

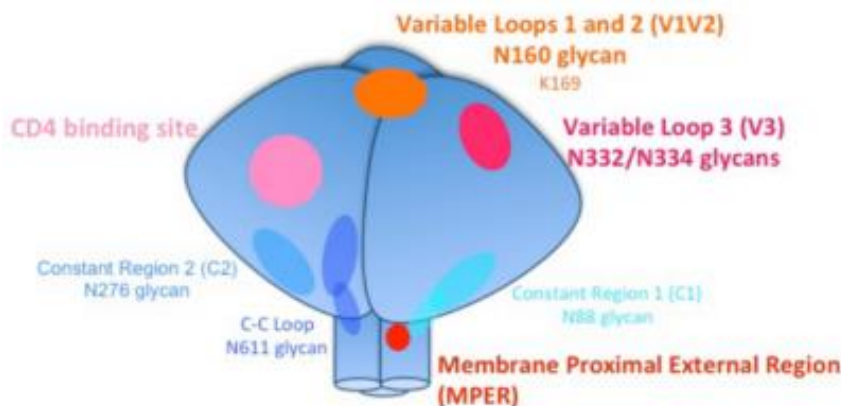
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SCIENCE SPOTLIGHT

# HIV-1 superinfection results in broad polyclonal neutralizing antibodies

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None of the four main epitopes on the HIV-1 envelope protein (CD4 binding site, N160 glycan in V1V2, N332 glycan in V3, and MPER; highlighted in warm colors and bold font), nor four additional sites (N276 glycan in C2, N611 glycan in C-C loop, N88 glycan in C1, K169 in V1V2; highlighted in blue colors and small font), are strongly targeted by neutralizing antibody responses in HIV-1 superinfected individuals from a Kenyan cohort. While the 4 main epitopes have been shown to be the dominant targets of broad and potent neutralizing antibody responses in individuals with a single infection from other cohorts, the absence of such a response in HIV-1 superinfected individuals suggests that their neutralizing antibody responses may be collectively mediated by diverse, polyclonal antibodies.

*Image provided by Dr. Valerie Cortez*

Development of a human immunodeficiency virus-1 (HIV-1) vaccine that elicits neutralizing antibodies (Nabs) that are both potent and broad remains a major public health goal. However, one of the main challenges of HIV-1 vaccine design is the diversity of HIV-1 subtypes that are currently circulating worldwide. One scenario that holds great potential to inform future vaccine design is HIV-1 superinfection (SI), defined as one person receiving sequential infections from different source partners. Previous studies in Dr. Julie Overbaugh's Laboratory (Human Biology Division) showed that a cohort of 12 superinfected women from Mombasa (Kenya) developed broader and more potent Nab responses than singly infected individuals (Cortez et al., 2012). However, it remains unclear whether SI and singly infected individuals differed in other ways, such as the specificity of the antibody response. A new Fred Hutch follow-up study by the Overbaugh lab, led by former graduate student Dr. Valerie Cortez and published in *PLOS Pathogens*, addressed this question by

mapping the antibody response of 21 superinfected women onto epitopes (parts of proteins or other antigens that bind antibodies) of the HIV-1 Envelope protein.

Previous studies on singly infected individuals with broad Nabs mapped the bulk of their neutralizing activity onto four major epitopes on the HIV-1 Envelope protein: the membrane proximal external region (MPER), the CD4 binding site, residues in the V1/V2 region, and the V3 loop (see figure). The study began by assaying post-SI plasma from all 21 women. MPER-specific antibodies were infrequently detected, and such antibodies appeared to arise over a year following SI. Next, the authors tested for CD4-binding site-specific antibodies in post-SI plasma by comparing binding with an Envelope core protein engineered to prominently display the CD4-binding site versus a mutant protein that harbored a deletion that abrogates the binding of CD4-specific antibodies. One out of the 21 women had antibodies that bound the wild-type Envelope more strongly than the mutant, but this individual's CD4-binding site-specific antibodies did not demonstrate neutralizing activity. Nabs that target either the V1/V2 region or the V3 loop require a glycan (a sugar moiety on a protein) at specific positions and comparisons of wild-type versus glycan deficient Envelopes failed to provide strong evidence for glycan-specific Nabs.

Beyond these four epitopes, several additional epitopes have been linked to newly characterized Nabs. To investigate further, the authors also engineered point mutations in these novel epitopes. Again, the antibodies targeted to the newly discovered epitopes did not appear to be major drivers of the SI response. Finally, the researchers employed computational analyses to corroborate the functional data, which confirmed that none of the 21 women developed a Nab response that could be ascribed with high confidence to a single known epitope. "Since none of neutralizing antibody responses from the 21 superinfected individuals strongly targeted any of the epitopes tested in our study, this may suggest that HIV-1 superinfection leads to a broad, polyclonal response that collectively mediates their ability to neutralize diverse HIV-1 envelopes. Continual study of the virus-antibody interplay in HIV-1 superinfected individuals may yield insights to how we can design sequential immunizations that elicit a diverse, polyclonal antibody response capable of recognizing globally diverse HIV-1 subtypes," said Dr. Cortez. In conclusion, a combination of functional and computational analyses enabled the authors to characterize the epitope targets of Nabs linked to SI for the first time.

[Cortez V, Wang B, Dingens A, Chen MM, Ronen K, Georgiev IS, McClelland RS Overbaugh J. 2015.](#) The broad neutralizing antibody responses after HIV-1 superinfection are not dominated by antibodies directed to epitopes common in single infection. *PLoS Pathog*, 11(7), e1004973.

See also:

[Cortez V, Odem-Davis K, McClelland RS, Jaoko W, Overbaugh J. 2012. \*PLoS Pathog\*, 8\(3\):e1002611. HIV-1 superinfection in women broadens and strengthens the neutralizing antibody response.](#)

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