ACTG A5351s: Effect of Immune-Modulatory Interventions on CMV Replication during ART

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BACKGROUND

Two trials explored the effect of immune-modulators on inflammation in people with HIV (PWH) on suppressive antiretroviral therapy (ART):

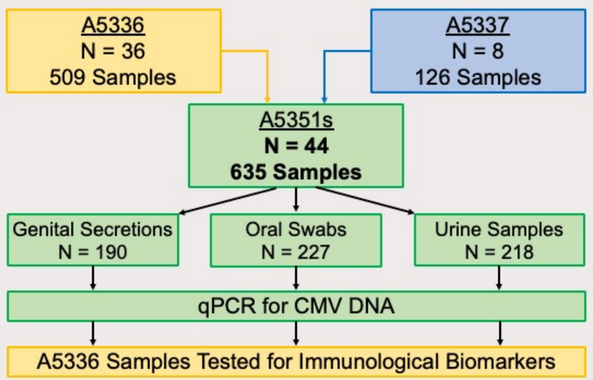
- **A5336** (ruxolitinib vs. placebo) revealed decreased immune activation (sCD14, CD38$^+$HDR$^+$ on CD4$^+$ T-cells) and cell survival (Bcl-2).
- **A5337** (sirolimus, single arm) revealed decreased cellular cycling (Ki67$^+$) and CD4$^+$ T-cell HIV DNA.

Overall Study Goal: To investigate if two immune-modulators (ruxolitinib and sirolimus) affected CMV shedding to elucidate a possible contributing effect of CMV replication on inflammatory outcomes in PWH.

METHODS

- A subset of participants, 36 from A5336 and 8 from A5337, were co-enrolled in this study (Figure 1).
- Genital, oral, and urine samples were assayed for CMV DNA by qPCR at baseline and longitudinally.
- **Statistics**: The proportion of participants with detectable CMV was compared between study arms using a Fisher's exact test with a 10% significance level. Box plots were generated for each trial (Figures 2 & 3).
- A5336 samples were tested for immunological biomarkers. Correlations between CMV DNA and these markers were examined at entry and week 5 and 10 by Spearman's correlations (Figure 4).

Figure 1. Make-up of A5351s participants and samples



There was no significant effect of immune-modulators on CMV DNA in PWH on ART with high baseline CD4$^+$ T-cells.

Figure 2. Box plot of CMV DNA levels on log10 scale in genital, oral, and urinary samples at entry, week 5, and week 10 in A5336 (ruxolitinib) participants. Whiskers represent the 3rd quartile plus 1.5 interquartile range. Outliers are plotted as individual points.

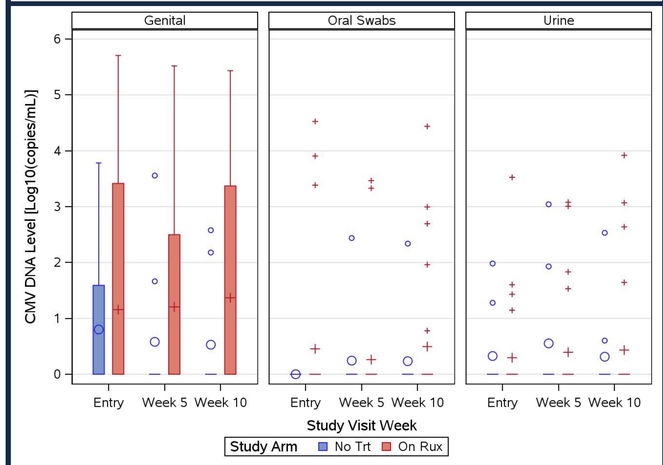
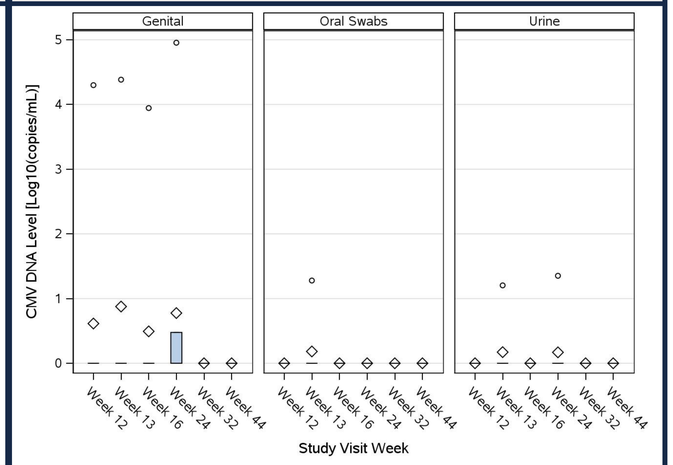


Figure 3. Box plot of CMV DNA levels on log10 scale in genital, oral, and urinary samples at entry, week 5, and week 10 in A5337 (sirolimus) participants. The diamond symbol represents the mean of CMV levels.



No differences in CMV DNA detectability or levels were found pre- or post-ruxolitinib in A5336 (Figure 2) or pre- or post-sirolimus for A5337 (Figure 3) at any mucosal site over time or between arms (all P values > 0.1).

Within A5336, there was a consistent positive association, at multiple time points and from multiple sample sites, between CMV DNA and Ki67$^+$ on CD4$^+$ and CD8$^+$ T-cells and CD38$^+$HLA-DR$^+$CD8$^+$ T-cells.

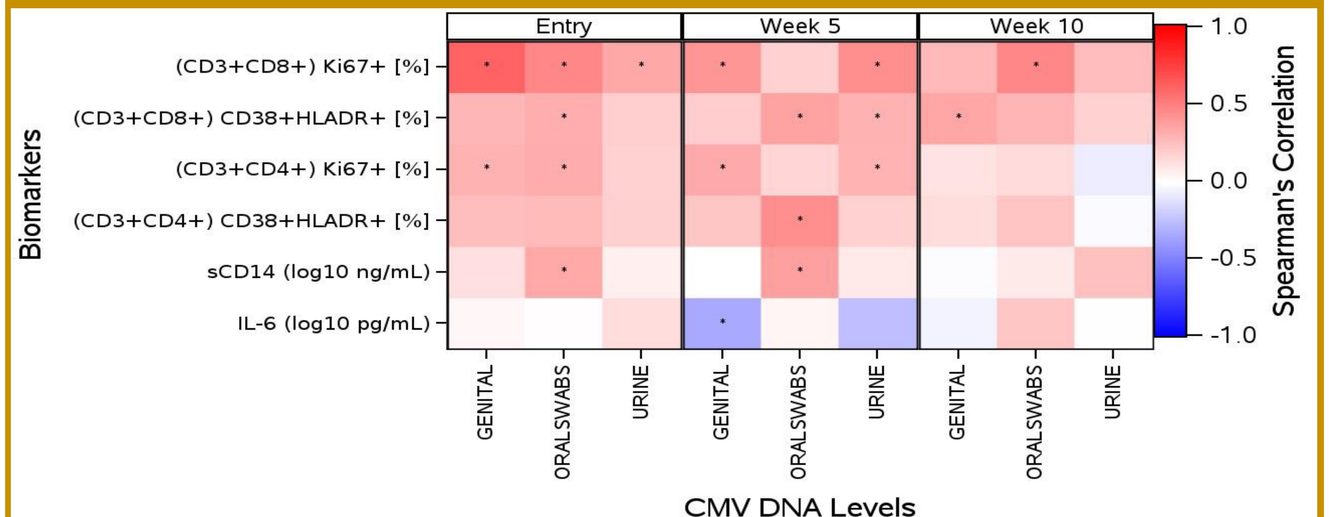


Figure 4. Association between CMV DNA level obtained from three sites and serum inflammatory biomarkers in A5336 participants at three timepoints: entry, week 5, and week 10. (*) represents Spearman's correlations ≥ 0.30.

RESULTS

- Median participant age was 49 years (range: 25-62 years), 77% were male sex (at birth), and 47% black race, non-Hispanic white.
- Median baseline CD4$^+$ T-cells were 859 cells/mm^3, and HIV RNA was <40 copies/mL in all but one participant. Baseline CD4/CD8 ratio was >1 in 61% of participants.
- The most common ART regimen was EFV/FTC/TDF (14 participants, 32%).
- CMV DNA was detected in 45 genital (29%), 19 oral (11%), and 31 urine (18%) samples.

CONCLUSIONS

- Our pilot study did not observe any significant effect of immune-modulators on CMV DNA in PWH on ART with high baseline CD4$^+$ T-cells.
- We did observe a consistent association between CMV levels and immune activation and cycling of CD4$^+$ and CD8$^+$ T-cells.

This association could have implications for HIV persistence, through expansion of CD4+ T-cells, and HIV-associated morbidity, through expansion of CD8+ T-cells as lower CD4+/CD8+ T-cell ratio is predictive of poor clinical outcome (Figure 4).

- Further research is warranted to explore whether limiting CMV replication in people with HIV affects levels of inflammation and long-term morbidity.
- Limitations of this study include the small number of participants.

ADDITIONAL KEY INFORMATION

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