Longitudinal Characterization of an Expanding Autologous Neutralizing Antibody Response After Early Antiretroviral Therapy

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In people living with HIV, recent studies highlight the role of autologous neutralizing antibodies (aNAbs) in post-treatment control. In early treated infection, aNAb lineages continue to develop on ART, and understanding how aNAbs arise is critical for antibody-based cure strategies. In a previous study, we profiled the aNAb response in an early ART-treated participant 8012, who sequentially developed aNAb activity against two transmitted/founder virus lineages (M2 and C8; 15 amino acid differences in gp160), and later enrolled in an ATI clinical trial (NCT04357821). To profile how individual monoclonal antibodies (mAbs) contributed to the aNAb response, we performed LIBRA-seq on PBMCs at weeks 80 and 417 on suppressive ART using M2 and C8 SOSIPs. MAbs were expressed as IgG1 and assayed for binding and neutralization. Epitope specificities were mapped using Competition ELISAs, Carterra epitope-binning, and neutralization of chimeric autologous Envs. Longitudinal plasma IgG neutralization revealed early aNAbs targeted a V1-dependent epitope in C8 (5 amino acids shorter, distinct PNGS vs. M2). High-titer C8 V1-dependent neutralization persisted until week 270, after which broad neutralization of all variants was detected. LIBRA-seq recovered 62 and 204 paired BCR sequences from weeks 80 and 417, respectively. Of the top 30 hits expressed as mAbs, 23 showed autologous binding and 14 displayed autologous neutralization across four categories: C8-specific (n=4; IC50: 2.7–30.5 μg/mL), M2-specific (n=1; IC50: 0.5 μg/mL), moderate cross-neutralizers (n=4; IC50: 15.8–43.9 μg/mL), and potent cross-neutralizers (n=5; IC50: 0.008–0.22 μg/mL). Six B cell lineages were identified; three spanned both timepoints, with lower somatic hypermutation at week 80. All five potent cross-neutralizers use IGHV3-33 and belong to two clonal families. Preliminary epitope mapping suggests strain-specific aNAbs compete with 35O22 at the gp41/120 interface, while potent cross-neutralizers target the V3-glycan site. Across 8+ years of ART, participant 8012's aNAb activity is driven by multiple B cell lineages, with early polyclonal responses focused on a V1-dependent epitope that evolve toward broader, more potent neutralization through multiple gene families and epitopes encompassing V3 and interface regions. These findings advance our understanding of the breadth and potency of polyclonal aNAb responses.