Table S1 related to Figure 2. Details of the N12-i3 and N5-i5 interfaces based on the N12-i3/N5-i5 Fab-gp120$_{93TH057}$core$_e$+N/C-M48U1 and N5-i5-gp120$_{93TH057}$core$_e$-CD4 structures as calculated by the EBI PISA server (http://www.ebi.ac.uk/msd-srv/prot_int/cgi-bin/piserver).

		N12-i3 Fab (1)-gp120$_{93TH057}$ core$_e$+N/C-M48U1	N12-i3 Fab (2)-gp120$_{93TH057}$ core$_e$+N/C-M48U1	N5-i5 Fab (1)-gp120$_{93TH057}$ core$_e$+N/C-M48U1	N5-i5 Fab (2)-gp120$_{93TH057}$ core$_e$+N/C-M48U1	N5-i5 Fab-gp120$_{93TH057}$ core$_e$-CD4 (4H8W)
Buried Surface Area, Å²	**gp120 total**	**831**	**780**	**924**	**920**	**918**
	8-stranded β-sheet	781	731	0	0	0
	Layer 1	50	49	746	753	756
	Layer 2	0	0	178	167	162
	Layer 3	0	0	0	0	0
	Heavy chain total	**764**	**659**	**686**	**668**	**679**
	FWR	22	10	4	4	3
	CDR H1	46	33	75	75	77
	CDR H2	446	434	386	372	366
	CDR H3	250	182	221	217	233
	Light chain total	**141**	**142**	**326**	**291**	**278**
	FWR	0	0	0	0	2
	CDR L1	9	10	129	130	112
	CDR L2	0	0	47	34	29
	CDR L3	132	132	150	127	135
	Heavy and light chain total	**905**	**801**	**1012**	**959**	**957**

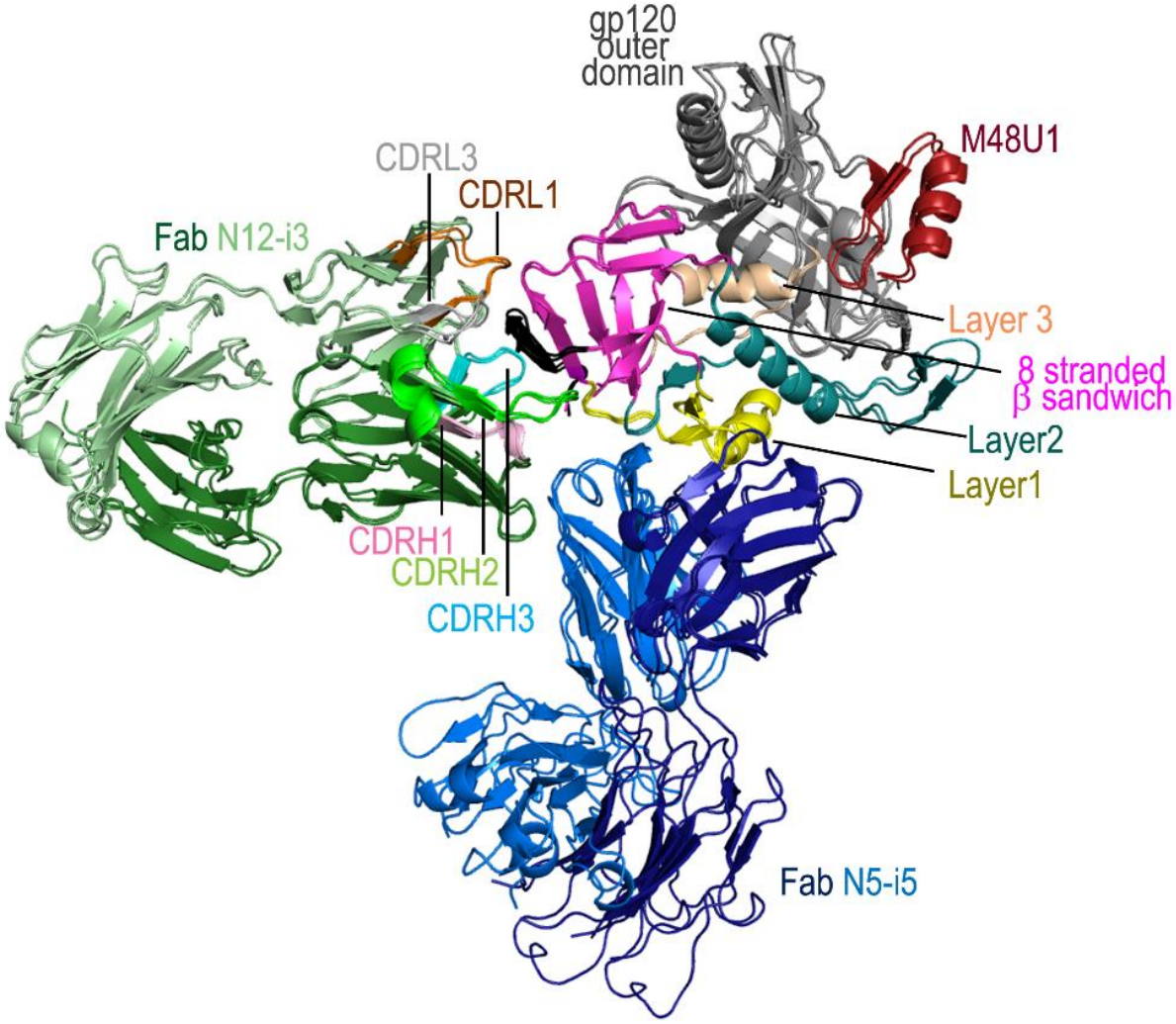

Figure S1 related to Figure 1. Comparison of the two copies of the N12-i3 Fab/N5-i5 Fab- N/C-termini-gp120$_{93TH057}$ -core$_e$-M48U1 complex from the asymmetric unit of crystal. The root mean square deviation (RMSD) between copies is 3.1 Å for all residues and 1.13 Å for all residues except the N5-i5 Fab constant region reflecting the different relative position of this region between copies. The N5-i5 Fab constant region had few crystal contacts and high B-factors in contrast to the N5-i5 Fab variable region which was well defined in the electron density. gp120 mobile regions and N12-i3 Fab CDRs are colored as shown. By binding the edge of the β-sheet at the eighth strand, N12-i3 is able to grasp both sides burying 1753 Å^2 (copy 1) [or 1632 Å^2 (copy 2)] total surface area at the interface. N5-i5 binds layers 1 (yellow) and 2 (dark teal) of the inner domain almost identically to its structure in the absence of N12-i3 (PDB: 4H8W).

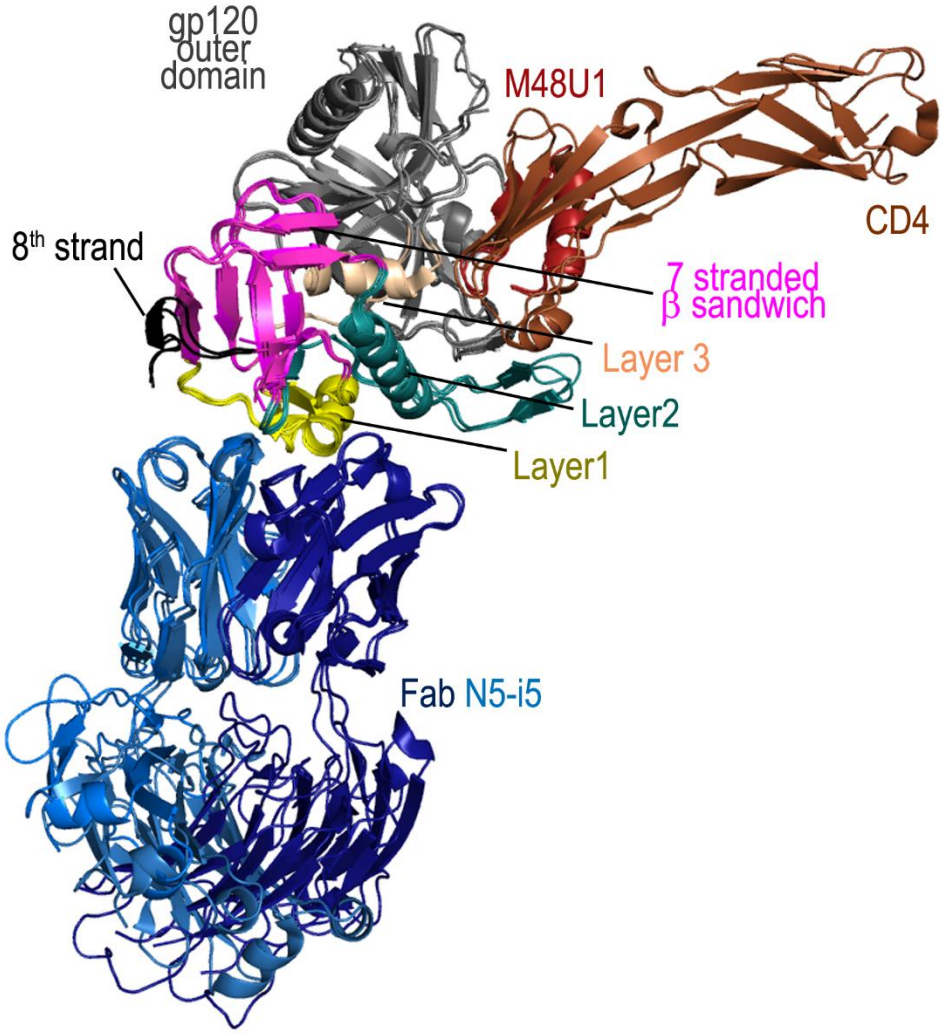

Figure S2 related to Figure 2. Comparison of N5-i5 bound to Env antigen in N12-i3 Fab/N5-i5 Fab- N/C-termini-gp120$_{93TH057}$ -core$_e$-M48U1 complex and N5-i5 Fab- gp120$_{93TH057}$ -core$_e$-*d1d2*CD4 complex (PDB: 4H8W, (Acharya et al., 2014)). Structures were superimposed based on gp120 molecule. The RMSD between gp120 and the N5-i5 variable region to 4H8W is 0.758 Å (copy 1) and 0.760 Å (copy 2). The RMSD between gp120 and the full N5-i5 Fab to 4H8W is 5.71 Å (copy 1) and 7.66 Å (copy 2). The larger RMSD values for the full complex are largely due to the differing positions of the N5-i5 constant region between copies in the crystal and between crystals and not structural changes within the Fab constant region.

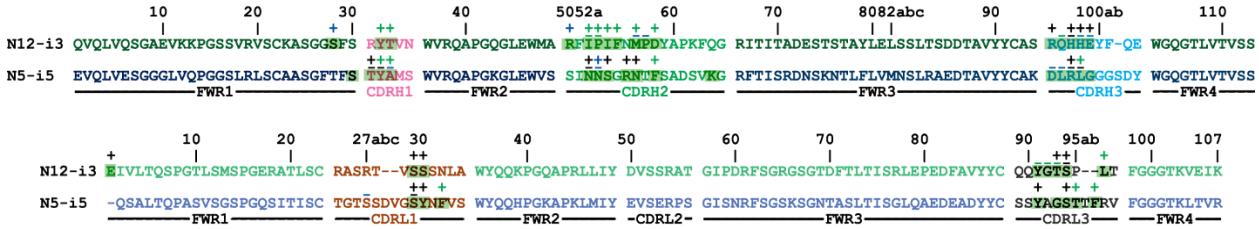

Figure S3 related to Figure 3. Antibody contact residues. mAb side chain (+) and main chain (-) contact residues colored green for hydrophobic, blue for hydrophilic and black for both as determined by a 5 Å cut off value over the corresponding sequence. CDRs are colored as in Figure 2 and 3 and buried surface residues as determined by PISA are shaded.

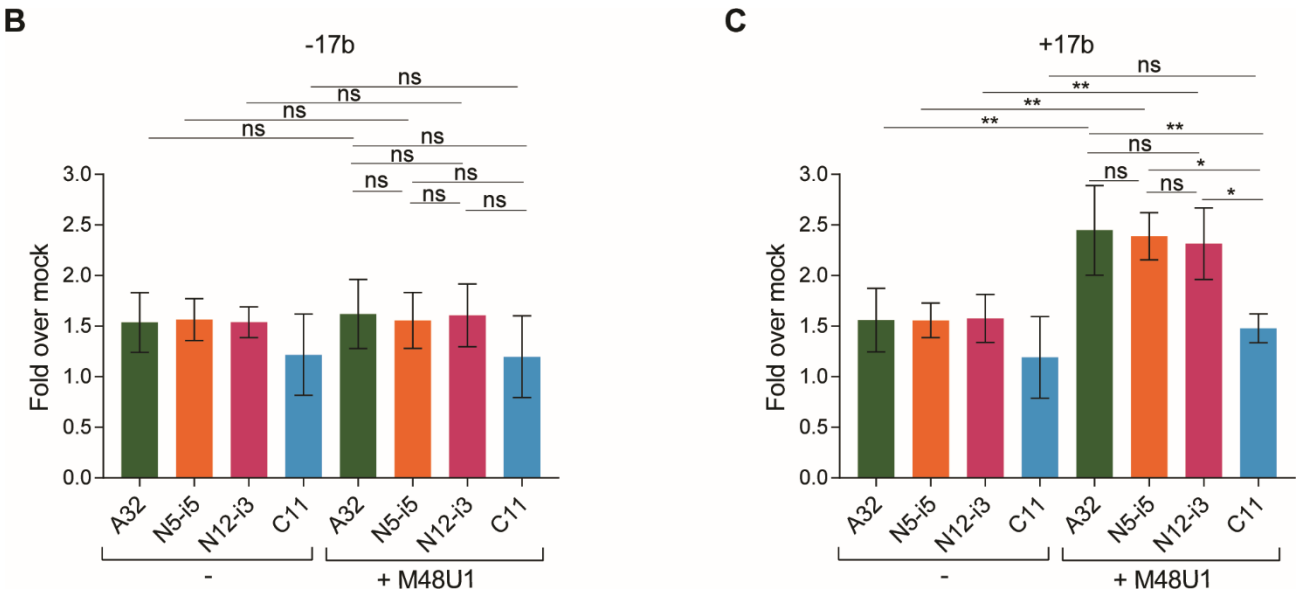

Figure S4 related to Figure 5. Exposure of Cluster A epitopes within the CEM.NKr cells infected with HIV-1NL-4.3 ADA/GFP virus. CEM.NKr cells were infected with HIV-1NL-4.3 ADA GFP virus, and 48h post-infection cells were stained with Alexa Fluor 647 labeled Cluster A mAbs in presence or absence of M48U1 (100nM) and/or mAb 17b (5µg/ml). The binding is shown as a mean and standard deviation of the mean fluorescence intensity over mock-infected cells. Data are the averages of four independent experiments. Statistical significant was evaluated using paired student t test, * P <0.05, ** P <0.01; ns, not significant.

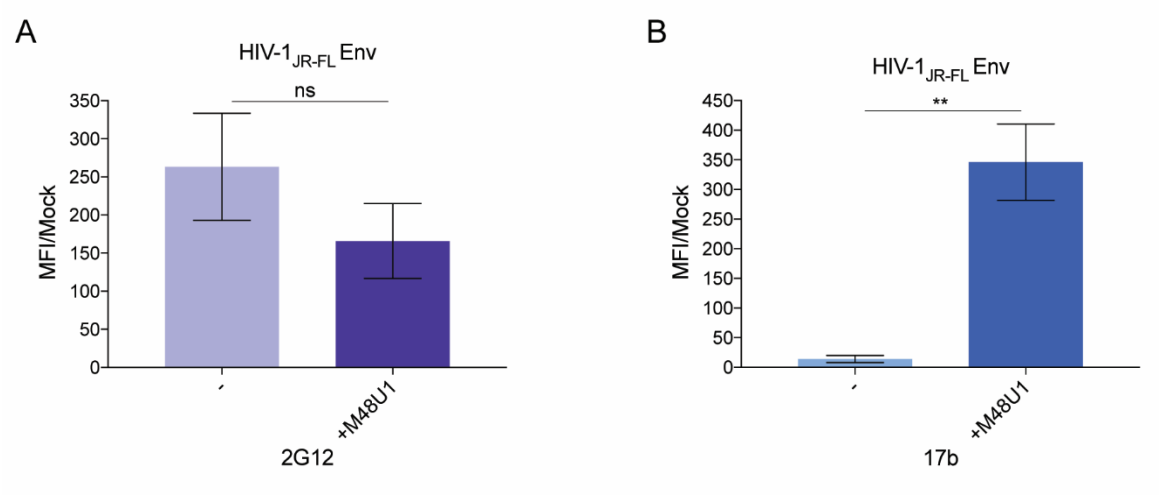

Figure S5 related to Figure 5. M48U1 exposes the 17b epitope at the surface of Env_{JRFL} expressing cells. 293T cells were transfected with an empty vector pcDNA3.1 plasmid or a plasmid expressing the cytoplasmic-tail-deleted HIV-1 Env_{JRFL}. Two days post-transfection Env expression was evaluated with the 2G12 antibody which recognizes the gp120 outer domain in the presence or absence of CD4 mimetic-M48U1 (100nM) by flow cytometry as described in Experimental Procedures.