Background: HIV infection induces immune dysregulation of both CD4 and CD8 T cell compartments. The anti-viral T cell pools in chronically infected patients are characterized by an exhausted activation phenotype, which is unable to control virus replication. ART can suppress HIV replication leading to stabilizing of CD4 T cell numbers and improving immune function. However, latent virus is not eliminated and the residual T cell pools do not overcome this state of T cell exhaustion. During non-controlled viral replication, the expression of Programmed Cell Death-1 (PD-1) on activated T cells is associated with T cell exhaustion and poor viral control. AGS-004 is a personalized dendritic cell (DC) loaded with RNA encoding autologous Gag, Nef, VPR, and Rev. AGS-004-001 is a Phase 2 trial designed to assess the efficacy and safety of AGS-004 during a 12 Week ART structured treatment interruption (STI) in chronic HIV-1 infected subjects. The goal of this immunotherapeutic intervention is to reverse this induction of T cell exhaustion leading to control of viral replication by inducing long-term immunity.

Methodology: Longitudinal blood draws where collected prior to AGS-004 dosing, after four doses of AGS-004 administered during ART, and after two doses during STI. Phenotype of HIV-specific CD4 and CD8 T cells and their proliferation capacity where determined by multi-color flow cytometry to determine the activation state of HIV specific T cells. Measurements of viral load were performed during these same time-frames. Associations between T cell proliferation, T cell activation state and viral control were determined.

Results: Positive changes in the magnitude of T cell proliferation to viral antigens after AGS-004 administration were detected in subjects with extended time to viral rebound during STI. Both activated CD4 and CD8 T cells lacking PD-1 where increased after AGS-004 administration in subjects with an extended time to viral rebound versus subjects with faster time to viral rebound measured during STI. Furthermore, subjects displaying rapid viral rebound had a greater number of exhausted CD57+/PD-1+ CD4 and CD8 effector T cells compared to subjects with an extended time to viral rebound.

Conclusions: Taken together, these data suggest that in study AGS-004-001 subjects with an extended time to viral rebound during STI demonstrated increases in CD4 and CD8 T cells with an activated phenotype. Furthermore, these same subjects displayed lower numbers of T cells expressing PD-1, a marker associated with dysfunctional CD4 and CD8 T cell activation. The role AGS-004 plays in the induction of an anti-HIV response geared towards delaying viral rebound during STI will be elucidated in the double blind placebo controlled phase 2 study AGS-004-003, currently underway.