SUSCEPTIBILITY TO bNAbs OF TRANSMITTED HIV-1 VARIANTS AMONG RECENT INFECTIONS IN FRANCE

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BACKGROUND

Pre-existing resistance to broadly neutralizing antibodies (bNAbs) restrains their use for prevention and treatment of HIV infection. In addition, an increasing resistance of HIV to neutralization over time has been observed arguing for a prospective monitoring of the sensitivity to bnAbs of all prevalent HIV subtypes. Here, we analyzed the susceptibility to bNAbs of HIV transmitted variants among recently infected individuals in France with a focus on evolution over time.

METHODS

- We assessed the sensitivity to seven bnAbs against a panel of **73 early-transmitted subtype B and CRF02_AG viruses** (the most prevalent subtypes in Europe) over a 25-year period of the French epidemic (1987-2012).
- **Samples were obtained during acute/recent infection** from individuals included in the ANRS PRIMO cohort.
- Env pseudoviruses were constructed and neutralization assays on TZM-bl cells were performed using bnAbs targeting the CD4-binding site (CD4bs; VRC01, 3BNC117), the V1/V2-glycan region (PG9, PGT145), the V3-glycan region (PGT121, 10-1074), and the gp41 membrane proximal external region (MPER; 10E8).

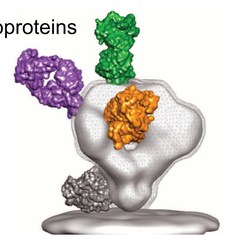
1985 1990 1995 2000 2005 2010

	Historical		Contemporary
B	11	15	14
CRF02_AG	-	10	23

IMPORTANCE : subtype B and CRF02AG are the 2nd (12.1%) and 4th (7.7%) most prevalent genotypes worldwide, respectively (1st and 2nd in France). CRF02AG represents 46.2% of viral subtypes in West Africa ((Hemmelaar et al. Lancet ID 2019, Visseaux et al. JAC 2020).

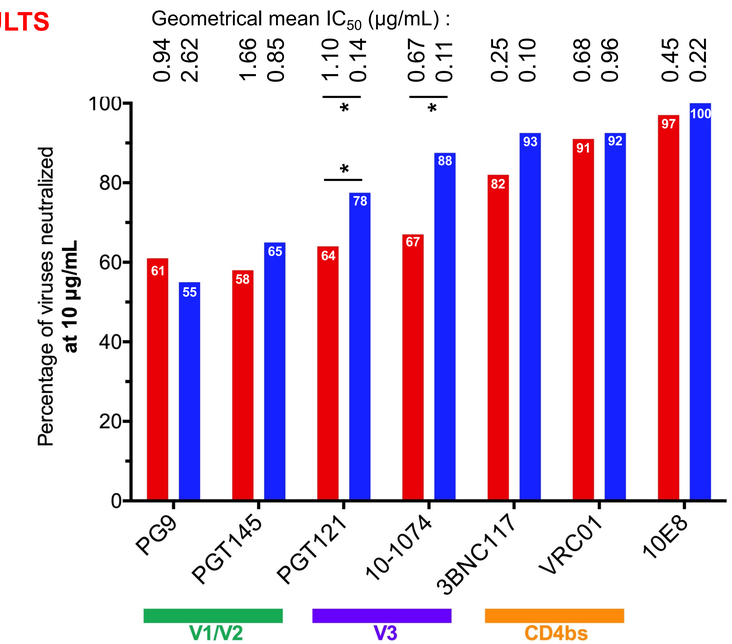
bNAbs target sites on the HIV-1 Env glycoproteins (F. Klein et al. Science 2013)

Grey : Env trimer
Green : V1/V2 site (PG9, PG145)
Purple : V3 supersite (PGT121, 10-1074)
Orange : CD4bs (VRC01, 3BNC117)
Dark grey : MPER (10E8)

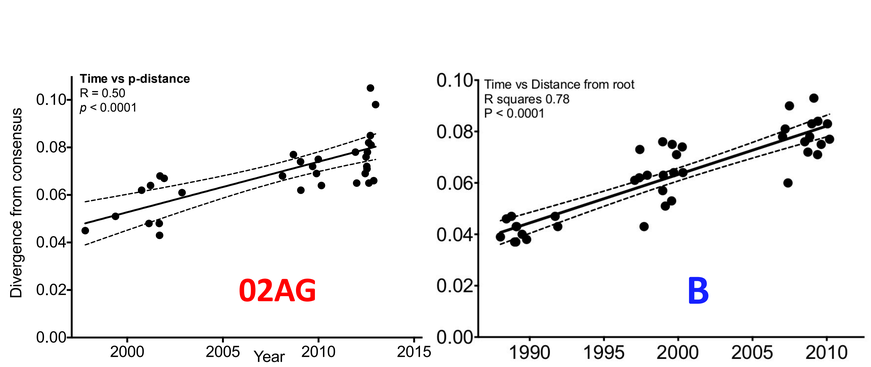


Viruses **resistant to bNAbs** are transmitted in France, requiring the use of **bNAb combinations to prevent the risk** of failure if used for PrEP or therapy. The drift of HIV-1 toward higher resistance to bNAbs will necessitate a continuous surveillance.

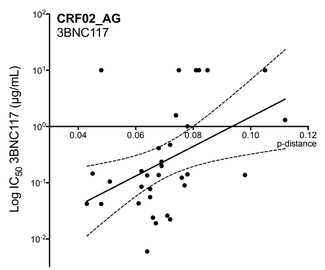
RESULTS



- Neutralizing data shows that viruses with IC_{50} > 10 µg/mL, e.g. highly resistant to neutralization, circulate, representing 35%-45% for bNAbs targeting the V1V2 domain, 12-36% for V3 and 7-18% for CD4bs and MPER. VRC01 neutralized 92% of all variants at the target concentration of 10 µg/mL. 3BNC117 IC_{50}s were the lowest of all bNAbs (respectively 0.01 et 0.25 µg/mL for B and CRF02_AG variants; Mann-Whitney P<0.05)
- CRF02AG were more resistant to bNAbs targeting V3 [significant difference in IC_{50}, number of strains resistant at 10 µg/mL and 1 µg/mL (not shown)]. This was associated with the loss of the potential site of N-glycosylation N332.



- Genetic distance from a consensus B or CRF02_AG correlates with calendar year and increases over time. Sequences were codon-aligned with CRF02_AG consensus sequence. After exclusion of hypervariable region, evolutionary divergence was estimated by distance matrix.
- IC_{50} values of a majority of bNAbs were positively correlated with genetic distance, indicating an increase in resistance with HIV-1 diversification in time. An example of correlation analysis with 3BNC117 and CRF02AG viruses and a sum up of correlation analyses are shown.



Correlation analysis : genetic distance *vs* IC_{50}	*P values*									
	PG9	PGT145	PGT121	10-1074	3BNC117	VRC01	NIH45-46^{G54W}	N6	10E8	8ANC195
B	0.04	< 0.01	0.04	0.25	0.04	0.03	0.05	/	0.18	0.04
CRF02AG	0.995	0.698	0.388	0.302	0.002	0.057	0.012	0.911	0.198	0.600

CONCLUSIONS

- Of the bNAbs in clinical development tested here, none neutralized 100% of T/F variants, indicating that combinations will be required to achieve a full coverage.
- As in other countries, we confirmed the natural drift of HIV-1 towards higher resistance to bNAbs for the most prevalent subtypes circulating in France, arguing for a continuous surveillance of HIV transmitted variants around the globe. We are currently updating the data with strains transmitted in 2017-2018.

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