The Barrier to HIV-1 Escape from Broadly Neutralizing Antibodies Varies Between Different HIV-1 Isolates

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Alex C. Stabell[1,2], Debby J. Park[2], Songhee Lee[2],Christy L. Lavine[4], Sebastian Majia Espinosa[4], Viren A. Baharani[2,3], Michael S. Seaman[4], Michel C. Nussenzweig[3,5], Marina Caskey[3] Paul D. Bieniasz[2,5],Theodora Hatziioannou[2].

1 Weill Cornell, Department of Infectious Diseases, New York, NY, 10065, USA; 2 Laboratory of Retrovirology, The Rockefeller University, New York, NY, 10065, USA; 3 Laboratory of Molecular Immunology, The Rockefeller University, New York, NY, 10065, USA; 4 Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.; 5 Howard Hughes Medical Institute, The Rockefeller University, New York, NY, 10065, USA

Background

Broadly neutralizing antibodies (bNAbs) against HIV-1 have re-invigorated research into antibody therapies and vaccination strategies for prevention, treatment, and cure because of their unique ability to neutralize diverse HIV-1 strains. While many HIV-1 isolates are initially susceptible to bNAbs, their ability to acquire resistance is unknown. Understanding the evolutionary barriers to bNAb resistance will inform the feasibility of using bNAbs as HIV-1 prevention, treatment, and cure.

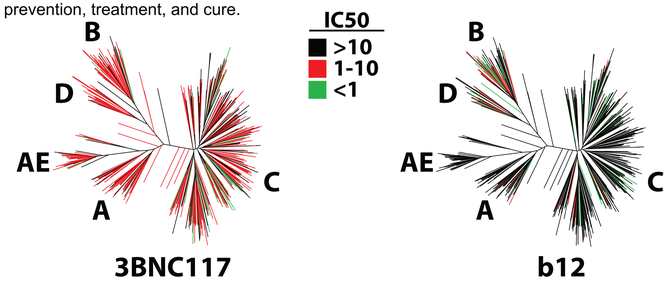
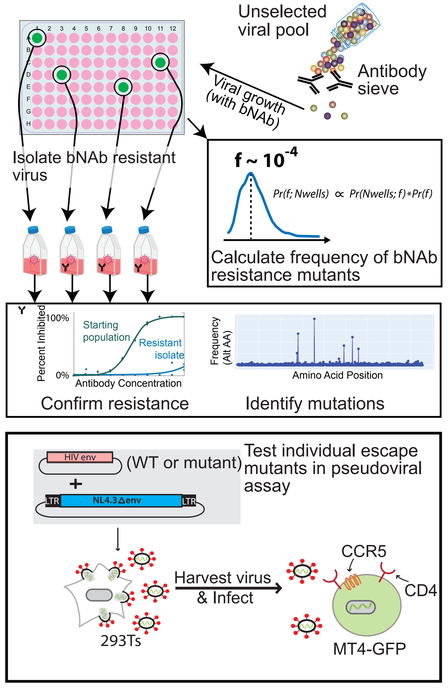


Figure 1: The inhibitory concentration that reduces the infectious titer by 50% (IC50) is mapped onto the same phylogeny for two CD4 binding site antibodies (3BNC117 and b12). 3BNC117 is more “broadly neutralizing” than b12.

Hypothesis

I hypothesize the genetic barrier to resistance is low for the broadly neutralizing antibody 3BNC117 and 10-1074 and most HIV-1 strains will only require a single amino acid change to gain resistance to each antibody.

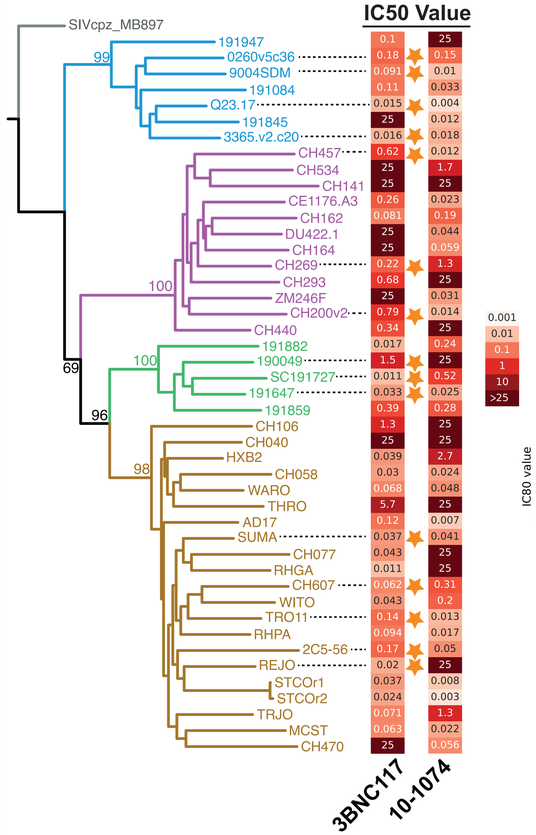
Methods



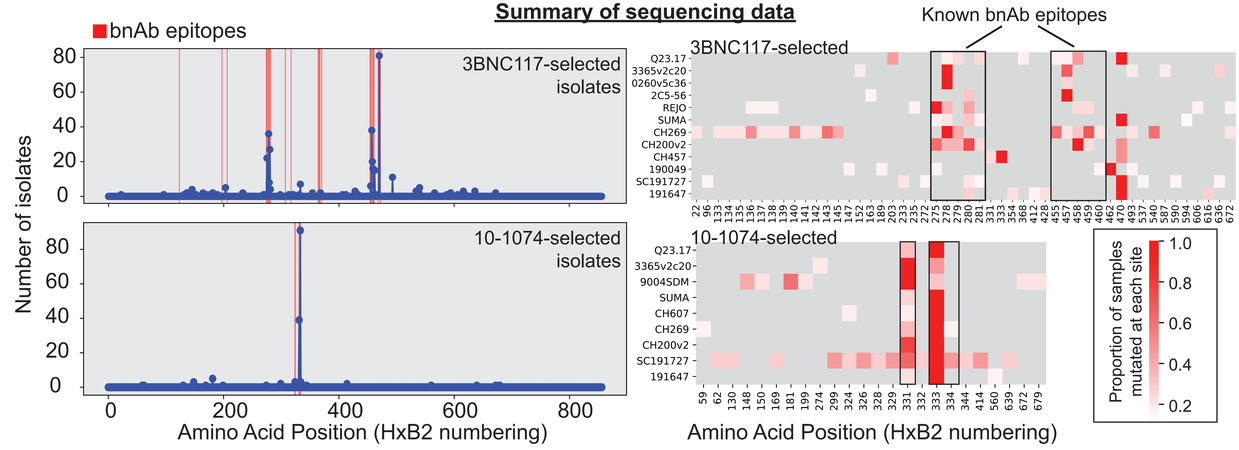
Overview of experimental procedure:
Each viral isolate used is replicated in MT4 cells in the absence of antibody to generate genetic diversity. This genetically diverse viral population is infected at 500 viruses per well in a 96-well plate in the presence of 3BNC117 or 10-1074. Spreading infection is monitored in an MT4 cell line that has a GFP reporter that indicates when the cells are infected. When there is evidence of antibody resistance (i.e. GFP-positive cells), the virus is grown in bulk culture in the presence of antibody and phenotypically characterized by confirming antibody resistance as well as short read sequencing to identify putative resistance mutations. The frequency of 3BNC117-resistance mutations is also estimated by using the known number of viruses used to infect each well and the number of wells that showed evidence of 3BNC117 resistance.

Results

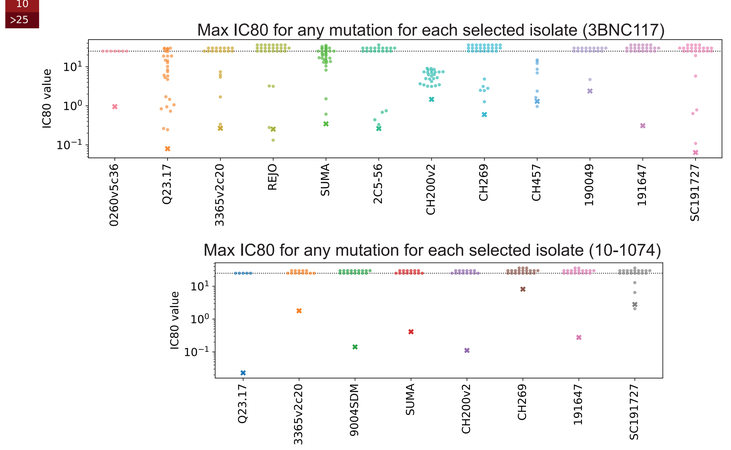
Phylogeny of HIV-1 group M with strains used in this study marked with

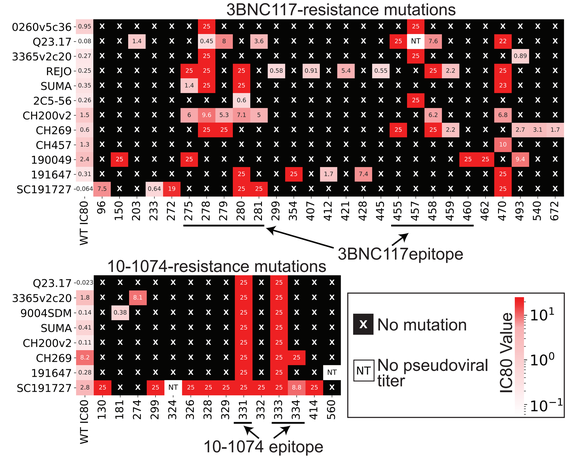


Summary of sequencing data

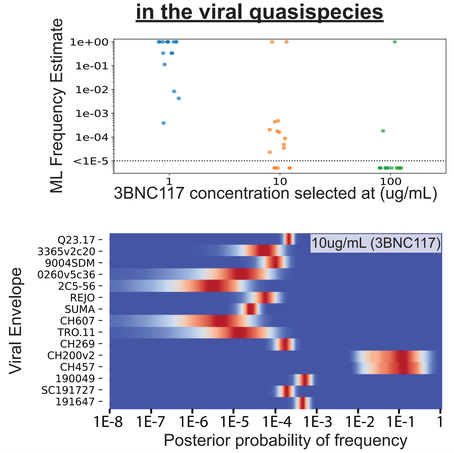


Characterization of Individual bnAb Escape Mutations

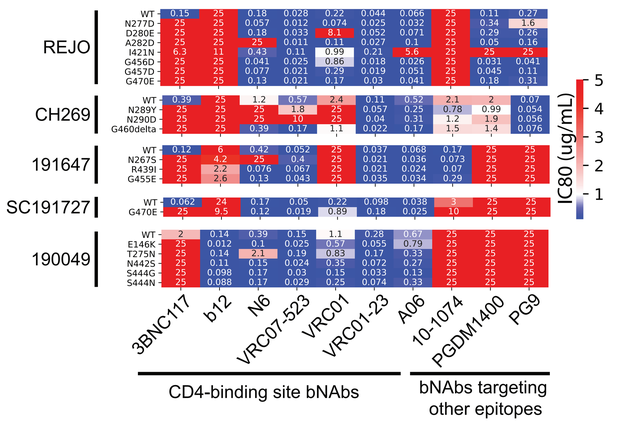




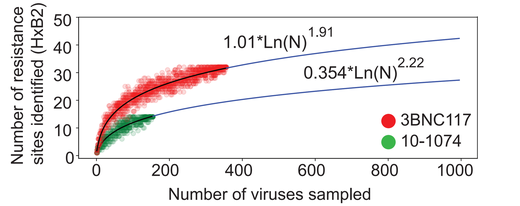
Phenotypically-estimated Frequence of bnAb-resistance in the viral quasispecies



Effect of 3BNC117-resistance mutations on other bnAbs



Rate of discovery of novel bnAb resistance sites



Conclusions

- Resistance develops in the viral quasispecies at different frequencies and is dependent on the starting genetic isolate
- Single amino acid substitutions in HIV-1 envelope were sufficient to confer a many orders-of-magnitude increase in inhibitory concentration for both 3BNC117 and 10-1074
- Resistance mutations selected for 3BNC117 can confer resistance to additional bnAbs, even those targeting different epitopes