> 10	> 10	4.99	> 10	> 10	1.60	> 10	> 10	> 10	> 10	> 10	0.30	> 10	> 10
	PG16	6.10	> 10	> 10	> 10	7.62	> 10	> 10	1.20	> 10	> 10	> 10	> 10	> 10	0.04	> 10	> 10
	PG9-PG16 RSH	0.02	0.60	> 1	> 1	> 1	> 1	0.88	0.20	> 1	> 1	> 1	> 1	> 1	0.02	> 1	> 1
BibNAbs	PG9-iMab	0.02	0.61	0.19	0.73	0.70	1.70	0.51	0.49	4.99	0.41	0.56	0.44	0.44	0.04	0.24	0.25
	PG16-iMab	0.01	0.24	0.06	0.94	0.59	2.95	0.14	0.48	> 10	0.20	0.35	0.22	0.15	0.001	0.48	0.56
Anti-V3	PGT121	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10
	PGT128	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10
	10-1074	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	2.86	> 10	> 10	> 10
Anti-MPER	2F5	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10
	4E10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10
	10E8	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	4.83	3.69	3.35	> 10
Others	8ANC195	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	0.31	> 10	> 10	> 10
	JM4SdAb	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	2.31	> 10	> 10	> 10
Anti-CD4	iMab	4.80	8.00	6.06	7.56	4.71	4.83	2.20	1.69	> 10	2.67	1.78	3.11	2.44	8.92	2.88	2.54

Sensivity to neutralization (IC_{50}) in TZM-bl cells of sixteen non-M primary isolates. Yellow cases and red cases show neutralizing activity between 1 and 10 µg/mL and below 1 µg/mL , respectively.

Two major conclusions

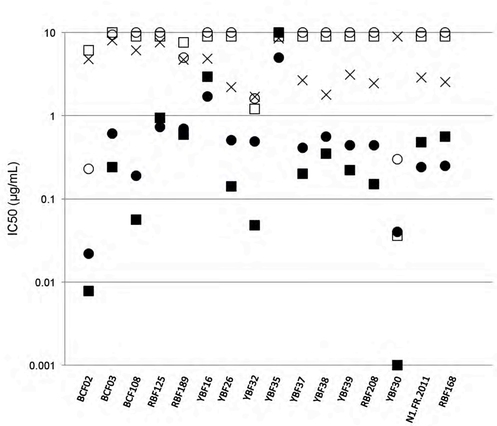
1: These data suggest that the neutralizing epitopes located at N160 glycan V1/V2 site are conserved within all groups of HIV-1 species.

2: The two bispecific bNabs exhibited exceptional breadth and potency toward a panel of diverse HIV-1 group non-M viruses.

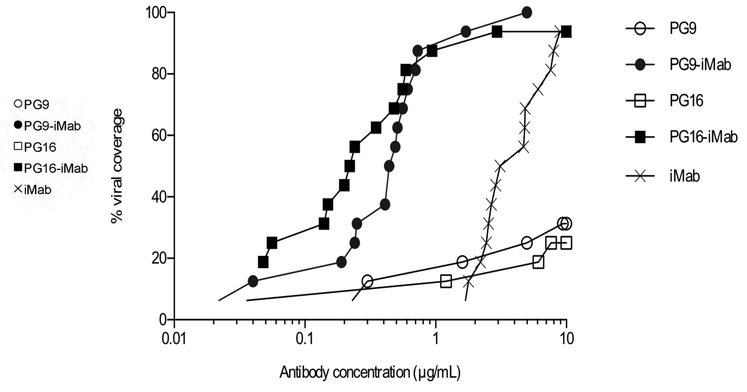
3: Neutralization breadth and potency of PG9-iMab and PG16-iMab, and parental Mabs against the panel of non-M viruses:



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Comparison of potency of PG9, PG16, iMab, PG9-iMab and PG16-iMab among all the 16 non-M PI.



Percentage viral coverage achieved by PG9, PG16, iMab, PG9-iMab and PG16-iMab

- The enhanced potency of the BibNabs was not simply due to the additive effects of the parental antibodies.
- The most sensitive viruses to the BibNabs were those the most sensitive to PG9 or PG16.

→ The high potency of the BibNabs was mediated by the gp120-binding activity of PG9 and PG16 scFvs.

Conclusion: The N160 glycan-V1V2 site is the most conserved neutralizing site within the four groups of HIV-1. It makes it a potentially interesting target for development of HIV vaccine immunogens. The corresponding bNabs could be useful for immunotherapeutic strategies in patients infected by non-M variants.

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