1610. Pervasive B cell Activation during Viremic HIV-1 Infection but Effective Responses with Appropriate Stimulation *in vitro*

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Background. HIV-1 infection is associated with increased rates of secondary infections and decreased antibody responses to protective vaccines. Identifying specific HIV-1-associated B cell defects may direct interventions to circumvent them.

Methods. We studied 34 viremic HIV-1-infected adults (HIV-1 + ; median CD4+ T cells 276/μL; HIV-1 RNA 320,289 copies/mL) and 20 HIV-1-seronegative age-matched control subjects. We measured frequencies and activation of circulating B cell subsets and T follicular helper cells (T_{FH}) by flow cytometry, expression of activation-induced cytidine deaminase (AID) and IL-21 by RT-qPCR, and B cell activating factor (BAFF) and IL-21 by ELISA. Cells were stimulated with surrogates for antigen (anti-IgM), cognate (anti-CD40), and soluble (IL-4) T cell factors. Values were compared by unpaired t, paired t, and Mann Whitney tests.

Results. At baseline, B cells from HIV-1+ adults showed perturbations in B cell subsets (increased immature transitional and IgM memory cells and decreased anergic cells) vs controls. Activation (CD21-) was increased across all 8 B cell subsets as were levels of B cell-activating constituents (BAFF and activated T_{FH} cells, but not IL-21) in HIV-1+ vs controls. However, upon stimulation *in vitro*, transitions from naïve to class-switch memory cells and activation of B cells from HIV-1+ increased significantly to levels comparable to those of controls, as did levels of AID, the protein that mediates antibody class switch.

Conclusion. Viremic HIV-1 infection perturbs circulating B cell subsets and activation from the earliest developmental stages of circulating B cells. However, with appropriate stimulation (cross-linking antigen and T cell factors), B cells can effectively activate and mature. These data provide impetus for novel and effective vaccine development to prevent secondary infections by circumventing these early B cell defects that may limit primary protective antibody responses.

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