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ART Reduces T Cell Activation and Immune Exhaustion Markers in HIV Controllers

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Abstract

BACKGROUND: Despite low or undetectable plasma HIV RNA, many HIV controllers (HCs) have detectable viral replication and elevated systemic inflammation. We assessed the effect of ART on HIV suppression, viral reservoir, immune activation, markers of inflammation, and quality of life in HCs.

METHODS: A5308 is a prospective, open-label study of RPV/FTC/TDF in ART-naive HCs with viral loads (VLs) <500 cp/mL for ≥12 months. After 48 weeks of ART, HCs had the option to be followed for an additional 48 weeks with optional ART. The primary outcome was the change in %CD38+HLA-DR+ CD8+ T cells after 24-48 weeks of ART. Outcomes were evaluated by repeated measures GEE models. Immune phenotyping was performed by flow cytometry. Soluble inflammatory markers were measured by ELISA. Residual viremia (RV) was measured by the integrase single-copy assay (iSCA); reservoir size by levels of total HIV DNA in CD4+ cells. Quality of life (QoL) was measured by the EQ-5D questionnaire.

RESULTS: Thirty-five HCs completed ≥24 weeks of ART and were analyzed. Before ART, HCs with undetectable VL by the iSCA had higher CD4+ counts than those with detectable VL (median 1128 vs. 659 cells/mm3, P=0.03) and lower levels of both CD8+ (median 19.4% vs. 26.5%, P=0.04) and CD4+ cell activation (2.3% vs. 2.9%, P=0.04). RPV/FTC/TDF was well tolerated, resulting in a modest, but significant improvement in self-reported QoL; two-thirds of HCs elected to continue ART through 96 weeks. ART was effective in further reducing RV: 19% of HCs had undetectable RV pre-ART vs. 94% after 24-48 weeks of ART (P<0.001). ART use resulted in a significant decline in the %CD38+HLA-DR+CD8+ cells at 24-48 (-4.0%, P=0.001) and 72-96 (-7.2%, P<0.001) weeks after ART initiation. After ART initiation, several markers of immune exhaustion (%PD1+, %TIGIT+, %CD160+ on CD8+ cells and %CD160 on CD4+ cells) declined. ART use decreased IP-10 levels, but increased levels of sCD163. There were no significant changes in the CD4+ counts or levels of total HIV DNA. Four HCs discontinued ART with ≥10 weeks of subsequent follow-up. All 4 HCs maintained VL<40 copies/mL at the last study time point, a median of 26 weeks after stopping ART.

CONCLUSIONS: One year of ART reduced T cell activation and markers of immune exhaustion in HIV controllers, in some cases with further decreases after two years of ART. ART was well tolerated and did not adversely affect controller status when discontinued. These results provide additional support for ART in HIV controllers.

Background

- HIV controllers suppress HIV in the blood to low levels without antiretroviral treatment (ART) and represent a natural model of a functional HIV cure.
- Despite low or undetectable plasma HIV RNA, viral replication appears to be ongoing in HIV controllers.
- HIV controllers are also reported to have higher levels of chronic inflammation, and increased rates of cardiovascular disease and hospitalization.
- We performed a prospective, open-label trial to assess the effect of RPV/FTC/TDF on HIV suppression, viral reservoir, immune activation, markers of inflammation, and quality of life in HIV controllers.

Objectives

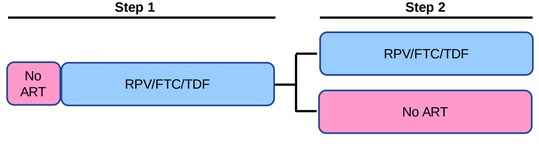
1. **Evaluate changes in CD4+ and CD8+ T-cell activation after initiation of RPV/FTC/TDF in ART-naïve HIV controllers.**
2. **Assess changes in plasma viral load and CD4+ cell count after ART initiation.**
3. **Determine changes in markers of inflammation and immune exhaustion.**
4. **Evaluate the tolerability of ART and changes in quality of life.**

Methods

Study Design

- A5308 was a prospective, open-label study of RPV/FTC/TDF in ART-naïve HIV controllers.
- Key inclusion criteria: 1) ART-naïve, 2) At least 2 viral loads <500 copies/mL for ≥12 months, 3) No known resistance mutations to RPV, FTC, or TDF.

Figure 1: Protocol Schema



Statistical Analysis

- Analysis of change from baseline after 24-48 weeks and after 72-96 weeks of ART were based on the estimated treatment effect from a repeated measures analysis using GEE.
- Within-participant slope (decline/year) from baseline were estimated using participant-specific linear regression models.
- Rank-based (Spearman) correlations for continuous outcomes, and exact Wilcoxon rank-sum and Fisher's tests for categorical outcomes were used to assess cross-sectional associations.

Figure 2: Participant Disposition

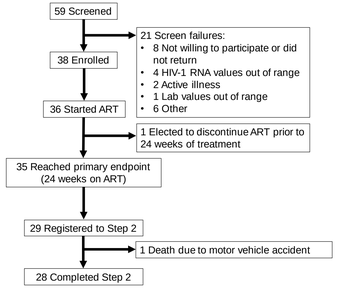


Table 1: Participant Characteristics

Characteristic	% or Median (N=35)
Female (%)	43%
Age (years)	47
Race/ethnicity (%)	
White, non-Hispanic	17%
Black, non-Hispanic	74%
Hispanic	9%
Pre-ART CD4+ count	655
Entry HIV-1 RNA <40 copies/mL (%)	37%
HLA*B27/57 (%)	57%

Results

ART Further Suppressed Residual Viremia by the Integrase Single-Copy Assay (iSCA), but has No Significant Effect on Total HIV-1 DNA, and Cell-Associated HIV-1 RNA (CA-RNA)

- Before ART, HIV controllers with undetectable iSCA viral load had significantly higher CD4+ counts than those with detectable iSCA viral load (median 1128 vs. 659 cells/mm^3, P=0.03).
- ART resulted in further suppression of low-level viremia: before ART, 19% of participants had an iSCA <0.6 copies/mL as compared to 94% of measurements after 24-48 weeks on ART (**Figure 3**).
- There were no significant changes in levels of HIV-1 DNA or CA-RNA with ART (**Figure 4**).

Figure 3: Proportion with Undetectable iSCA

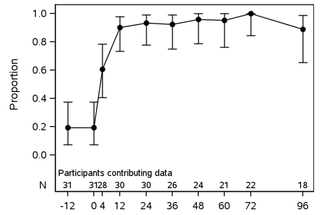
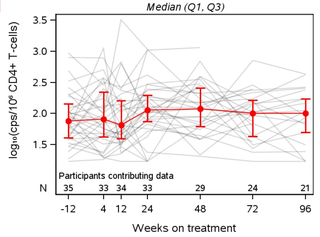


Figure 4: Changes in HIV-1 DNA



ART Reduces Levels of Immune Activation and Exhaustion in HIV-1 Controllers

- RPV/FTC/TDF had no significant effect on CD4+ counts (**Figure 5**).
- ART use resulted in a significant decline in the %CD38+HLA-DR+ CD8+ cells at 24-48 weeks (-4.0%, P=0.001) and 72-96 weeks after ART initiation (-7.2%, P<0.001, **Figure 6**).
- After ART initiation, several markers of immune exhaustion (%PD1, %TIGIT, %CD160 on CD8+ cells and %CD160 on CD4+ cells) declined (**Figure 7**).
- ART decreased IP-10 levels, but increased levels of sCD163.

Figure 5: Stable CD4+ Cell Counts

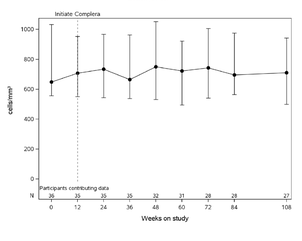


Figure 6: Decline in %CD38+HLA-DR+ CD8+ Cells with ART

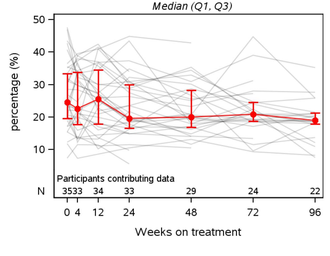
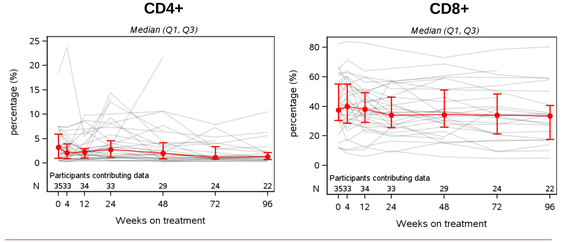


Figure 7: Changes in %CD160 in CD4+ and CD8+ Cells



ART was Well-Tolerated and Improved Quality-of-life

- RPV/FTC/TDF was well-tolerated by the HIV-1 controllers with two-thirds electing to continue ART through 96 weeks of the study.
- ART resulted in a modest, but significant improvement in self-reported quality of life (QoL) as measured by the EQ-5D questionnaire (QoL change -0.07, P<0.05).

Maintenance of HIV-1 Controller Status after ART Discontinuation

- Four HIV-1 controllers discontinued ART with at least 10 weeks of follow-up.
- All four individuals maintained viral load <40 copies/mL at the last study time point, a median of 26 weeks after stopping ART.

Conclusions

- **One year of RPV/FTC/TDF reduced T cell activation and markers of immune exhaustion in HIV-1 controllers, in some cases with further decreases after 2 years of ART.**
- **ART further suppressed low-level viremia in HIV-1 controllers, but this was not associated with significant changes in HIV-1 DNA, or CA-RNA levels.**
- **While pre-ART CD4+ counts were higher in HIV-1 controllers with lower viral loads, ART initiation did not lead to significantly increased CD4+ counts.**
- **RPV/FTC/TDF was well-tolerated by HIV-1 controllers and resulted in a modest, but significant improvement in quality-of-life.**
- **ART did not adversely affect HIV-1 controller status when discontinued.**
- **These results provide additional support for ART in HIV-1 controllers.**

Acknowledgements

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