Structural deviations of mutant HIV-1 glycoprotein-120 (gp120) compared to the wild type gp120 explain the failure of passive immunization.

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Passive immunization strategy for neutralizing the HIV-1 antigens has been a failure due to highly error-prone and rapid replication of the virus which incorporates mutations in the viral proteins. The glycoprotein-120 (gp120) is coded by the viral envelope gene and is exposed to the host immune system during HIV-1 infection. However, due to mutations in gp120, the antibodies produced by the host neutralize the viral particles unsuccessfully. In this communications, we evaluated the structural deviations of one of the gp120 mutants compared to the wild type gp120 and conclude that the mutation are capable of generating structural deviations that are as small as 10 Å to the highest deviation being >35 Å, measured between the C-alpha atoms. These structural deviations explain in part the failure of passive immunization strategy. In light of this study, we believe that such structural studies will help further to improve the passive immunization strategy in the future.

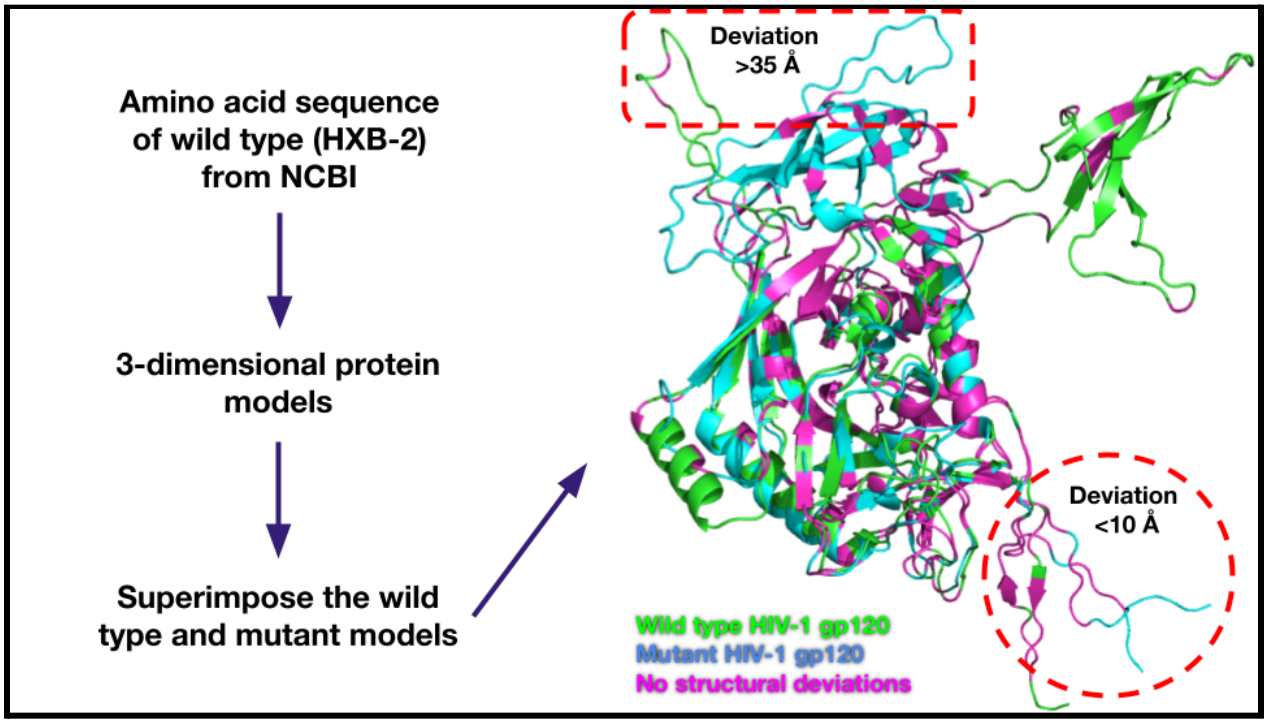

Figure 1. Overall workflow of comparing the 3D models to evaluate the structural deviations in HIV-1 gp120 mutants.

HIV-1 glycoprotein-120 (gp120) is very critical for successful viral replication as it helps the virus to bind and enter the host $CD4^+$ T-cells. The viral gp120 is one of the surface proteins that is exposed to the host immune system hence it is a desirable target for passive immunization strategies to neutralize the viral particles (1). However, mutations in gp120 pose a threat to the currently existing neutralizing antibodies used for passive immunization. In this study the structural deviations of a mutant gp120

was evaluated against the wild type gp120 as shown in Figure 1. The amino acid sequences of wild type (HXB-2 strain) gp120 and the clinical mutant (ATN variant) gp120 were obtained from the hivmut.org (2). The sequences were then uploaded to the SWISS MODEL server (3, 4) to build 3-dimensional models of both separately. These models were then superposed onto each other to evaluate the structural deviations using molecular graphics software.

Once both the models are properly superposed, then the C-alpha root mean square deviation (RMSD) was calculated wherever there was an apparent structural deviation. RMSD values <1 Å were ignored due to protein flexibility and anything >2 Å was considered for the analysis. During this analysis, the side chain RMSDs were ignored. Except for the core of the protein, most of the domains showed considerable RMSD values ranging from 10 Å to >35 Å as shown in Figure 1. In spite of such significant RMSD values, 50% of the two models aligned with <1 Å RMSD values indicating that the mutant gp120 did not lose its structural integrity needed for its function in helping the viral entry into the host cells. Mutant gp120 variants with high structural deviations would pose a high threat to the currently existing antibodies. During superposition of the two models, certain parts did not align well because of the amino acid sequence difference arising from the severe mutations. Such non-aligned domains of the mutant models were carefully analyzed to understand whether the high RMSD value contributes to the failure of passive immunization. The details provided here are based on only one mutant and is not enough to make any plausible conclusions on the structural deviations and needs more mutant models to support our hypothesis (5). Furthermore, the 3-dimensional model building software may or may not be robust to fill the gaps of discontinuous sequence in the mutant models owing to the huge sequence diversity thus generating a limitation to the structural analysis of these models. In future, various servers could be used to build these mutant models to test whether the model building servers have differences in building the diverse mutant models of gp120.

Currently, we are in the process of building more than 100 mutant models to evaluate their structural deviations from the wild type to make suggestions for the improvement of passive immunization strategies in the future. The data obtained from the *in silico, in vitro* and *in vivo* studies will be published in the future issues of TCABSE-J.

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