Suppressing Asymptomatic CMV with Letermovir Reshapes Cardiometabolic Proteome in Treated HIV

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BACKGROUND

People with HIV (PWH) have higher risk of cardiometabolic disease than those without HIV despite antiretroviral therapy (ART).

STUDY GOAL

To assess whether letermovir for 48 weeks reduces plasma sTNFR2 (primary endpoint) and other inflammation and cardiometabolic indices versus no anti-CMV treatment.

METHODS

Study Design: Phase II, randomized, open-label, multicenter trial to evaluate the anti-inflammatory efficacy of letermovir 480 mg once daily for 48 weeks in PWH and asymptomatic CMV with ART-mediated suppression.

Study visits: Blood collection pre-treatment, treatment initiation, weeks 4, 8, 24, 46, 48, 52, 60. Mucosal sampling (genital, oral) pre-treatment, treatment initiation, weeks 8, 46, 48, 52, 60.

Planned futility analysis: Performed after the first 40 participants (of 180 planned) reached their 8-week study visit.

Statistical analysis: Continuous changes in plasma biomarkers (ELISA and Olink Inflammation and Cardiometabolic Explore panels) and binary CMV shedding in genital secretion and saliva compared between arms with linear mixed or logistic models, adjusting proteomic analyses for False Discovery Rate.

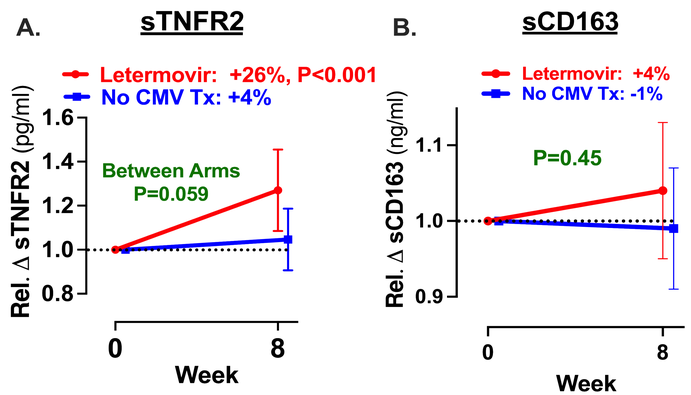
Letermovir is safe and broadly reduces immunologic and cardiometabolic biomarkers in people with HIV.

Table 1. Baseline Characteristics

Characteristics	Letermovir	No CMV Treatment
N	18	21
Sex at birth (female) %	22	33
*Age	59 (55, 60)	57 (52, 62)
Race %		
Native American	0	5
Black	44	33
White	50	62
Other	6	0
Ethnicity %	0	0
Not Hispanics or Latino	100	100
CD4 T Cells < 350 cells/mm^3 %	44	43
*CD4 T Cells count (cells/mm^3)	389 (268, 809)	384 (299, 655)

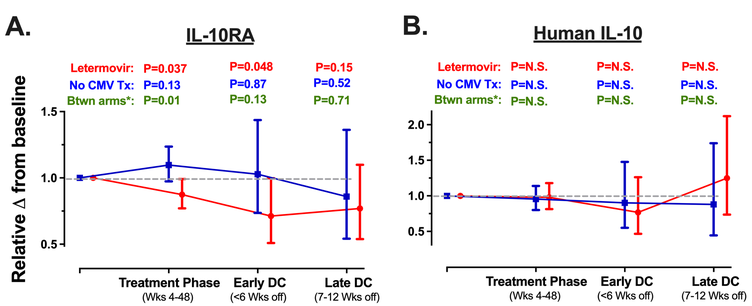
**Legend: ***Median [IQR]. Of 42 participants enrolled at 15 U.S. research sites, 39 contributed to the week 8 per-protocol futility analysis (18 letermovir, 21 no CMV treatment). Participants were stratified by CD4 count and sex at birth. One participant was inadvertently included in the abstract who had been disenrolled for taking a prohibited medication after screening. That participant was removed from the per-protocol analysis presented in the poster.

Figure 1. Futility Analysis: Letermovir unexpectedly increased sTNFR2 and had little effect on sCD163



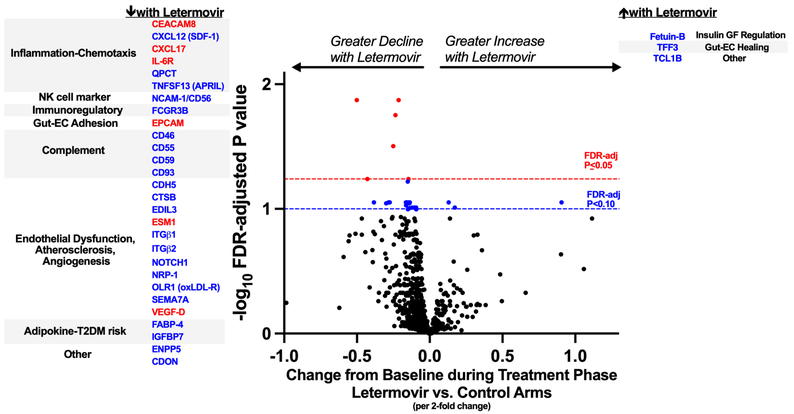
Legend: **Panel A (sTNFR2).** Within the letermovir arm, the mean (95% CI) change was +0.100 (0.036, 0.163) $\log_{10}$ pg/mL, while in the no treatment arm the mean change was +0.017 (-0.041, 0.075) $\log_{10}$ pg/mL. The mean difference (letermovir effect) was +0.083 (-0.003, 0.169) (p=0.059). **Panel B (sCD163).** Within the letermovir arm the mean (95% CI) change was +0.015 (-0.023, 0.053) $\log_{10}$ ng/mL, while in the no treatment arm the mean change was -0.005 (-0.040, 0.030) $\log_{10}$ ng/mL. The mean difference (letermovir effect) was +0.020 (-0.032, +0.071) (p=0.45).

Figure 2. Suppression of CMV viral IL-10 may have contributed to the increase in plasma sTNFR2.



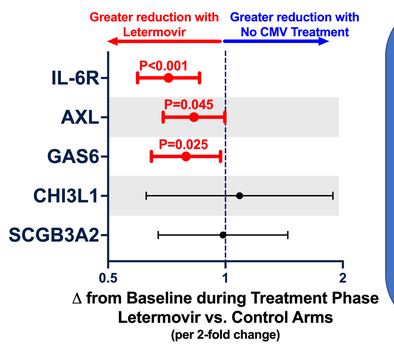
Legend: **Panel A.** Letermovir caused a significant decline in IL-10RA during treatment (p=0.037), and to a greater degree than in the control arm (P=0.01). **Panel B.** No change in human IL-10 was observed in either arm. CMV viral IL-10 was not reliably detectable in plasma.

Figure 3. Letermovir broadly impacts immunologic and cardiometabolic biomarkers in people with HIV.



Legend: 28 plasma inflammation and cardiometabolic proteins declined more in the letermovir than no treatment arm, while 3 increased to a greater degree with letermovir (FDR-adjusted P<0.05 [red] and P<0.10 [blue]). Given the exclusion of the participant who had been disenrolled from the study, 5 analytes that had met the FDR significance thresholds in the abstract, while still nominally significant, no longer meet FDR-corrected P value thresholds (e.g., IL1b, VCAM-1, FCRL6, CCL22, and TFPI).

Figure 4. Letermovir suppresses 3/5 proteins causally linked to CVD Events by Mendelian Randomization



- Reilly et al conducted the first Mendelian Randomization study of causal determinants of CVD events in treated HIV. (Reilly et al, JID, 2023)
- These 5 proteins were the only ones causally linked to CVD events.
- Letermovir decreased three of them (IL-6R, AXL, GAS6) to a greater degree than in the control arm.
- AXL and GAS6 are unique causal predictors of CVD in HIV.
- AXL/GAS6 also linked to transplant vasculopathy (Glinton, J Heart Lung Transpl, 2021)

Safety: Adverse events were similar between arms. No grade ≥3 reported related to study treatment.

Antiviral activity: Letermovir suppressed CMV DNA in oropharyngeal washes and semen at all on-treatment timepoints.

CONCLUSIONS

Letermovir-mediated suppression of asymptomatic CMV replication in people with treated HIV:

- Was safe and well tolerated
- Unexpectedly increased sTNFR2, which led to early study termination.
  - Possible consequence of decreased immunoregulatory CMV viral IL-10.
- Suppressed many inflammatory and cardiometabolic markers linked to CVD and cancer risk.
- Decreased 3 of 5 proteins causally linked to cardiovascular events in treated HIV by Mendelian Randomization (IL-6R, AXL, GAS6).

IMPLICATIONS

While the clinical significance remains unclear, this is the first study to show that a specific inhibitor of CMV – without direct activity against other herpesviruses – is safe and has broad impact on immunologic and cardiometabolic biomarkers in people with treated HIV.

Asymptomatic CMV remains an important interventional target to pursue in future studies.

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