Evaluation of HIV-1 Reservoir Characteristics in a Therapeutic HIV-1 *gag* Vaccine Trial

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Abstract

BACKGROUND. ACTG A5197 was a randomized, placebo-controlled trial of a therapeutic rAd5 HIV-1 *gag* vaccine in participants on suppressive antiretroviral therapy. The vaccine induced HIV-1 Gag-specific CD4+ interferon-γ-producing cells, which was correlated with lower viral rebound during an analytic treatment interruption (ATI). We investigated the effects of vaccination on HIV-1 reservoir characteristics prior to the ATI.

METHODS. Participants received the vaccine/placebo at study weeks 0, 4, and 26 prior to a 16-week ATI at week 38. Cell-associated HIV-1 RNA and DNA (CA-RNA and CA-DNA) and HIV-1 residual viremia (RV) by a single-copy assay were quantified at weeks 0, 8, and 38. HIV-specific CD4+ and CD8+ activity were assessed by an intracellular cytokine staining assay.

RESULTS. At week 8, after two doses of the vaccine/placebo, modest differences between study arms were noted both in the levels of RV (vaccine [N=65] vs. placebo [N=30]: median 0.7 vs. 1.1 cp/mL, P=0.08) and proportions of individuals with detectable RV (37% vs. 57%, P=0.08). Participants in the vaccine arm with undetectable RV had a significantly higher frequency of both HIV-1 Gag-specific CD4+ interferon-γ-producing cells (undetectable [N=39] vs. detectable [N=24]: 277 vs. 161 cells/10^6 lymphocytes, P=0.03) and CD8+ interferon-γ-producing cells (undetectable [N=39] vs. detectable [N=24]: 1326 vs. 669 cells/10^6 lymphocytes, P=0.04). By week 38, however, no significant differences were observed in the numbers of Gag-specific CD4+ or CD8+ interferon-γ-producing cells between those with and without detectable RV in the vaccine arm. Therapeutic vaccination did not induce significant changes in CA-RNA or CA-DNA prior to ATI. At study entry, CA-RNA and CA-DNA levels were correlated with the numbers of HIV-specific CD4+ interferon-γ-producing cells (CA-RNA [N=93]: r = -0.23, P=0.03 and CA-DNA [N=93]: r = -0.28, P<0.01) and CA-RNA was associated with RV (r = 0.23, P=0.04, N=77). These associations weakened after vaccination and were not significant at weeks 8 and 38. Plasma HIV-1 RNA set point during the ATI was significantly associated with pre-ATI week 38 CA-RNA and CA-DNA (CA-RNA [N=90]: Spearman r = 0.51, P<0.01 and CA-DNA [N=93]: r = 0.47, P<0.01).

CONCLUSIONS. Early in the vaccination course, higher frequencies of Gag-specific CD4+ and CD8+ cells were associated with lower levels of RV, but this effect waned over time. Higher pre-ATI CA-RNA and CA-DNA levels were associated with higher viral load set point during the ATI, but were not significantly altered by the therapeutic vaccine. In this study, therapeutic HIV vaccination induced HIV-specific T cells, but more potent immune responses may be needed to reduce the latent HIV-1 reservoir.

Background

- ACTG A5197 was a randomized, placebo-controlled trial of a therapeutic rAd5 HIV-1 *gag* vaccine in participants on suppressive antiretroviral therapy (**Figure 1**).
- The vaccine induced HIV-1 Gag-specific CD4+ interferon-γ-producing cells, which was correlated with lower viral rebound during an analytic treatment interruption (ATI).
- The impact of the A5197 therapeutic vaccination on HIV reservoir levels is unknown.

Objectives

1. **Determine the impact of the A5197 therapeutic vaccination on the HIV reservoir.**
2. **Evaluate the relationship between HIV reservoir levels and both T cell activation and viral rebound kinetics during the ATI.**

Methods

Data Sources, Study, and Subject Selection

- Participants received the vaccine/placebo at study weeks 0, 4, and 26 prior to a 16-week ATI at week 38
- Cell-associated HIV-1 RNA and DNA (CA-RNA and CA-DNA) and HIV-1 residual viremia (RV) by a single-copy assay (SCA) were quantified at weeks 0, 8, and 38 (**Figure 1**).
- HIV-specific CD4+ and CD8+ activity were assessed by an intracellular cytokine staining assay.

Statistical Analysis

- Associations between HIV reservoir levels and either immune status or viral rebound kinetics were assessed by Spearman correlation, Wilcoxon rank sum test, and Fisher's exact test.

Figure 1: Study Protocol

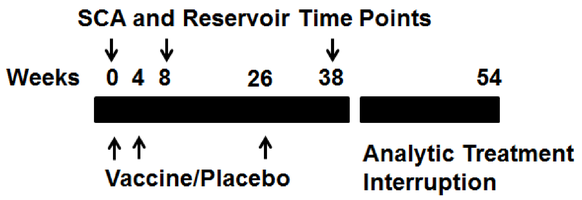
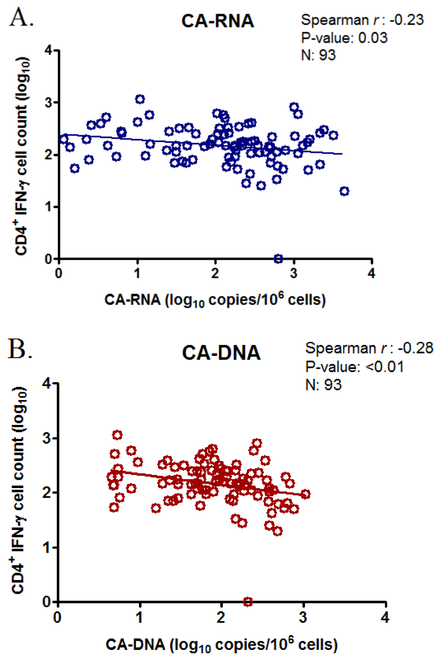


Figure 2: Association at Baseline between HIV-Specific CD4+ Response and CA-RNA and DNA Levels



Results

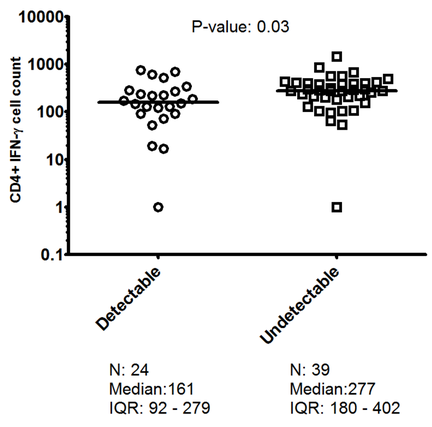
Baseline HIV Reservoir Levels and Immune Status

- At study entry, residual viremia was significantly associated with levels of CA-RNA (Spearman r = 0.23, P=0.04, N=77), but not CA-DNA.
- CA-RNA and CA-DNA levels were both correlated with the numbers of HIV-specific CD4+ interferon-γ-producing cells (**Figure 2**).
- CA-RNA and CA-DNA levels were also correlated with percentages of CD8+/CD38+ cells (CA-RNA: r = -0.26, P=0.01, N=90 and CA-DNA: r = -0.22, P=0.04, N=90).

Therapeutic Vaccination and HIV Reservoir Levels

- At week 8, modest differences between study arms were noted both in the levels of RV (vaccine vs. placebo: median 0.7 vs. 1.1 cp/mL, P=0.08) and proportions of individuals with detectable RV (37% vs. 57%, P=0.08).
- At week 8, subjects in the vaccine arm with undetectable RV had a significantly higher frequency of both HIV-1 Gag-specific CD4+ IFN-γ-producing cells (**Figure 3**) and CD8+ IFN-γ-producing cells (undetectable vs. detectable: 1326 vs. 669 cells/10^6 lymphocytes, P=0.04).
  - -- This association was no longer detectable by week 38.
- Therapeutic vaccination did not induce significant changes in CA-RNA or CA-DNA prior to ATI.

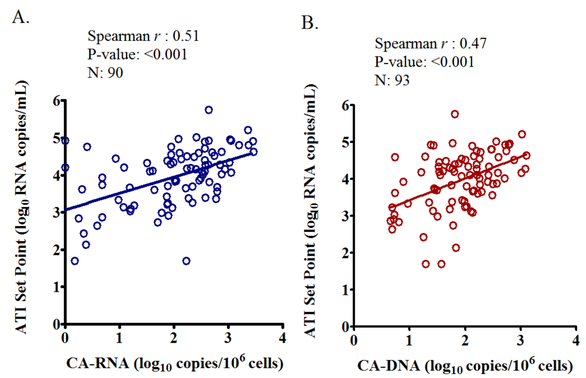
Figure 3: Higher Frequencies of HIV-Specific CD4+ Cells Associated with Lower Residual Viremia at Week 8



HIV Reservoir Levels Predict ATI Viral Load Set Point

- Plasma HIV-1 RNA set point during the ATI was significantly associated with pre-ATI week38 CA-RNA and CA-DNA (**Figure 4**).

Figure 4: Pre-ATI HIV-1 CA-RNA and CA-DNA Predict Viral Load Set Point



Conclusions

- Residual HIV viremia was significantly associated with levels of cell-associated HIV RNA.
- At baseline, HIV reservoir levels were associated with both CD8+ T-cell activation and HIV-specific CD4+ activity.
- Early in the vaccination course, higher frequencies of Gag-specific CD4+ and CD8+ cells were associated with lower levels of RV, but this effect waned over time.
- Higher pre-ATI CA-RNA and CA-DNA levels were associated with higher viral load set point during the ATI, but were not significantly altered by the therapeutic vaccine.

Implications

- **The A5197 therapeutic HIV vaccine induced HIV-specific T cells, but more potent immune responses may be needed to reduce the latent HIV-1 reservoir.**
- **HIV reservoir levels are associated with immune activation and may be useful as predictors of viral rebound kinetics during treatment interruption.**

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