Sex Differences in Immunologic Response to Letermovir-Mediated CMV Suppression in People with HIV

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Rebecca A. Abelman[1], Adam Olshen[1], Kristine M. Erlandson[2], Douglas W. Kitch[3], Shirley Qiu[3], Yoshinori Fukazawa[1], Noah Aquino[1], Scott L. Letendre[4], Lawrence Fox[5], John Koethe[6], Priscilla Hsue[7], Davey Smith[4], Michael L. Freeman[8], Sara Gianella[4], Peter W. Hunt[1] for the ACTG A5383 Study

[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Colorado, Aurora, CO, USA, [3]Harvard T.H. Chan School of Public Health, Boston, MA, USA, [4]University of San Diego, San Diego, CA, USA, [5]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [6]Vanderbilt University, Nashville, TN, USA, [7]University of California Los Angeles, Los Angeles, CA, USA, [8]Case Western Reserve University, Cleveland, OH, USA

BACKGROUND

- In ART-suppressed people with HIV (PWH), asymptomatic CMV suppression with letermovir reduced several inflammatory proteins causally linked to cardiovascular disease and cancer, but whether these changes are modified by sex remains unclear.
- Letermovir also caused an early transient increase in sTNFR2 at week 8, potentially due to suppression of CMV's immunoregulatory viral IL-10 (vIL-10).
- As women may have less STAT3 signaling after IL-10 receptor (IL-10R) stimulation than men (Islam et al, 2022), we hypothesized that early sTNFR2 changes might also be modified by sex.

METHODS

- A5383 was a 1:1 randomized clinical trial of the CMV terminase inhibitor letermovir vs no CMV treatment for 48 weeks in ART-suppressed PWH. The primary outcome was sTNFR2 levels.
- Enrollment was stratified by sex and CD4+ T cell count.
- Plasma inflammatory proteomics with 726 proteins (Olink Inflammation and Cardiometabolic Explore panels) were assessed longitudinally (median 6 timepoints/participant).
- Sex-by-treatment arm interactions were evaluated during the treatment period with linear mixed models, and linear splines employed to assess sTNFR2 changes.

RESULTS

- 39 randomized participants with post-entry data were included (28 men; 11 women; median age 58 years).

In ART-suppressed PWH and CMV, inflammatory proteome suppression with letermovir occurred in both sexes, but was greater in women.

Figure 1. Greater Declines in Inflammatory and Cardiometabolic Risk Proteins in Women than Men with Letermovir during Treatment Phase.

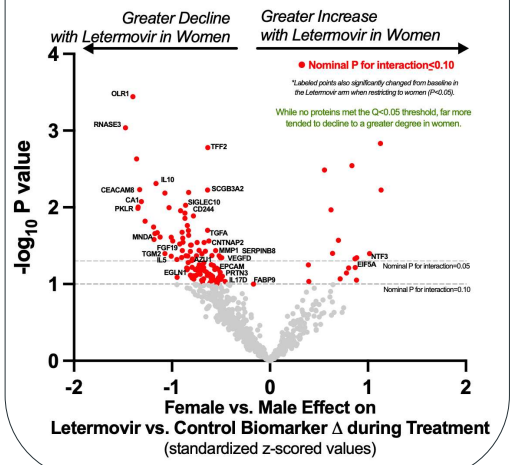


Figure 2. KEGG Pathways Associated with Inflammation, Cancer, and Cardiovascular Risk Declined to a Greater Degree in Women than Men.

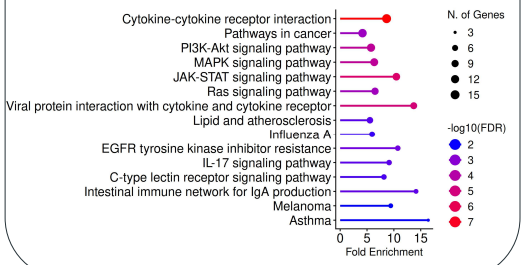


Figure 3. Men but Not Women Had Letermovir-mediated Declines in IL-10RA Levels.

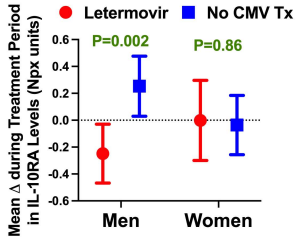
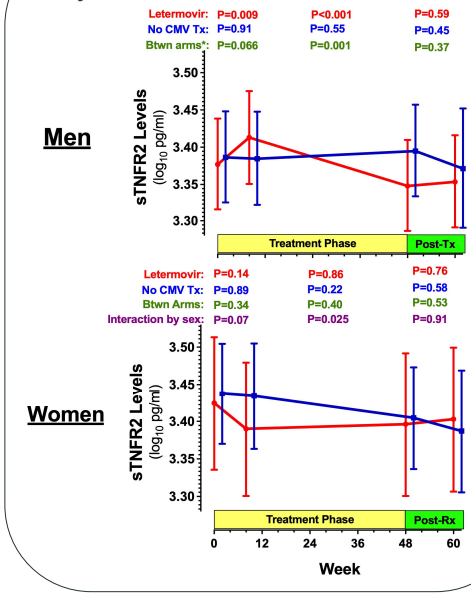


Figure 4. Men but Not Women Had Transient Early Letermovir-mediated Increases in sTNFR2.



CONCLUSIONS

- While inflammatory proteome suppression with letermovir occurred with both sexes, suppression tended to be greater in women than in men, including several pathways linked to cancer and cardiovascular risk.
- Letermovir-mediated declines in immunoregulatory IL-10R activity and early transient increases in sTNFR2 were also only observed in men.
  - *Had the trial been conducted only in women, it wouldn't have stopped early.*
- Whether letermovir treatment differentially alters clinical outcomes by sex in treated PWH with asymptomatic CMV merits further study.

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AUTHOR CONTACT INFORMATION:

Rebecca.Abelman@ucsf.edu

PLAIN LANGUAGE SUMMARY

While letermovir decreased inflammation in most people with treated HIV and asymptomatic CMV, women had greater declines in men. The transient early increase in one inflammatory marker (sTNFR2) that caused the early termination of the study was only observed in men.