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Two strategies have been proposed for the rationale design of vaccine immunogens that elicit broadly neutralizing antibodies against HIV-1. One strategy involves exploiting functional constraints, focusing on regions of the envelope where function requires conservation and exposure. This strategy has lead to the identification of coreceptor-binding-site antibodies as well as antibodies reactive with the site of T-20 binding. One drawback of this strategy, however, is the limited potency of the antibodies thus far identified. A second strategy involves the characterization of rare broadly neutralizing antibodies such as 2G12, 2F5, 4E10 and b12. Unfortunately, strains of virus resistant to these antibodies evolve with relative ease. We used X-ray crystallography to define functional constraints related to binding of the CD4 receptor and found that the site of initial CD4 contact on gp120 is the epitope for the broadly neutralizing antibody, b12. Functional analysis allowed us to transcend the particulars of b12 binding to focus on the conserved site of initial CD4 contact. The results suggest that a combination of functional analysis and potent antibody characterization may provide design clues necessary to create immunogens capable of eliciting potent broadly neutralizing antibodies.