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# HIV Escape From Peptide Fusion Inhibitors

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HIV envelope glycoprotein (Env) mediates infection by fusing virus with cellular membranes. Fusion inhibitors, a new class of antiretroviral drugs, inhibit HIV infection by binding to gp41 to form a peptide-gp41 6HB that is fusion-incompetent. To understand resistance mechanisms to peptide fusion inhibitors that will aid development of new drugs, we generated an escape-mutant virus against an N-peptide inhibitor. We found that two mutations in gp41, one each in the N- and C- heptad repeats, confer early resistance to the N peptide. These same mutations also confer resistance to a C peptide inhibitor. This is the first report of cross-resistance among peptide fusion inhibitors. Curiously, the N mutation alone or in combination with C mutation also conferred increased sensitivity to soluble CD4 and was associated with faster growth kinetics and larger syncytia. These results suggest global changes in Env involving receptor activation and fusion kinetics. Using thermal denaturation studies, involving N and C peptides containing wild type (Nw or Cw) or resistance residues (Nm or Cm), which self-assemble into a 6HB, we showed that the N mutation improved the energetics of the viral 6HB, however, the energetics of the 6HB formed with the inhibitor and the N and C peptides is not afffected. Thus, our results demonstrate a resistance pathway that appears to involve both kinetic and thermodynamic factors that regulate virus entry and work indirectly to reduce the ability of fusion inhibitors to bind Env.