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=60]: median 0.7 vs. 1.1 copies/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 and CA RNA- and CA DNA-producing cells (undetectable [N=36] vs. detectable [N=42]: 326 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=0.01 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=90]: 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 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.

Results

Baseline HIV Reservoir Levels and Immune Status

• At study entry, residual viremia was significantly associated with lower 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 proportions of CD8+ CD438 (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 copies/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.

Conclusions

• Residual HIV viremia was significantly associated with levels of cell-associated HIV RNA.
• At baseline, HIV reservoir levels were associated with both CD6+ 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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Figure 1: Study Protocol

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

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

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

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).