HIV Controllers Maintain Viral Suppression despite Waning T Cell Responses on ART

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Abstract

Background: Robust HIV-specific T cell responses are a hallmark of HIV controllers (HCs). We assessed the impact of antiretroviral therapy (ART) on HIV-specific T cell responses and the ability of HCs to maintain HIV suppression after discontinuation of ART.

Methods: A5308 is a prospective, open-label study of rilpivirine, emtricitabine and tenofovir disoproxil fumarate (RPV/FTC/TDF) in ART-naive HCs with viral loads (VLs) <500 cp/mL for ≥12 months. HIV-specific T cell responses were measured by intracellular cytokine staining assays in response to HIV gag pool stimulation. Outcomes were evaluated by repeated measures GEE models. In addition, viral load outcomes from HCs in the UCSF SCOPE cohort were included if they had been treated with ART with subsequent VL measurements after ART discontinuation.

Results: Thirty-five HCs completed ≥24 weeks of ART in A5308 and were analyzed. Before ART, higher levels of HIV-specific CD4+ and CD8+ T cell responses were associated with undetectable viremia either by the integrase-single copy assay or the Abbott viral load assay. After 24-48 weeks of ART, significant decreases were observed in a broad range of HIV-specific CD4+ and CD8+ T cell responses. These included CD4+ T cells expressing IFNγ (-0.32 percentage points (%) [95% confidence interval -0.50%, -0.14%], p<0.001), IL2 (-0.19% [-0.37%, -0.02%], p=0.03), TNFα (-0.53% [-1.09%, 0.02%], p=0.06), and CD8+ cells expressing IFNγ (-0.23% [-0.47%, 0%], p=0.05), TNFα (-0.32% [-0.58%, -0.07%], p=0.01), and CD107 (-0.38% [-0.82%, 0.06%], p=0.09). Furthermore, significant reductions were found in the percentages of polyfunctional HIV-specific CD4+ and CD8+ cells expressing multiple cytokines (CD4+ IFN-γ+ TNFα+ CD107+: -0.08%, p=0.004; CD8+ IFN-γ+ TNFα+ CD107+: -0.13%, p=0.001). Four HCs from A5308 and 5 HCs from the UCSF SCOPE study discontinued ART after a median [Q1, Q3] of 33 [25, 65] weeks of treatment. Two of the HCs had detectable VLs immediately preceding ART initiation. In the first 24 weeks after ART discontinuation, only 1 of the 9 HCs had a detectable VL (107 HIV RNA copies/mL).This participant also had the highest pre-ART VL (53 HIV RNA copies/mL).

Conclusions: ART significantly reduces both HIV-specific CD4+ and CD8+ T cell responses in HIV controllers. ART did not adversely affect controller status as HIV controllers maintained a low viral load after ART discontinuation.

Background

- HIV controllers (HCs) are able to suppress plasma viremia spontaneously, i.e. in the absence of ART, and robust HIV specific T cell responses are characteristic of HCs.
- Current guidelines recommend ART in all people after diagnosis of HIV infection, including in HCs.
- It is unclear how the T cell responses in HCs are affected by ART and whether controller status is preserved if ART is ever stopped.
- We therefore analyzed the impact of ART on HIV-specific T cell responses in HCs, and their ability to maintain HIV suppression after discontinuation of ART in A5308, a prospective, open-label trial to assess the effects of RPV/FTC/TDF on HIV suppression in HCs, as well as in the SCOPE study, a large, observational study that monitors HIV infected individuals longitudinally.

Objectives

1. **Analyze changes in CD4+ and CD8+ T-cell responses on RPV/FTC/TDF in ART-naive HCs.**
2. **Determine whether HCs are able to control viral replication after cessation of ART.**

Methods

Study Design

- A5308 is a prospective, open-label study of RPV/FTC/TDF in ART-naive HCs.
- A5308 key inclusion criteria: 1) ART-naive, 2) At least 2 VLs <500 copies/mL for ≥12 mT, and 16 weeks off ART
- SCOPE is an observational, prospective study of HIV infected volunteers designed to provide a specimen bank of samples and large clinical database. We screened the SCOPE database for additional HCs that had stopped ART.
- Screening criteria for SCOPE participants: 1) ART-naive 2) At least 2 VLs <500 copies/mL for ≥12 months 3) At least one timepoint >12 months prior with VL <1,000 copies/mL 4) At least 16 weeks on ART and at least 16 weeks off ART
- In A5068 participants, HIV specific T cell responses were measured by intracellular cytokine staining assays upon gag pool stimulation and outcomes were analyzed by repeated measures GEE models.

Figure 1: A5308 Protocol Schema and Participant Disposition

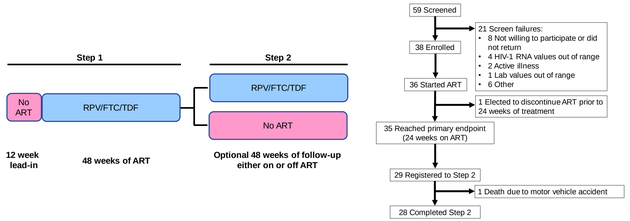


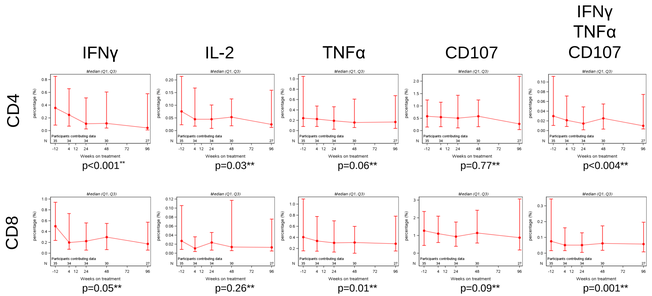
Table 1: Participant Characteristics

Characteristic	A5068 % or Median (N=35)	Participants from SCOPE % or Median (N=5)
Female (%)	43%	0%
Age (years)	47	54
Race/ethnicity (%)		
White, non-Hispanic	17%	80%
Black, non-Hispanic	74%	unknown
Hispanic	9%	unknown
Pre-ART CD4+ count	655	690
HIV Suppression at entry*	37%	60%
HLA-B*27/57 (%)	57%	80%

i.e. <40 copies/ml (%) in A5608, <75 copies/ml (%) in SCOPE

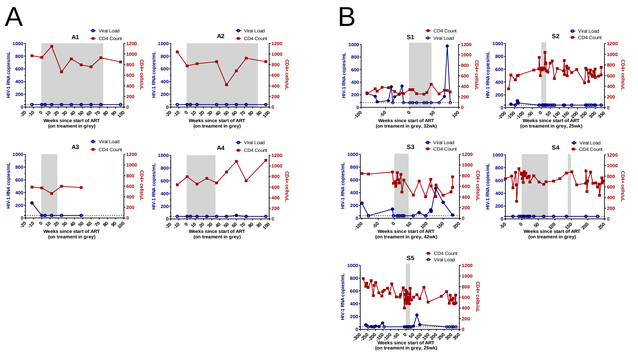
Results

Figure 2: Changes in CD4+ and CD8+ T Cell Responses on Antiretroviral Therapy*



*% CD4+ and CD8+ T cells expressing one or multiple cytokines (median and 95% CIs)
**p-values represent changes in each cytokine from pre-ART to 24-48 weeks on ART by repeated measures GEE models*

Figure 3: CD4+ T Cell Counts and Viral Loads of Four A5308 (A) and Five SCOPE (B) Participants Who Discontinued Antiretroviral Therapy



CD4+ and CD8+ T Cell Responses in HCs are Waning During ART (Figure 2)

- Thirty-five HCs in A5308 completed ≥24 weeks of RPV/FTC/TDF treatment
- After 24-48 weeks of ART, significant decreases in a broad range of HIV-specific CD4+ and CD8+ T cell responses were detected.
- CD4+ T cell fractions positive for the following single markers declined significantly: IFNγ (-0.32 percentage points (%) [95% confidence interval -0.50%, -0.14%], p<0.001), IL2 (-0.19% [-0.37%, -0.02%], p=0.03); TNFα did not quite reach significance (-0.53% [-1.09%, 0.02%], p=0.06).
- CD8+ T cells showed decline for the fractions expressing IFNγ (-0.23% [-0.47%, 0%], p=0.05), TNFα (-0.32% [-0.58%, -0.07%], p=0.01), and CD107 (-0.38% [-0.82%, 0.06%], p=0.09).
- Moreover, we observed significant reductions in polyfunctional T cell responses for both CD4+ and CD8+ T cells: CD4+ IFN-γ+ TNFα+ CD107+:-0.08%, p=0.004; CD8+ IFN-γ+ TNFα+ CD107+: -0.13%, p=0.001.

Maintenance of HIV Controller Status After ART Cessation (Figure 3)

- In A5308, four HCs discontinued ART, and were subsequently monitored over at least 10 weeks (Figure 3A).
- Three out of these four continued to have viral suppression during further observation which was at least 10 weeks, one participant experienced a single VL over threshold but HIV was undetectable at all other post-treatment timepoints, including the last timepoint more than 60 weeks after ART cessation.
- Five additional HCs that stopped treatment were identified on screening the SCOPE database.
- Three of the five had transient VLs above threshold, but all participants were suppressed at the last available timepoints.

Conclusions

- **CD4+ and CD8+ T cell responses in HIV controllers waned on ART.**
- **HIV controllers in the A5308 and SCOPE studies were able to control HIV after treatment was stopped.**
- **There is continued uncertainty about the risks and benefits of ART for HIV controllers. The presented results indicate that such treatment is unlikely to adversely influence controller status.**

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