

**POSTER 2****DEFINING THE STRUCTURAL AND FUNCTIONAL ROLES OF MUTATIONS IN gp120 ASSOCIATED WITH THE EMERGENCE OF HIV-1 CLINICAL RESISTANCE TO THE CCR5 ANTAGONIST VICRIVIROC**

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Previous studies using heterologous chimeric envelopes showed that a C2-V5 domain from a vicriviroc (VCV)-resistant lab-adapted HIV-1 strain was sufficient to transfer resistance to a susceptible clone<sup>1</sup>. Here we used the same strategy to analyze the determinants of resistance from an HIV env gene isolated from a subject that exhibited viral rebound in a VCV clinical trial. C2-V5 env domains obtained at baseline and at study discontinuation were cloned from one subject isolate (#91) into an ADA gp160 expression vector. The chimeric HIV-1 env gene from subject #91 contained 6 amino acid changes in the V3 loop and one change in the C4 region relative to the baseline clone. Pseudoparticles generated with this env were completely resistant to VCV. Mutation of residues E315Q/ G321R and F317L in the tip and the stem of the V3 loop region from the resistant env restored complete and partial susceptibility to VCV, respectively; whereas mutation of V3 loop residues N320D and K328E and the C4 amino acid change R429G significantly reduced pseudovirus infectivity but did not alter the resistant phenotype. Individual forward mutagenesis of each of the 6 amino acid residues associated with resistance was not sufficient to confer the resistant phenotype to the baseline chimeric gp120. Structural modeling<sup>2</sup> of the resistant env demonstrated that specific mutations identified in the V3 loop map to putative binding domains for the ECL2 and N-terminal regions of CCR5.

Overall, we have identified residues in the stem and tip region of the V3 loop of this isolate that are important for VCV resistance and other likely compensatory mutations in the V3 stem, base and C4 region that affected viral infectivity. Individual point mutations introduced into the baseline clone failed to confer resistance, suggesting that a combination of mutations is necessary for VCV resistance. Currently, no consistent pattern of VCV resistance mutations has been identified; however results from this study suggest that mutations in the V3 loop and C4 region can be important determinants of the resistant phenotype.

1. Ogert et al., 2008 Virology 373, p387
2. Huang et al., 2007 Science 317, p1930