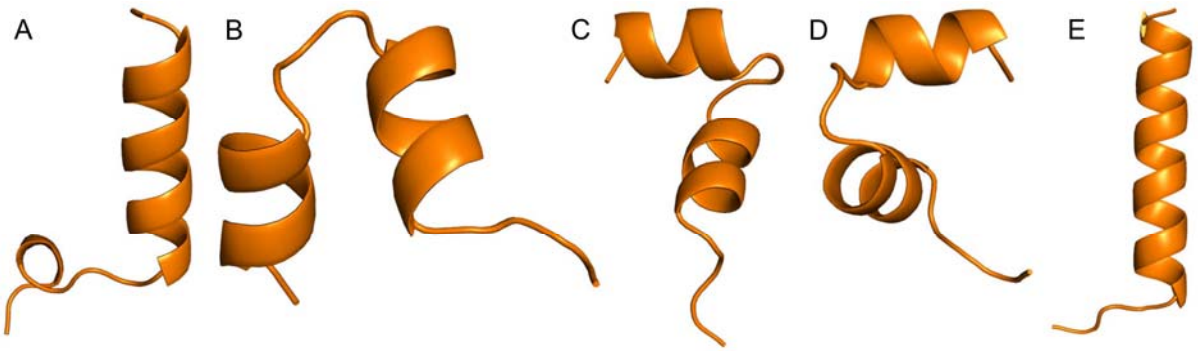
Supplementary Table 1. Molar ratios of lipids utilized in preparation of liposomes mimicking cellular compartments (21)

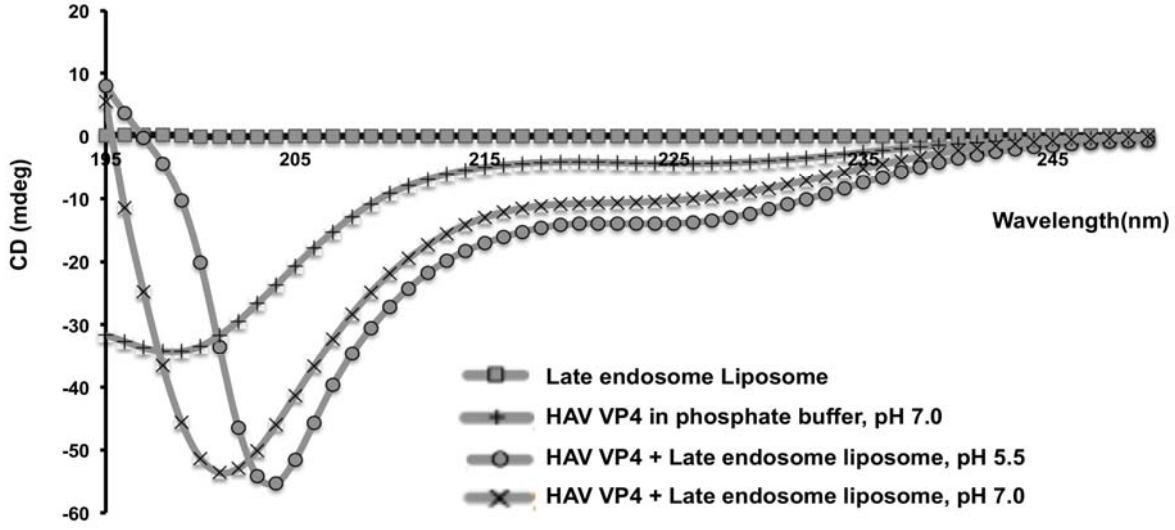
Liposomes	**Mammalian plasma membrane**	**Late Endosome**	**Endoplasmic raticulum**	**Golgibody**
Cholesterol	50	50	15	20
Phosphatidyl Choline	20	25	52	50
Phosphatidyl Ethanolamine	11	10	30	17
Sphingomyelin	13	5	0	10
Phosphatidyl Serine	6	1	3	3
Phosphatidyl Glycerol	0	0	0	0
BMP (bis(monoacylglycero)phosphate)	0	9	0	0

Supplementary Table 2. Hydrogen bond interactions obtained from the interaction and penetration of HAV VP4 with POPC membrane during the course of three different MD simulations.

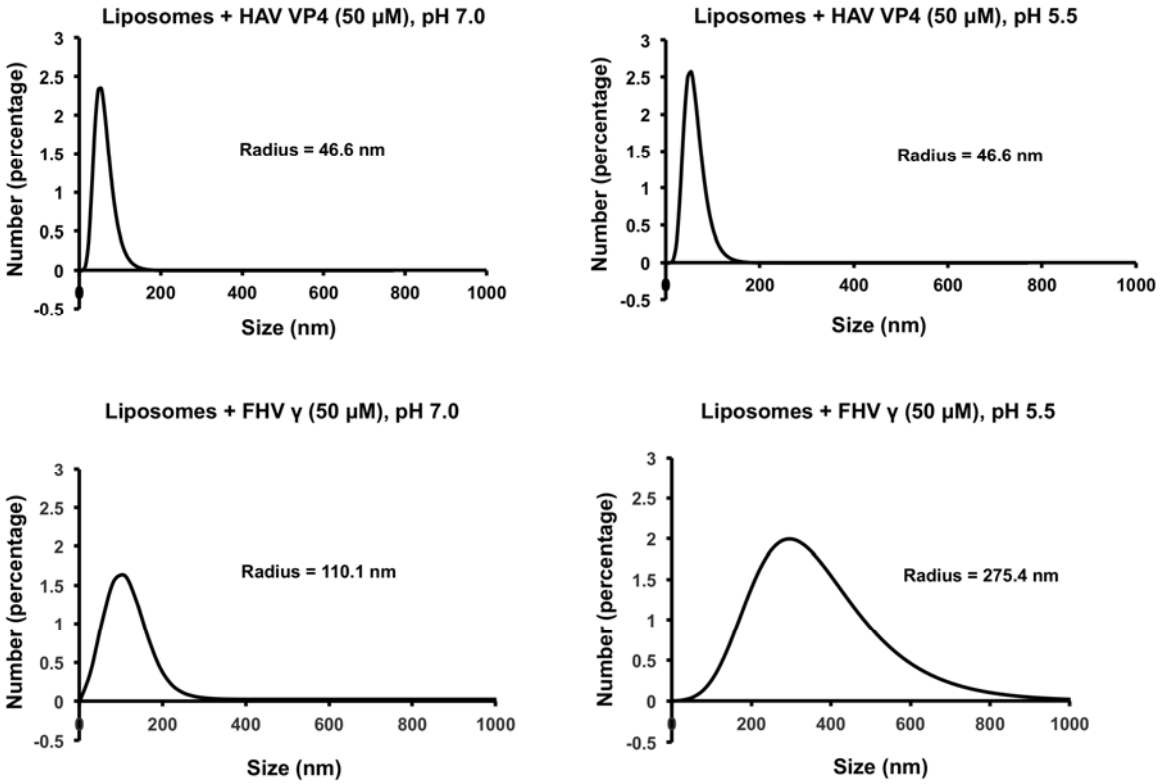
(1) N-terminus of VP4 facing towards the membrane		
Donor	**Acceptor**	**H-bonding occupancy (%)**
Met1	POPC162	77.57
	POPC165	69.84
Arg5	POPC52	48.89
	POPC54	57.93
	POPC58	42.48
	POPC165	50.48
Asn2	POPC52	68.50
	POPC165	57.12
Ser4	POPC52	64.33
(2) C-terminus of VP4 facing towards the membrane		
Ile8	POPC232	22.83
Ser4	POPC175	28.12
Arg5	POPC94	42.96
(3) VP4 oriented and placed parallel to the membrane		
Met1	POPC58	66.25
	POPC161	43.63
Asn2	POPC58	73.68
Arg5	POPC52	59.71
	POPC54	67.51
	POPC165	55.32



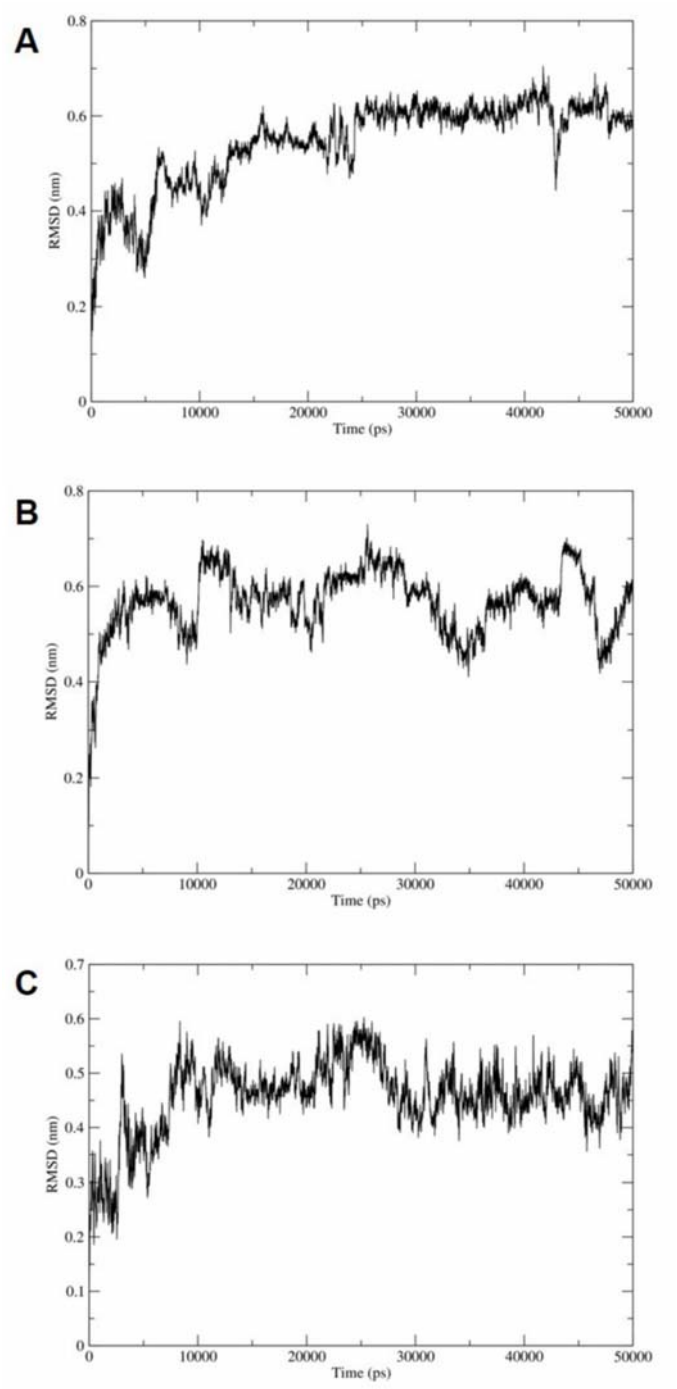
Supplementary Figure 1: Predicted 3D structure snapshots, from (A) to (E), of HAV VP4 from Bhageerath-H. The total energy obtained for (A-E) are (-342.958 kcal/mol, -328.128 kcal/mol, -327.623 kcal/mol, -308.649 kcal/mol, -307.647 kcal/mol) respectively. The lowest energy structure shown in panel-A was used for the MD simulations.



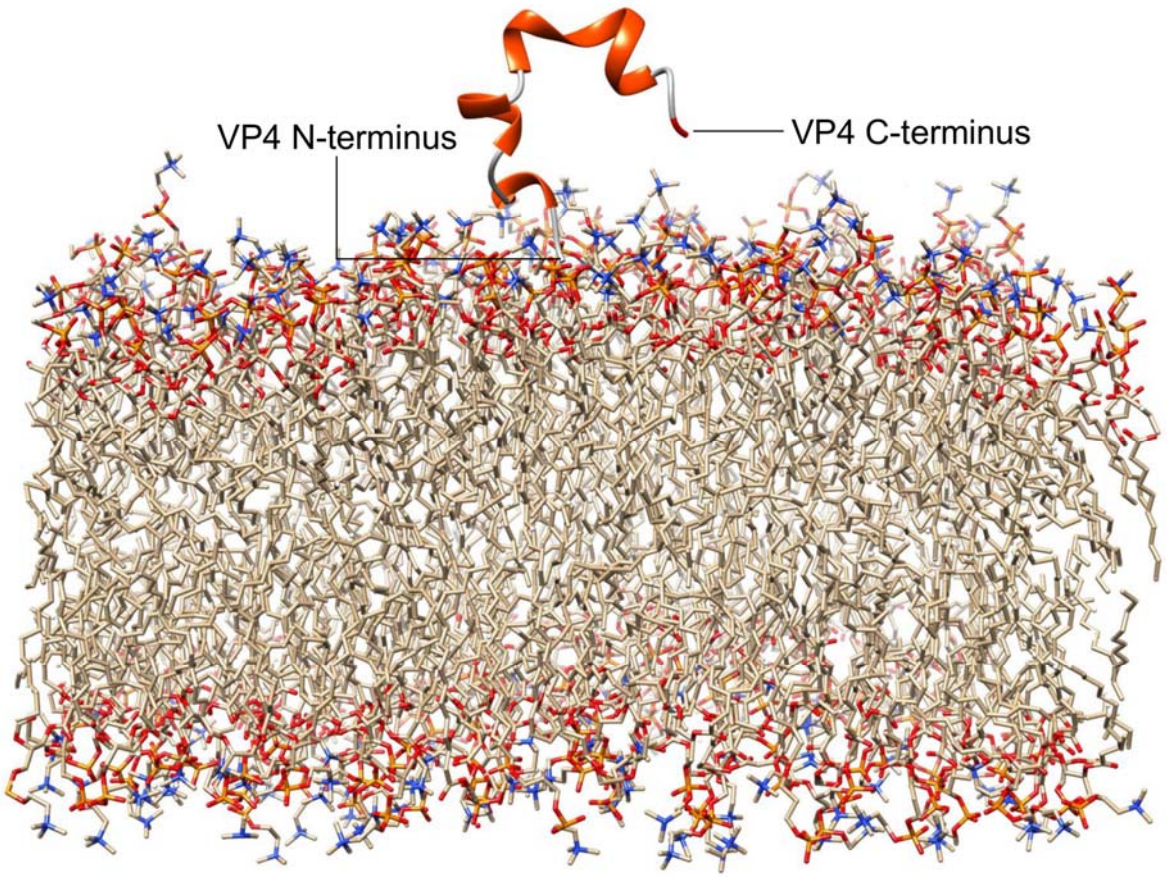
Supplementary Figure 2: Circular Dichroism spectroscopy of 50 µM HAV VP4 in presence of liposomes mimicking late endosomal vesicles, at pH 7.0 or pH 5.5.



Supplementary Figure 3: Dynamic light scattering studies, showing the mean hydrodynamic radius or R_h(mean) of liposomes mimicking late endosomal compartments, after 20 minutes of incubation with 50 µM of HAV VP4 or FHV γ1, at pH 7.0 and 5.5.



Supplementary Figure 4: Root mean square deviation (RMSD) of the Cα backbones of VP4 referring to the starting structure as a function of simulation time. (A) A stable backbone RMSD of VP4 obtained from the simulation when the N-terminus of the peptide oriented and placed towards the membrane surface (B) Unstable backbone RMSD observed when the C-terminus of the peptide placed towards the membrane and (C) a stable RMSD of the Cα backbone of VP4 when it is placed parallel to the membrane.



Supplementary Figure 5: Snapshot of VP4 showing a circular ring like structure (N- and C-termini approaching close to each other) with respect to the membrane surface obtained from the simulation. The C-terminal α-helical domain appears to be conserved, which may help in providing stability to the peptide while the N-terminus region is showing to interact and penetrate with the membrane.