Based on mutagenesis and structural studies of human immunodeficiency virus (HIV) envelope proteins, the loop region of gp41 is thought to directly interact with gp120. The importance of the HIV gp41 loop region to envelope function has been systematically examined by alanine scanning of all gp41 loop residues and the subsequent characterization of the mutagenic effects on viral entry, envelope expression, envelope processing, and gp120 association with gp41. With respect to the wild-type gp41, mutational effects on viral entry fall into four classes as follows: 1) little or no effect (G594A, S599A, G600A, K601A, N602A, G603A, V608A, and K617A); 2) significantly reduced entry (I595A, L602A, I603A, V608A, and K617A); 3) abolished entry (L593A, W596A, G597A, T606A, W610A, W614A, S618A, and I622A); and 4) enhanced entry (T605A, P609A, S613A, E620A, and Q621A). The reduced functionality of many mutants was apparently due to either disruption of envelope processing (L593A and T606A), viral incorporation of the envelope (W610A, W614A, and I622A), or increased dissociation of gp120 (W596A, G597A, and S618A). The extreme sensitivity of the gp120-gp41 interaction to alanine substitution (e.g. the G597A and S618A mutants are relatively conservative substitutions) suggests that this association is an attractive and novel target for future drug discovery efforts.

Infection with the human immunodeficiency virus (HIV) begins when the virus particle attaches to the cell surface and the viral membrane fuses with the target cell membrane, thereby allowing entry of the viral genetic material (reviewed in Ref. 1). The viral envelope proteins gp120 and gp41, which form a non-covalent complex on the viral surface, play critical roles in viral attachment and membrane fusion (2). gp120 mediates the attachment step via interactions with CD4 and chemokine co-receptors found on the surface of target cells (3), and gp41 mediates the membrane fusion step. The critical roles of gp120 and gp41 suggest that they are potential targets for future antiviral therapies.

There is a relatively large amount of structural information available for the envelope proteins of HIV and the analogous envelope proteins of simian immunodeficiency virus (SIV). For example, there is a crystal structure of the HIV gp120 core domain in a ternary complex with domains of the CD4 receptor and an antibody that binds to the co-receptor binding site (4). Moreover, there is extensive information on the extracellular domains, or ectodomains, of HIV and SIV gp41 from x-ray, NMR, and molecular modeling studies (5–12). In the case of the crystal structures of gp41, these domains lack a conserved loop region that connects the N- and C-helices (5–7, 10, 11). In contrast, the NMR structure of the SIV gp41 ectodomain includes the central loop (8, 9). At present, there is no structural information available for the gp120-gp41 complex; however, based on previous mutagenesis studies, the central loop of gp41 is one site of non-covalent interactions with gp120 that are critical to HIV entry (13–17). Other regions of gp41, such as the N-helix, have also been implicated in forming a direct interaction with gp120 (18). In the present study, we present the first systematic mutation study of the importance of each gp41 loop residue to gp41 function with the long-term goal of identifying gp41 regions that are attractive sites for drug intervention.

MATERIALS AND METHODS

Mutants were prepared from plasmid pHXB2 (19) using the Stratagene QuikChange II XL site-directed mutagenesis kit with subsequent verification by DNA sequencing. The functionality of gp41 mutants was determined in a luciferase-based entry assay (20). For this assay, plasmids pHXB2 (bearing wild-type or mutant gp41) and pNL4–3.Luc.R-E–(20) were co-transfected by calcium phosphate precipitation into 293T cells, which were maintained in Dulbecco’s medium with 10% fetal calf serum, 1 mM L-glutamine, 1% penicillin-streptomycin, and 0.5 mg/ml G418. Forty-eight hours post-transfection, the medium was harvested and filtered through a 0.45-micron filter to make the virus stock. For an assay of viral entry, U87/CD4/CXCR4 cells (3), which were maintained in Dulbecco’s medium with 15% fetal bovine serum supplemented with 1 mg/ml purinocin, 300 μg/ml G418, 1% L-glutamine, and 1% penicillin-streptomycin, were seeded at 1 × 10^6 cells/well to a 12-well cell culture plate in a volume of 1 ml. The following day, 500 μl of the virus stock was added to each of the wells of the U87 cells after removal of the medium. The plates were incubated overnight at 37 °C in a CO2 incubator. After ~16 h, the virus was aspirated and replaced with US7 medium, and the cells were allowed to rest for another 24 h. Luciferase activity was measured using the luciferase assay system from Promega and a Berthold FB12 luminometer running Sirius software. The experiments were run in triplicate from transfection to assay of luciferase activity and, thus, the uncertainties represent all parts of the experiment. For Western blot analysis, the 293T cell lysates were collected using lysis buffer (50 mM Tris (pH 7.5), 150 mM NaCl, 5 mM EDTA, 0.5% Nonidet P-40, and 0.1% SDS). The virus pellet was prepared by ultracentrifugation on a cushion of 20% sucrose at 55,000 rpm for 1 h using a Beckman SW55Ti rotor. The pellets were re-suspended in the lysis buffer described above. Cell lysates and virus pellets were normalized for total protein concentration using the Coomassie protein assay kit (Pierce) and p24 expression by Western analysis. After electrophoresis, transfer, and blocking (washing with Tris-buffered saline plus 0.1% Tween 20 (TBST) and subsequent blocking with TBST plus 5% dry milk for gp41 and SuperBlock (Pierce) for gp120), the blots were probed with either goat anti-HIV-1 gp120 polyclonal antibody (United States Biological) or mouse anti-HIV-1 gp41 monoclonal antibody (Chessie 8; National Institutes of Health AIDS Research and Reference Reagent Program). The secondary antibody used was peroxidase-conjugated.
AffiniPure rabbit anti-goat (Jackson ImmunoResearch Laboratories, Inc.) or anti-mouse IgG (H+L) (Bio-Rad).

RESULTS

Design of gp41 Loop Mutants—Based on the NMR structure of the SIV gp41 ectodomain (8,9), the HIV-1 loop is expected to consist of 30 residues (amino acids 593 to 622 of HXB2 HIV-1), which are shown in Fig. 1. With respect to the gp41 of HIV-2 and SIV, there is a four-residue insertion in the HIV-1 gp41 loop (amino acid sequence ASWS). Disrupting the insertion, 12 of the remaining 26 residues are conserved between HIV-1, HIV-2, and SIV to give 46% sequence identity. In the present study, 26 alanine substitutions of the HIV-1 gp41 loop region were generated (Fig. 1). The conserved cysteines at positions 598 and 604 were not substituted, because a previous study suggested that single-site mutations result in improperly processed protein (21).

Viral Entry of gp41 Loop Mutants—The effects of the gp41 mutations on viral entry were first assayed by a luciferase-based assay in which viral entry is proportional to the observed luciferase activity (20). As shown in Fig. 2 and summarized in Table I, the effects of the mutations range from the near complete abolishment of viral entry (e.g. L593A) to significant enhancement of viral entry (e.g. T605A). The mutants can be divided into the following four categories: 1) no effect with respect to virus expressing wild-type gp41 (defined as 40–160% of wild-type entry); 2) decreased viral entry (defined as 2–10% of wild-type entry); 3) abolished viral entry (defined as <2% of wild-type entry); and 4) enhancement of viral entry (defined as >200% of wild-type entry). Category 1 mutants, which exhibit minimal effects on viral entry, include G594A, S599A, G600A, K601A, N611A, S615A, N616A, and L619A. In general, this class of residues is not conserved among the three viral families (Fig. 1). Exceptions are Asn-616 and Leu-619, for which the alanine substitutions exhibit little effect on viral entry despite conservation in HIV-2 and SIV gp41 (Fig. 1). The results for the

![Amino acid sequence alignment of HIV-1, HIV-2, and SIVsm gp41 loop regions (22). Glycosylation sites occur at Asn-611 and Asn-616. Residues that are substituted by alanine are denoted on the bottom line. Numbering corresponds to that of HIV-1 HXB2.](Image 2)

![Luciferase reporter assay for viral entry. The bar graph is presented on a log scale. The error bars represent the S.D. of three separate experiments.](Image 3)
Mutagenesis of the HIV gp41 Loop

| Mutant | Infectivity | gp160 cells | gp120 cells | gp41 cells | gp120 virus | gp41 virus |
|--------|-------------|-------------|-------------|------------|-------------|------------|
| WT$^a$ | 100         | +++         | +++         | +++        | ++          | +++        |
| L593A  | 1           | +++         | —           | —          | —           | —          |
| G594A  | 160         | +++         | +++         | +++        | ++          | ++         |
| E595A  | 7           | +++         | +           | +          | +           | +          |
| W596A  | 1           | +++         | —           | +          | —           | —          |
| G597A  | 1           | +++         | —           | —          | +           | —          |
| S599A  | 140         | +++         | +++         | +++        | +           | +          |
| G600A  | 60          | +++         | +++         | +++        | +           | +          |
| K601A  | 54          | +++         | +++         | +++        | +           | +          |
| L602A  | 2           | +++         | +++         | +++        | +           | +          |
| L603A  | 8           | +++         | +++         | +++        | +           | +          |
| T605A  | 460         | +++         | +++         | +++        | +           | +          |
| T606A  | 1           | +++         | —           | —          | —           | —          |
| V608A  | 7           | +++         | —           | —          | —           | —          |
| P609A  | 210         | +++         | +++         | +++        | +           | +          |
| W610A  | 1           | +++         | —           | —          | —           | —          |
| N611A  | 63          | +++         | +++         | +++        | +           | +          |
| S613A  | 230         | +++         | +++         | +++        | +           | +          |
| W614A  | 7           | +++         | +++         | +++        | +           | +          |
| S615A$^b$ | 43        | +++         | +++         | +++        | +           | +          |
| N616A  | 70          | +++         | +++         | +++        | +           | +          |
| K617A  | 9           | +++         | +           | +          | +           | +          |
| S618A$^b$ | 1         | +++         | +++         | +++        | +           | +          |
| L619A  | 86          | +++         | +++         | +++        | +           | +          |
| E620A  | 230         | +++         | +++         | +++        | +           | +          |
| Q621A  | 220         | +++         | +++         | +++        | +           | +          |
| I622A  | 1           | +++         | +           | +          | +           | +          |

*a* Wild-type.

*b* gp41 shifted to a lower molecular weight, suggesting a higher degree of glycosylation.

TABLE I
Summary of viral entry and the level of gp160, gp120, and gp41 detected in the cell lysates and virus of the wild-type and alanine mutants of HIV gp41

Gp120 association was based on qualitative analysis of Western blots of cell lysates and virus where — is <10%, + is 10–40%, ++ is 40–70%, and +++ >70%.

Reduced incorporation into the virus; (iv) decreasing the affinity of the interaction between gp41 and gp120, thereby resulting in dissociation (or "shedding") of gp120 into the media; or (v) the formation of a gp41-gp120 complex that cannot support the attachment or fusion steps of viral entry. On the other hand, mutational enhancement of viral entry could be due to the following: (i) increased envelope expression, stability, or incorporation resulting in increased concentration of envelope proteins at the virus surface; (ii) enhancement of the gp120-mediated viral attachment step; or (iii) enhancement of the gp41-mediated membrane fusion step. Many of these scenarios can be distinguished by a Western blot analysis of the envelope present in cell lysates or virus. For example, the presence of gp160 in cell lysates reflects expression, the presence of gp41 in cell lysates demonstrates processing, the presence of gp41 in virus demonstrates incorporation into the viral particle, and the presence of gp120 in cell lysates and the virus indicates that gp120 is associated with gp41 and is not shed into the media. In Fig. 3, a Western blot analysis of the wild-type and mutant envelope proteins present in cell lysates is presented. In addition, we have probed for the presence of gp41 and gp120 in virus to corroborate the results of the cell lysates and to establish incorporation of gp41 and gp120 into the virus. A summary of the two assays is presented in Table 1. In the case of the wild-type, the cell lysates exhibit all three envelope species, and, thus, the envelope is expressed and processed, and gp120 remains associated with gp41, as expected. The category 1 mutants (G594A, S599A, G600A, K601A, N611A, S615A, N616A, and L619A), which are those that exhibit minimal effects on viral entry, exhibit a pattern of envelope proteins that is similar to that of the wild-type, as would be expected. In the case of the category 2 mutants (L593A, L602A, I603A, V608A, and K617A), which are those mutants that exhibit a significant deleterious effect on viral entry but do not abolish it, a variety of causes is implicated by the Western blot analyses. For example, I595A and I603A exhibit gp41 in the cell lysates, but the low levels of gp41 in the virus suggests that gp41 has been inefficiently incorporated into the virus. Low levels of gp41 and gp120 are observed in both cell lysates and the virus of V608A, indicating that the mutation has partially disrupted envelope processing and perhaps gp120 association with gp41. On the other hand, gp41 is observed in both cell lysates and the virus of K617A, but gp120 is reduced, suggesting that shedding of gp120 may be significant. Interestingly, L602A exhibits wild-type-like levels of gp41 and gp120 and, thus, its lower functionality is apparently due to either perturbation of the gp120-mediated attachment step or perturbation of the gp41-mediated membrane fusion step. In the case of the category 3 mutants (L593A, W596A, G597A, T605A, W610A, W614A, S618A, and I622A), the observed functionalities are apparently due to a variety of causes. For example, the low levels of gp41 in the cell lysates and viruses of L593A, T605A, W610A, W614A, and I622A suggest that these mutants are not efficiently processed. On the other hand, W596A, G597A, and S618A exhibit the presence of gp41 in cell lysates and viruses but significantly reduced levels of gp120, which suggests that these mutations cause shedding of gp120. Interestingly, S618A would be expected to abolish the glycosylation of Asn-616. Indeed, the S618A gp41 exhibits a lower molecular weight in Fig. 3, which is consistent with this notion. In light of the observations for N616A, which would also abolish the glycosylation of residue 616 but exhibits little effect on viral entry, the reduced functionality of S618A most likely arises from a direct interaction between Ser-618 and gp120 and not from the absence of glycosylation at Asn-616. Finally, in the case of the category 4 mutants (T605A, P609A, S613A, E620A, and Q621A), which are those that enhance viral entry, all of these mutants exhibit a similar pattern as the wild-type in cell lysates and viruses and, thus, they are expected to act by enhancing the viral attachment and/or membrane fusion steps.
is evidenced by low levels of gp41 in cell lysates and the virus. gp41, as evidenced by the presence of gp41 and the absence of mutation, was due to the dissociation of gp120 from the ectodomain. Interestingly, previous studies of mutations to Leu-593, Thr-605, and Ile-603 have characterized mutant W596M, which similarly exhibited reduced function in the absence of gp120 dissociation (13). In another study, Cao et al. observed that V608S abolished syncytia formation due to the mutants T605A and P609A, which were found to exhibit enhanced viral entry with respect to the wild-type, and, thus, it is tempting to suggest that they cause a reorientation of the gp120 ectodomain with respect to gp41. Finally, it is of interest to consider the location of the mutations in the structure of gp41. As noted above, there is a high-resolution structure of the SIV gp41 loop available from x-ray or NMR studies (8, 9), but no structural information is available for the HIV gp41 loop from x-ray or NMR studies (10). Of special interest are the nonnative disulfide mutants—of particular interest are the SIV gp41 loop (Fig. 4). Mutations that significantly decrease viral entry are colored orange; mutations that abolish viral entry are colored red; mutations that increase viral entry are colored green. Coordinates of HIV gp41 were taken from the model by Caffrey (12), which is based on the NMR structure of the SIV gp41 ectodomain (9). Single letter amino acid abbreviations are used with position numbers.

**TABLE II**

| Mutant | Ref. 16 fusion (gp120) | Ref. 17 fusion (gp120) | Present work fusion (gp120) |
|--------|------------------------|------------------------|-----------------------------|
|        | %                      | %                      | %                           |
| WT     | 100 (+ + +)            | 100 (+ + +)            | 100 (+ + +)                 |
| L593A  | 16 (—)                 |                         |                             |
| K595A  | 95 (+ + +)             | 7 (+ +)                |                             |
| W596A  | 45 (—)                 | 1 (—)                  |                             |
| W596F  | 53 (+ + +)             |                         |                             |
| W596L  | 15 (+)                 |                         |                             |
| G597A  | 7 (—)                  |                         |                             |
| G597P  | 7 (—)                  |                         |                             |
| G597S  | 7 (—)                  |                         |                             |
| K601A  | 54 (+ + +)             |                         |                             |
| K601E  | 35 (+)                 | 95 (+ + +)             |                             |
| K601H  | 103 (+ + +)            |                         |                             |
| K601Q  | 77 (+ + +)             |                         |                             |
| T606A  | 0 (—)                  | 1 (—)                  |                             |
| W610A  | 0 (—)                  | 1 (—)                  |                             |
| W610F  | 8 (—)                  |                         |                             |
| W610H  | 9 (—)                  |                         |                             |
| S613A  | 8 (+ + +)              | 230 (+ + +)            |                             |
| W614A  | 1 (—)                  |                         |                             |

* Fusion levels were determined by a cell-cell fusion assay, and the gp120 association was based on qualitative analysis of Western blots of cell lysates (where — is <10%, + is 10–40%, ++ is 40–70%, and +++ is >70%).*

Mutagenesis of the HIV gp41 Loop

**DISCUSSION**

**Previous Studies of gp41 Loop Mutants**—As discussed in the Introduction, a number of previous studies have characterized the effects of single-site mutations in the HIV gp41 loop, and, thus, it is of interest to compare the conclusions of these studies in light of the present work. Table II, we have summarized our results along with those from two previous studies that characterized some similar gp41 loop mutations in a similar manner (16, 17). In general, the membrane fusion properties are in agreement with the exception of I595A, which exhibited significant effects to viral entry in our assay in contrast to a previous report (17). Note that in both studies the I595A mutation did not appear to result in significant dissociation of gp120 (Table II). Differences in mutational effects can be attributed to different assays of envelope function (e.g. cell-cell fusion or viral entry). In the case of mutations to Lys-601, 605, and 609, all previous studies suggest little impairment of function and little effect to gp120 association, a result that is in agreement with our characterization of K601A (Table II). Moreover, Cao et al. (13) observed that V608S abolished syncytia formation due to a lack of gp120 association with gp41, a result that is similar to our results for V608A. Previous mutations to Trp-596 and Gly-597 suggested that the mutations impaired function due to dissociation of gp120, which is in agreement with the results presented herein (Table II). An exception is the relatively conservative mutation W596F, which exhibited reduced function in the absence of gp120 dissociation. In another study, Cao et al. have characterized mutant W596M, which similarly exhibited decreased function in the absence of gp120 dissociation (13). Interestingly, previous studies of mutations to Leu-593, Thr-605, Trp-610, and Trp-614 suggested that the impaired function of mutations was due to the dissociation of gp120 from gp41, as evidenced by the presence of gp41 and the absence of gp120 in cell lysates (16, 17). In contrast, our observations of the equivalent mutations indicate that they are improperly processed and/or that gp41 is not incorporated into the virus, as evidenced by low levels of gp41 in cell lysates and the virus.
fusio" form, in which the N- and C-helices are not associated, to a "fusio" form in which the N- and C-helices are associated (reviewed in Ref. 25, but for an alternative model cf. Ref. 9). Consequently, the loop structure presented in Fig. 4 may only represent the fusion conformation; however, the proposed conformational changes occur in the helical domains, and we are not aware of any evidence that suggests that the loop region, which includes a conserved disulfide bond, undergoes a large change in structure. Thus, we feel that the structure shown in Fig. 4 represents the best available model for the HIV gp41 loop. In this discussion, mutants that have little or no effect on viral entry (i.e. category 1) are not considered further. The side chains of mutants that significantly decrease viral entry (i.e. category 2) are colored orange (Fig. 4). The side chains of mutants that essentially abolish viral entry (i.e. category 3) are colored red (Fig. 4). The side chains of mutants that enhance viral entry (i.e. category 4) are colored green (Fig. 4). Based on the Western blot analysis presented above, mutant L593A abolishes viral entry by reducing processing, and Gly-597 abolishes viral entry by causing dissociation of gp120. As is apparent in Fig. 4, the side chains of Leu-593 and Gly-597 are not exposed (i.e. they occur in the gp41 interior), suggesting that their effects are propagated to nearby residues that bind directly to gp120 (however, an alternative interpretation is that the gp41 loop is in a different conformation and that in this conformation Leu-593 and Gly-597 are exposed). Mutants W596A, L602A, I603A, T606A, V608A, W610A, W614A, K617A, and S618A, which exhibit significantly reduced viral entry, are clearly located on the exterior of the gp41 loop, a region that has been suggested by previous mutagenesis studies to be the site of gp120 binding (cf. discussion above). In the cases of the mutants T606A, W610A and W614A, the reduced viral entry is apparently due to decreased processing and/or incorporation into the virus. In the case of mutants W596A, V608A, K617A, and S618A, they exhibit significant dissociation of gp120, which suggests that the mutation disrupts stabilizing interactions with residues of gp120. Accordingly, these results can be used to map the apparent binding surface of gp120 on the surface of gp41 (Fig. 4). Interesting exceptions of this group include L602A and I603A, which exhibit normal gp120 binding and, thus, their non-functionality is apparently due to disruption of gp120-mediated viral attachment (e.g. through long-range propagated effects) or alternatively due to disruption of gp41-mediated membrane fusion (e.g. by binding to gp120 with higher affinity and thereby not allowing gp120 to dissociate from gp41, or by preventing a necessary reorientation). We note that the SOS mutation of the HIV envelope, which has a nonnative disulfide bond between gp41 residue 605 and a residue of gp120 (15), is clearly located within the proposed binding face. Moreover, the SOS mutant has been shown to bind to the receptor but is only functional for viral entry upon reduction of the disulfide bond, which indicates that dissociation or reorientation of the gp41-gp120 complex is critical to viral entry (26, 27). Interestingly the side chains of mutants T605A, P609A, S613A, E620A, and Q621A, which exhibit enhanced viral entry, all occur on the gp41 exterior as shown by Fig. 4. As discussed above, their increased efficacy could be directed at either the gp120-mediated attachment step or the gp41-mediated fusion step. In light of the sensitivity of gp120 binding to this region of the gp41 loop, we favor the latter explanation. In any case, future in vitro and in vivo studies of the L602A and I603A, which greatly inhibit viral entry, and the T605A, P609A, S613A, E620A, and Q621A, which enhance viral entry, are clearly warranted to better understand envelope function. For example, more conservative substitutions could be probed to give greater insight into the structure-activity relationship of the side chain. Finally, we note that many of the substitutions that exhibit the largest results are relatively conservative. For example, substitution of glycine by alanine (G597A) or substitution of serine by alanine (S618A) results in abolished function due to dissociation of gp120. This suggests that the gp120-gp41 interaction is relatively labile in vivo and may indicate that this interaction presents an attractive and novel site of therapeutic intervention. Accordingly, mutation sites that disrupt gp120 binding can be used in two ways for the design of antivirals as follows: (a) the mutation sites define the target site; or (b) the structure of the wild-type side chain that forms the interaction with gp120 could potentially serve as a template for rational drug design.

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