Enhanced B Cell Priming Leads to Rapid Induction of Broadly Neutralizing HIV-1 Apex Antibodies

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Broadly-neutralizing antibodies (bNAbs) target conserved epitopes on the HIV-1 envelope glycoprotein (Env), are protective in passive immunization studies, and are thought to be a necessary component of a protective HIV-1 vaccine. Recently, we showed that efficient B cell precursor priming is the principal bottleneck to elicit V2 apex bNAbs (Habib et al. *Science Immunology*, 2026). Building on insights from human V2 apex bNAbs, we engineered a novel CAP256-based HIV Env immunogen called OPT4, designed to increase V2 apex bNAb precursor priming. Infection of 14 rhesus macaque monkeys (RMs) with OPT4-expressing viruses induced potent bNAb in 13 of 14 animals, with plasma neutralization breadth reaching as high as 90% on a 21-virus panel. MAbs isolated from these animals were similarly broad and potent, with cryo-EM structures revealing canonical needle-like CDRH3 binding, typical of rhesus and human V2 apex bNAbs. To understand this unprecedented bNAb development, we sorted epitope-specific B cells 12 weeks post-infection. OPT4-infected animals primed an average of 13 V2 apex bNAb-like B cell lineages per RM. This is in stark contrast to 12 RMs infected with wildtype Envs, Q23.17, CH505 or CAP256SU, that have a propensity to induce V2 apex bNAb, where the priming rate was 0.4 (33-fold difference). We extended this analysis to 115 RMs infected with 16 different wildtype Envs where priming rate per 12-week interval was 0.03 (418-fold difference). Following Env–antibody coevolution longitudinally, we identified five Env residues or loop features under positive selection associated with bNAb maturation. We designed a vaccine regimen in which rhesus macaques were primed with OPT4 and boosted with OPT4 sequences harboring these evolution-guided mutations. This germline-line targeted lineage-based vaccine regimen induced heterologous plasma neutralization in 8 of 8 vaccinated macaques after only five immunizations over 36 weeks. This is the first study to use insights from HIV infection to rationally design a sequential prime-boost vaccination strategy that successfully elicits bNAbs in an outbred animal model. Based on our findings, OPT4 immunogens are currently being evaluated in a Phase I/IIa clinical trial (HVTN 322).