cART reduces antibody-dependent cellular cytotoxicity to HIV: Implications for Therapeutic Vaccines

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Background: Combination anti-retroviral therapy (cART) has proven effective in the control of HIV infection but it cannot eliminate HIV and treatment is life-long. HIV-specific cytotoxic T lymphocyte responses decline following cART but alterations in other HIV-specific immune responses that may assist in clearing latent HIV infection, specifically antibody-dependent cellular cytotoxicity (ADCC), are unknown. We hypothesized that ADCC immunity may decline in HIV-infected subjects on cART, which has implications for therapeutic vaccines to control HIV infection.

Methods: A cohort of 49 cART-naive HIV-infected subjects in Thailand started cART at baseline. The median baseline CD4 count was 186 cells/µl (range: 10-350 cells/µl) and viral load was 4.9 log10 copies/ml (range: 2.9-6.3 log10 copies/ml). Longitudinal blood samples were collected up to 96 weeks (median CD4 count: 338 cells/µl range: 113-990 cells/µl; median viral load: < 40 copies/ml, range: 40-137 copies/ml). Serum samples were analyzed for ADCC-mediated killing against HIV-1 envelope protein subtype AE (Env/AE) targets using the RFADCC assay. ADCC antibody responses to Env/AE peptide pools were measured using the NK cell activation ADCC assay. The total HIV-specific antibody binding titers against Env/AE were measured by ELISA.

Results: A significant reduction in Env-specific ADCC-mediated killing ($p < 0.0002$) was observed between baseline (median: 11.8%, IQR: 7.7-14.1%) and week 96 (median: 7.7%, IQR: 3.9-10.3%) in the RFADCC assay. In the NK cell activation ADCC assay, an initial screening showed a reduction in Env-specific NK cell activation in 26/49 (53%) subjects. A 10-fold reduction in ADCC endpoint titers between baseline and week 96 was detected in both RFADCC and NK activation ADCC assay in the subset of samples tested. Serum Env-specific antibody binding titers significantly decreased 10-fold after 96 weeks of cART (baseline: median: 5 log10, IQR: 4.5-5; week 96: median: 4 log10, IQR: 3.5-4.5; $p < 0.0001$).

Conclusion: This longitudinal study showed a significant reduction in HIV-specific ADCC in HIV-infected subjects following cART. This may reduce the capacity for ADCC to clear or control reactivated latent HIV. ADCC-based therapeutic vaccines and/or modulation of ADCC effector functions could assist in the control of HIV and the ability to clear reactivated latently infected cells to cure HIV.