Continuous Increase in HIV-1 Resistance to Neutralization by bNAbs over the past 30 Years.

H.M. Fritsch[1], J. Migraine[1], C. Houdré[1], A. Moreau[1], E. Roch[1], V. Andriantsoanirina[2,3], F. Mammano[1], V. Lorin[4], H. Mouquet[4], C. Goujard[2,3], M-L. Chaix[5,6], L. Meyer[2,3], K. Stefic[1,7], on behalf of the *ANRS PRIMO Cohort Study Group.*

1 INSERM U1259, Université de Tours, Tours, France, 2 INSERM U1018, Université Paris Saclay, CESP, Paris, France, 3 Assistance Publique-Hôpital de Paris, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France 4 Institut Pasteur, Université Paris Cité, Humoral Immunology Unit, Paris, France, 5 INSERM U941, Université Paris Diderot, Paris, France, 6 Assistance Publique-Hôpital de Paris, Laboratoire de Virologie and CNR VIH, Hôpital Saint-Louis, Paris, France, 7 Laboratoire de Virologie and CNR VIH, Centre Hospitalier Régional Universitaire de Tours, Tours, France

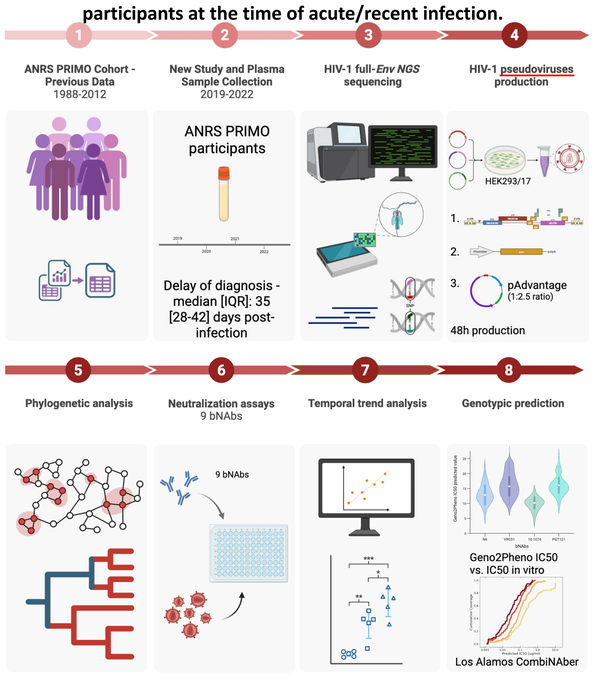
575

PURPOSE

The **efficacy of broadly neutralizing antibodies (bNAbs)** is affected by the **genetic diversity of HIV-1** and the **ongoing escape from autologous neutralizing Abs at the population level**. We investigated the current state of neutralization sensitivity of recent **transmitted/founder (T/F) variants**, with a **focus on subtype B and CRF02_AG**, the predominant clades in North America, Western Europe and Western Africa.

METHODS

The study was performed in the ongoing ANRS PRIMO Cohort, which includes participants at the time of acute/recent infection.



RESULTS

Figure 1. HIV-1 envelope glycoprotein epitopes targeted by broadly neutralizing antibodies evaluated in this study.

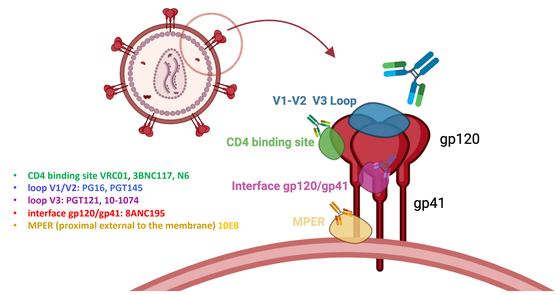


Figure 2. Temporal dynamics of HIV-1 genetic diversity in subtype B and CRF02_AG.

- HIV-1 genetic diversity increased progressively over time in both subtype B and CRF02_AG.
- Both 02AG and B showed a star-like shape distribution of newly sampled isolates across the phylogeny, suggesting a good representativeness of our datasets.

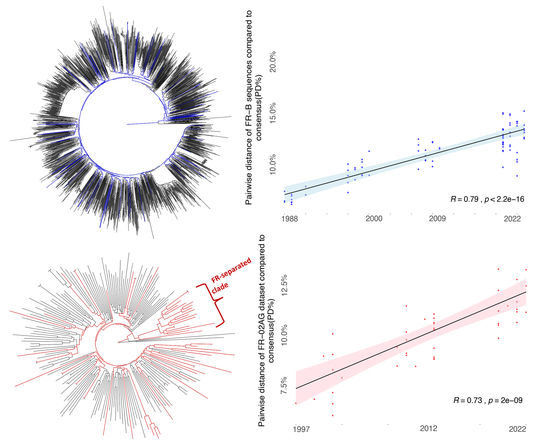


Figure 5: Comparison between *in vitro* and *Geno2Pheno* predicted HIV-1 IC50 in subtypes B and CRF02_AG.

- With high variability and systematic deviations, genotype-based prediction accuracy is subtype- and bNAb-dependent.

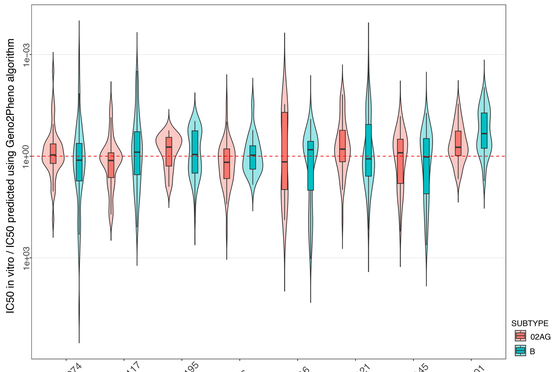


Table 1: Summary of the neutralization profiles of recent viruses against a panel of 9 bNAbs already in use in clinical trials.

- **Recent T/F viruses, including subtype B, are largely** resistant to **VRC01**.
- **Most viruses are resistant to VRC01**, whereas N6 and 3BNC117 remain effective.
- **Some viruses already show resistance to N6**, despite its high potency and breadth.
- **Resistance to 10-1074 and 3BNC117** in 21-22% of viruses, with implications for long-acting bNAb strategies.

	bNAbs (IC50 > 1 µg/mL)								
	CD4BS			V1/V2		V3		MPER	gp120-41 interface
Subtype	*VRC01 R(%)*	*N6 R(%)*	*3BNC117 R(%)*	*PG16 R(%)*	*PGT145 R(%)*	*10-1074 R(%)*	*PGT121 R(%)*	*10E8 R(%)*	*8ANC195 R(%)*
B (n=31)	21 (67.7)	6 (19.3)	7 (22.6)	19 (61.3)	10 (32.25)	8 (25.8)	11 (35.5)	8 (25.8)	25 (80.6)
02AG (n=22)	13 (59.1)	2 (9.1)	5 (22.7)	6 (27.3)	12 (54.5)	6 (27.3)	8 (36.4)	10 (45.45)	20 (90.9)
A1 (n=7)	3 (42.9)	1 (14.3)	1 (14.3)	3 (42.9)	3 (42.9)	0	0	2 (28.6)	3 (42.9)
F1 (n=5)	3 (60)	0	1 (20)	1 (20)	2 (40)	1 (20)	2 (40)	1 (20)	4 (80)
URFs (n=10)	5 (50)	0	2 (20)	5 (50)	5 (50)	3 (30)	3 (30)	2 (20)	3 (30)
C (n=11)	4 (36.4)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	0	0	2 (18.2)	3 (27.3)
06CPX (n=3)	2 (67)	1 (33)	2 (67)	1 (33)	0	0	1 (33)	1 (33)	2 (67)
G (n=2)	1 (50)	0	1 (50)	2 (100)	1 (50)	2 (100)	1 (50)	0	2 (100)
B-LIKE (n=2)	0	0	0	1 (50)	1 (50)	0	0	1 (100)	1 (100)
F2 (n=1)	1 (100)	0	0	1 (100)	1 (100)	1 (100)	1 (100)	0	0
42BF (n=2)	1 (100)	0	0	1 (100)	1 (100)	0	0	0	0
All Subtypes (n=96)	54 (56.25)	11 (11.46)	20 (20.83)	41 (42.71)	37 (38.54)	21 (21.87)	27 (28.12)	27 (28.12)	63 (65.62)

R(%) represents the number and percentage of resistant viruses defined as IC_{50} > 1 µg/mL.

Figure 3: Temporal trends of HIV-1B neutralization sensitivity across broadly neutralizing antibodies and correlation with pairwise distance.

- Significant temporal increases in IC_{50} for almost all bNAbs (Jonckheere–Terpstra, $p < 0.05$).
- IC_{50} values positively correlated with genetic distance for all bNAbs (3BNC117 shown as an example; Spearman, $p < 0.05$), demonstrating the impact of viral diversification on evolving neutralization phenotypes.

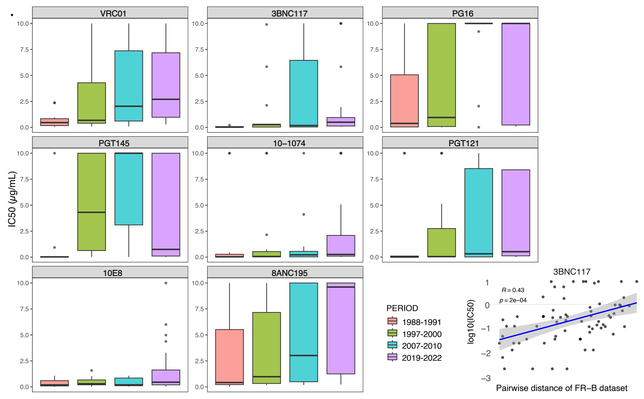
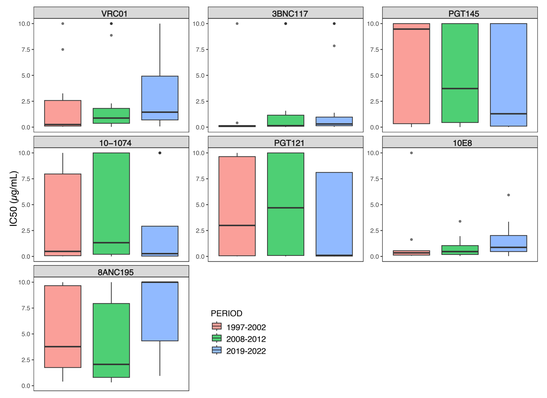


Figure 4: Temporal trends in CRF02_AG neutralization sensitivity to bNAbs

- Significant temporal increases in IC_{50} for several bNAbs but not those apex-directed (Jonckheere–Terpstra, $p < 0.05$).
- This highlights subtype-specific evolutionary and antigenic dynamics.



		VRC01	3BNC117	PG16	PGT145	10-1074	PGT121	10E8	8ANC195
GEOMETRIC MEAN IC50	4 Periods	1,398	0,196	1,545	0,816	0,182	0,276	0,315	1,931
	1988-1991	0,411	0,024	0,339	0,039	0,090	0,048	0,168	0,672
	1997-2000	1,091	0,129	0,781	2,091	0,095	0,175	0,281	1,240
	2007-2010	1,640	0,215	5,419	3,676	0,135	0,297	0,216	2,026
	2019-2022	2,341	0,514	2,133	0,770	0,397	0,676	0,519	3,618
Jonckheere test (p-value)		*0.0008*	*<0.0001*	*0.012*	*0.07*	*0.01*	*0.003*	*0.049*	*0.001*

		VRC01	3BNC117	PGT145	10-1074	PGT121	10 E8	8ANC195
GEOMETRIC MEAN IC50	3 Periods	0.947	0.291	1.248	0.459	0.643	0.492	3.532
	1997-2002	**0.428**	**0.129**	1.364	0.483	0.895	**0.361**	**3.500**
	2008-2012	**0.885**	**0.271**	1.580	0.693	1.060	**0.408**	**2.100**
	2019-2022	**1.473**	**0.458**	0.903	0,284	0.288	**0.704**	**6.278**
Jonckheere test (p-value)		*0.02*	*0.03*	*0.77*	*0.79*	*0.91*	*0.03*	*0.01*

	% of viruses IC50 below 0.1				% of viruses IC50 superior or equal to 1			
	1987-1991	1996-2000	2006-2010	2019-2022	1987-1991	1996-2000	2006-2010	2019-2022
VRC01	18,2	6,7	7,1	0,0	18,2	46,7	57,1	**73,7**
3BNC117	**72,7**	40,0	42,9	15,8	0,0	20,0	28,6	26,3
PG16	45,5	26,7	7,1	10,5	36,4	46,7	**92,9**	**84,2**
PGT145	**81,8**	6,7	7,1	10,5	9,1	60,0	**85,7**	52,6
10-1074	**72,7**	60,0	42,9	41,2	18,2	20,0	21,4	41,2
PGT121	**72,7**	60,0	42,9	11,8	18,2	26,7	42,9	58,8
10 E 8	45,5	20,0	21,4	23,5	18,2	13,3	14,3	11,8
8ANC195	9,1	0,0	0,0	0,0	36,4	46,7	57,1	**94,1**

	% of viruses IC50 below 0.1			% of viruses IC50 superior or equal to 1		
	1997-2002	2008-2012	2019-2022	1997-2002	2008-2012	2019-2022
VRC01	30,0	10,0	0,0	30,0	50,0	75,0
3BNC117	40,0	34,8	8,3	10,0	30,4	33,3
PGT145	16,7	11,5	25,0	58,3	61,5	58,3
10-1074	30,0	21,7	25,0	40,0	52,2	41,7
PGT121	33,3	26,9	33,3	58,3	57,7	66,7
10E8	20,0	8,7	16,7	20,0	26,1	33,3
8ANC195	0,0	0,0	0,0	90,0	65,2	100,0

Table 2: Predicted coverage of single bNAbs and combinations against a panel of 166 HIV-1 T/F viruses (1988–2022).

- Combinations of multiple bNAbs outperform single antibodies in predicted coverage and potency.

Best single bNAb and combinations using additive model predictions and target concentration = 1.0 ug/ml for viruses sampled from 1988-2022.

Combination	Class	IC50 Geometric Mean	Coverage at IC50 < 1.0 ug/ml
10-1074+10E8+3BNC117+PG16	CD4bs+MPER+V1/V2-glicano+V3-glicano	0.02716	100.0
10-1074+10E8+3BNC117	CD4bs+MPER+V3-glicano	0.04379	100.0
10-1074+N6	CD4bs+V3-glicano	0.08778	95.8
N6	CD4bs	0.28666	84.1

TAKE HOME MESSAGES

- **HIV-1 evolution over time** is accompanied by measurable changes in bNAbs sensitivity over time at the population level, with **subtype-specific evolutionary trajectories**.
- **Across all viruses and subtypes of our T/F panel, multi-epitope bNAb combinations** achieve the highest predicted breadth and potency, outperforming single antibodies and mitigating subtype-specific differences.
- **Genotype-based algorithms imperfectly predict in vitro susceptibility.**
- Correlation of *in vitro* results with clinical efficacy in ongoing trials is needed, along with continuous surveillance of neutralization sensitivity

CONTACT INFORMATION

H. Fritsch – hegger.fritsch@univ-tours.fr / hegger.fritsch@chu-orleans.fr;
K. Stefic – karl.stefic@univ-tours.fr
INSERM U1259 MAVIVHe, 10 boulevard Tonnellé, 37000 Tours, France

ACKNOWLEDGEMENTS

We thank the participants of the ANRS PRIMO cohort and the clinicians who referred them to the study. Financial support was provided by ANRS MIE (grant ECTZ229440)