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Structural Basis of HIV-1 gp120 Conformational Mobility. Peter D. Kwong[a], Marie Pancera[a], Shahzad Majeed[a], Yih-En Andrew Ban[b], Lei Chen[a], Chih-chin Huang[a], Leopold Kong[a], Young Do Kwon[a], Jonathan Stuckey[a], Tongqing Zhou[a], James E. Robinson[c], William R. Schief[b], Joseph Sodroski[d], Richard Wyatt[a]. [a]*Vaccine Research Center, National Institutes of Health, Maryland, USA.* [b]*Department of Biochemistry, University of Washington, Washington, USA.* [c]*Department of Pediatrics, Tulane University Medical Center, Louisiana, USA.* [d]*Department of Caner Immunology and AIDS, Harvard Medical School, Massachusetts, USA.*
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The viral spike of HIV-1 is composed of three gp120 glycoproteins attached non-covalently to three gp41 transmembrane moieties. Viral entry is initiated by binding to the CD4 receptor on the cell surface, which induces large conformational changes in gp120. These changes not only provide a model for receptor-triggered entry, but also alter the sensitivity of the spike to antibody-mediated neutralization. While some of the details of the CD4-induced conformational change have been visualized by crystal structures [1,2] and EM tomograms [3], the critical gp41-interactive region of gp120 was missing from previous atomic-level characterizations. Here we report the structure of an HIV-1 gp120 core with intact gp41-interactive region bound to CD4 and a CD4-induced antibody. Newly defined gp120 elements proximal to the gp41 interface complete a 7-strand β-sandwich, which appeared invariant in conformation. Loops excursions, emanating from the sandwich, form three topologically separate - and structurally plastic - layers, topped off by the highly glycosylated gp120-outer domain. EM tomograms and crystals structures were consistent with a model in which the layers act as a shape-changing spacer, controlling movement between structurally conserved modules of outer domain and gp41-associated β-sandwich. A "layered"-gp120 architecture thus provides a mechanism for extensive conformational mobility, both to move in the viral spike without triggering the metastable gp41-fusion machinery and to fold into alternative conformations required to fulfill biological functions of receptor binding and immune evasion.

[1] Kwong P.D., et al., *Nature*, **1998**, 393, 648. [2] Chen, B., et al., *Nature*, **2005**, 433, 834. [3] Liu J., Bartesaghi A., Borgnia M.J., Sapiro G., Subramaniam S., *Nature*, **2008**, 455, 109.

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