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Immunogenicity and structure of a stabilized HIV-1 clade C Env from a pediatric elite neutralizer in complex with an autologous bnAb

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Introduction: The envelope (Env) glycoproteins derived from circulating viruses in elite-neutralizers (ENs), who naturally develop potent broadly neutralizing antibody (bnAb) responses, serve as a potential template for HIV-1 vaccine design. Here, we investigated the immunogenicity and structure of a clade C HIV-1 Env trimer (330) derived from the pediatric elite-neutralizer AIIMS_330.

Methods: The 330 Env was engineered as SOSIP.664, NFL.664, and multivalent ferritin-nanoparticle (NP) immunogens. Biophysical and antigenic properties were assessed using HIV-1 trimer-specific bnAbs and non-neutralizing antibodies. Immunogenicity was evaluated in rabbits immunized with Addavax-formulated SOSIP.664, NFL.664, or ferritin NP immunogens (n = 4), with an adjuvant only placebo group (n = 2). Structural characterization was performed by cryo-electron-microscopy (cryo-EM) using the autologous Env 330 SOSIP.664 trimer in complex with the bnAb 44m.

Results: The 330 Env trimers exhibited native-like antigenic properties, high thermostability, strong binding to trimer-specific bnAbs, and limited reactivity with non-neutralizing antibodies. Immunization of rabbits elicited strong autologous neutralizing antibody responses together with modest heterologous Tier-1 neutralization. Autologous neutralizing responses were significantly higher for ferritin-NP (P = 0.019) and SOSIP.664 (P = 0.048) than for NFL.664, with no significant difference between ferritin-NP and SOSIP.664 (P = 0.681). A 5.1 Å cryo-EM reconstruction of the autologous Env 330 SOSIP.664–44m complex revealed native-like presentation of the N332-V3 supersite. The structural analysis further suggested the interacting Env contacts E293, R327, K337, and K446, along with glycans N332, N326, N442, and N448 with the bnAb-44m. We identified R327 of the conserved GDIR-motif and the N332 glycan, within the V3-loop, as