IDENTIFICATION OF NOVEL HIV-1 ENVELOPE MUTATIONS THAT CONFER RESISTANCE TO VRC01

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Abstract

The Antibody Mediated Prevention Trials showed that passively infused VRC01, a potent and broadly neutralizing antibody, was able to protect individuals against HIV-1 infection if they were exposed to sensitive viruses. However, breakthrough HIV-1 infections occurred when individuals in the VRC01 arms were exposed to viruses either resistant to VRC01 or to sensitive viruses when participants were in a VRC01 serum trough. We identified seven individuals with multi-lineage breakthrough HIV-1 infections, where one variant was resistant to VRC01 but another was VRC01 sensitive. By comparing the Env sequences of the resistant and sensitive clones from each participant, we identified mutations that were predicted to confer differential VRC01 neutralization phenotypes. These mutations were reverted to sensitive residues by site-directed mutagenesis, and the wildtype and mutant envelopes were screened against VRC01 and other CD4 binding site antibodies in TZM-bl neutralization assays. In four of the seven pairs of clones, a single mutation was sufficient to confer sensitivity to VRC01. In each case, the mutations responsible for the differential neutralization phenotypes occurred at different sites across the Env, such as 279 and 280 in loop D, 369 in the CD4 binding-loop and 459 between β23 and the V5 loop. In two cases, the resistant backbones were mutated (through generation of chimeras) to contain either the entire V1V2 region or the β23-V5 loop of their matched sensitive clones. This resulted in the transfer of 8 or 20 amino acid mutations to confer VRC01 neutralization sensitivity. We were unable to identify the mutations conferring VRC01 resistance in one participant, where the resistant and sensitive clones differed by both length and 100 amino acid changes. Interestingly, all VRC01 resistant clones were sensitive to other, clinically relevant, related CD4 binding-site bNAbs, such as VRC07-523 LS and N6, which are being tested in future passive immunization trials. Further studies will investigate the kinetics of VRC01 resistance mutations within the AMP multi-lineage transmissions over time.