Evaluation of structural deviations in HIV-1 gp-120 clinical mutant models to guide the HIV-vaccine design towards passive immunization.

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Human immunodeficiency virus type-1 (HIV-1) infection causes a multi-symptomatic syndrome known as the acquired immunodeficiency syndrome (AIDS) by weakening the human immune system thus giving a chance for opportunistic pathological conditions. Rapid and error-prone replication of HIV-1 is one of the major causes for the failure of anti-retroviral therapy as well as passive immunization thus limiting the possibilities for vaccine design. In this study, the structural model of wild type HXB2 HIV-1 envelope protein, gp-120 was compared against the molecular models of 170 known clinical mutant HIV-1 gp-120. Major structural deviations were observed in the mutants that explain the failure of passive immunization strategies used as a part of the treatment. These structural deviations will further be used to understand the full spectrum of antibodies that are needed to neutralize the structurally distorted gp-120 clinical mutants towards designing a vaccine. This study provides plenty of structural insights into the structural flexibility seen in the HIV-1 gp-120 clinical mutants providing basis for future antibody engineering.

Keywords: HIV/AIDS, Vaccines, clinical mutants, drug-resistance, computational modeling.

Acquired immunodeficiency syndrome (AIDS) is caused due to accumulation of opportunistic pathological conditions such as bacterial, fungal and viral infections including Kaposi's Sarcoma due to weak immune system. The human immuno -deficiency virus type-1 (HIV-1) infection targets the $CD4^+$ T-cells in the human immune system. Loss of such infected T-cells leads to a weaker immune system. Due to the rapid and error-prone replication process of HIV-1, the viral genome incorporates random mutations that result in the production of mutant viral proteins with altered structures. For example, the glycoprotein 120 (gp120) of HIV-1 is one of the viral proteins that is exposed to the outside of the viral envelope and can be detected by the human immune system. However, due to mutations in gp120, the antibodies produced by the host immune system fail to neutralize the mutant variants of gp120 and pose a threat to the passive immunization therapies (1). Along these lines, it has been a very challenging task to design a vaccine. In this study we hypothesized that one can generate the 3-dimensional models of all the available clinical isolates of gp120 and evaluate the structural deviations compared to the wild type (HXB2 strain) HIV-1 gp120 model. By understanding and evaluating the structural deviations of all the possible mutant variants of HIV-1 gp120 compared to the wild type HXB-2 one can redesign the currently used antibodies for better potency in the future.

HXB2	00GBAC4001	02CM_0016BBY	A32989	1058_11	04CM_632_28
ANT	VI991	CM53657	BO02_BOL119	HXB2_LAI_III..	02CM_A1394
MVP5180	VI997	05MYKL045_1	01BR125	BK132	96CM_1849
98CMU2901	56	05MYKL007_1	PE02_PCR0155	BREPM11948	97GA_TB45
ANT70	96CM_4496	JKT194_C	03BRRJ327	BREPM12313	97CD_MBFE185
99SE_MP1300	95CM_1816	OUR2478P	UY04_4022	BREPM12609	92UG037
U14788	MP818	569M	ARMA159	BREPM12817	92RW008
RBF168	J11233	05GX001	01BR087	02CD_MBTB047	05AF094
GR84_97PVMY	J11451	CM240	04BRRJ179	02CD_KS069	05AF026
94CY032_3	03GH173_06	A280	07BR_FPS625	97CD_KTB119	05AF095
GR11_97PVCH	BFP90	01CM_4412HAL	96FR_MP411	97ZR_EQTB11	00CMNYU1162
04ZASK146	EE0359	ELI	CH80	96CM_MP535	00CMNYU830
ETH2220	EE0369	KNH1254	03BRRJ103	97CDKTB49	01CM_0001BBY
XJDC6431_2	06CM_BA_040	KER2003	93BR020_1	04CD_FR_KZS	02CM_3097MN
nx2	J11243	KSM4001	FIN9363	CM53379	POC44951
95IN21068	J11223	94UG114	VI850	CU68	IBNG
97CNGX_6F	DRCBL	96TZ_BF071	P1942	CU14	CM53392
XJDC6441	92NG083	96TZ_BF061	X2457_2	97KR004	00CMNYU926
98CN009	J11456	96TZ_BF110	luBF_05_03	01CM_1445MV	CU29
110PA	HH8793_12_1	04BRRJ115	X623	KNH1271	CU38
04BR142	X2456_2	04BRSQ46	X605	97CDKTB48	CU7
BR025_d	PT2695	05BRRJ200	00PTHDE10	94CY017_41	SIVcpzMT145
04BR137	CB378	VI1310	99TH_R2399	pBD6_15	US_Marilyn
04CMU11421	CB118	UY04_3987	M169	PS1044_Day0	YBF30
J_97DC_KTB14..	CB347	UY05_4752	99TH_MU2079	00IC_10092	DJO0131
SE9280_7887	CB471	AR02_ARG1139	BREPM16704	99DE4057	
N26677	Cu103	X492	671_00T36	96GH2911	
N18380	95CM_MP255	VI961	BREPM119	95SN1795	
N28353	95CM_MP257	A32879	KAL153_2	97CM_MP814	

Table 1. List of gp120 clinical mutants.

Materials and Methods: The HXB2 gp120 amino acid sequence was obtained from the online HIV clinical mutations database (https://hivmut.org) (2). This sequence was then submitted to the SWISS MODEL server (https://swissmodel.expasy.org/) to generate a 3-dimensional model of HXB2 gp120 (3, 4). Similarly, the amino acid sequences of more than 100 gp120 clinical mutants were taken from the database and were submitted to the SWISS MODEL server. All the 3-dimensional models were then downloaded and structural analysis was performed using PyMOL. The 3-dimensional models of each of the gp120 mutants were superposed onto the 3-dimensional model of the HXB2 (5).

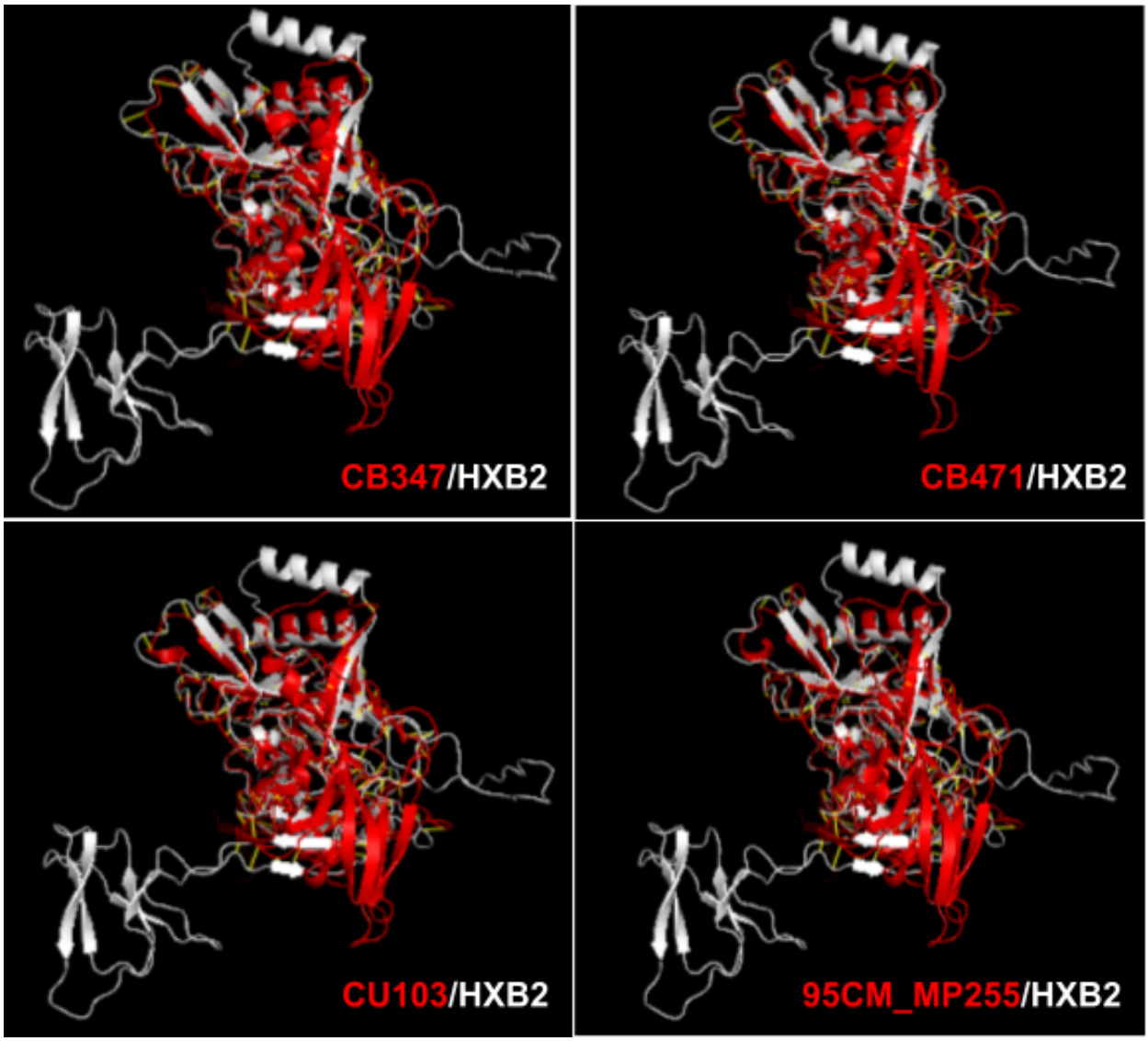

Figure 1. Structural deviations of representative mutants (red color) vs. HXB2 (white color).

The C-alpha to C-alpha distances were measured wherever a structural deviation was noticed. If the deviation was less than or equal to 1 Å then it was ignored as insignificant owing to the protein backbone flexibility. However, any structural deviations more than 1 Å were considered for the current analysis as significant. Ramachandran plots were automatically generated by the SWISS MODEL server.

Results and Discussion: Structural analysis of 169 clinical mutant HIV-1 gp120 models in comparison to the wild type (HXB-2) revealed significant structural deviations indicating that the mutations in gp120 indeed cause major challenges in maintaining the proper antigen shape that can be consistently recognized by the neutralizing antibodies resulting in the failure of passive immunization therapies. All mutants showed at least a minimum deviation of >10 Å with respect to HXB2.

Interestingly while building the homology models of some of the mutants of gp120, we observed that the sequence alignment was low due to which the model building protocol might have deviated. However, we are currently in the process of checking the possibility of this issue by using other model building servers and software. Along these lines, we decided to analyze the relative deviations among the mutants with respect to the wild type, HXB-2 instead of absolute deviations of each mutant. During this process, we clustered the mutant models into similarity clusters based on their sequence homology. After building the models the actual comparison was performed within each cluster and between clusters. The cluster analysis will be published in the future issues of TCABSE-J.

Conclusion: Based on the current study, it is evident that re-designing the neutralizing antibodies is needed to improve the potency of the passive immunization therapy owing to the large structural deviations in the clinical mutants of HIV-1 gp120 models compared to the wild type, HXB-2. In future, this data will be used for antibody engineering and vaccine design to protect humans from HIV-1 infection. HIV-1 vaccine related data will be published in the future issues of TCABSE-J.

Supplementary data: Supplementary data for this article is available online along with this article.

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Conflict of interest: This research article is an ongoing project currently at TCABS-E, Rajahmundry, India. The authors invite collaborations without any conflict of interest.