EPIGENETIC IMPACT IN CSF CELLS FROM 48 WEEKS OF ADJUNCTIVE TELMISARTAN IN ACUTE HIV

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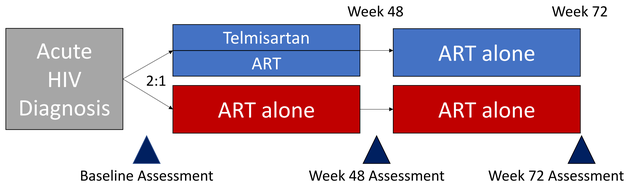
BACKGROUND

- Telmisartan, an angiotensin II receptor antagonist, is known to reduce inflammation.
- In a randomized trial, we examined whether 48 weeks of sustained adjunctive telmisartan initiated with antiretroviral therapy (ART) in acute HIV infection (AHI) would modify HIV's impact on the central nervous system (CNS).
- While we observed no significant changes in soluble makers of CNS inflammation or injury markers due to telmisartan, we did not evaluate its effects on cells within the CNS.
- Here, we investigated if telmisartan modified epigenetic states in cerebrospinal fluid (CSF) cells.

METHODS

- 21 male participants with AHI were randomized 2:1 to initiate treatment with ART +/- telmisartan; after 48 weeks, all individuals received ART alone.



Telmisartan initiated during AHI alters epigenetic states of genes related to inflammation, immune response, and cellular proliferation in CSF cells.

RESULTS

	ART+Tel (n=14)	ART Alone (n=7)	P-value
Age (years)	29 (23-40)	28 (24-32)	0.79
Male (n, %)	14 (100%)	7 (100%)	1.0
Sex with men (n, %)	14 (100%)	7 (100%)	1.0
Education	9/14 high school 5/14 college/technical	4/7 high school 3/7 college/technical	0.78
Days of infection	15 (11-20)	21 (16-26)	0.03
Fiebig stage	4/14 Fiebig I-II 10/14 Fiebig III-V	2/7 Fiebig I-II 5/7 III-V	1.0
Plasma HIV RNA (log_{10} copies/mL)	5.9 (5.2-6.4)	5.8 (5.4-6.6)	0.94
CD4+ T cell count (cells/uL)	377 (265-455)	457 (251-666)	0.23
CSF HIV RNA (log_{10} copies/mL)	2.8 (2.2-4.1)	4.4 (2.7-4.7)	0.19

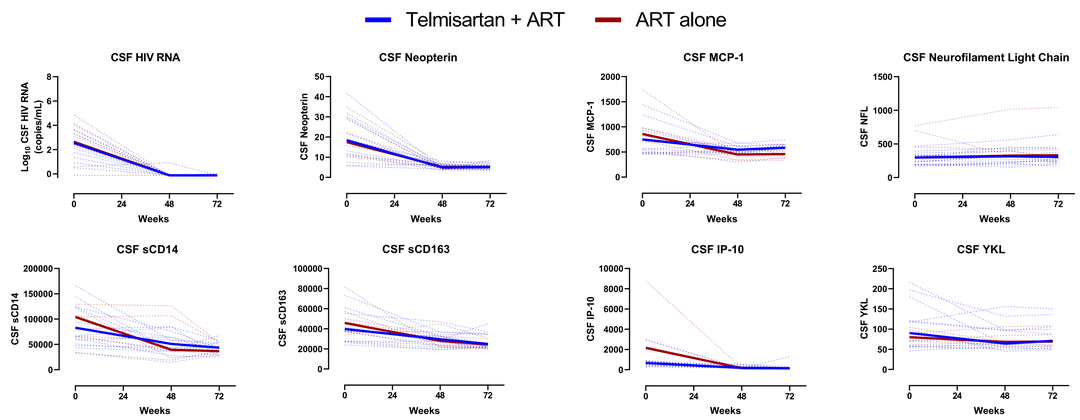


Figure 2. Cerebrospinal fluid biomarkers of viral replication, inflammation, and CNS injury for participants randomized to telmisartan + ART or ART alone at baseline and Weeks 24-72. Peluso et al. CROI 2019.

Genome-wide DNA methylation profiling of Cerebrospinal Fluid Cells at Baseline Week 0, Week 48, and Week 72.

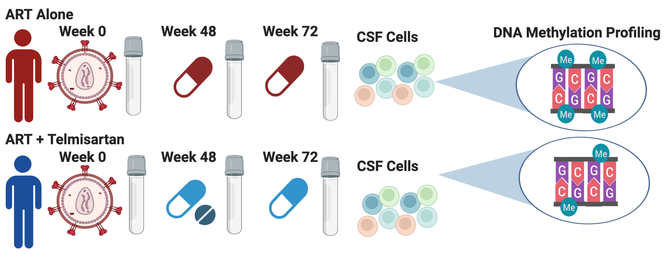


Figure 1. We utilized a new ultra-low DNA input assay to measure genome-wide DNA methylation (DNAm) epigenetic profiles in CSF cells at 48 and 72 weeks from 21 participants with AHI that were randomized 2:1 to initiate treatment with ART +/- telmisartan for 48 weeks. We used R to analyze DNA methylation data and identify differentially methylated loci using a linear model with FDR correction.

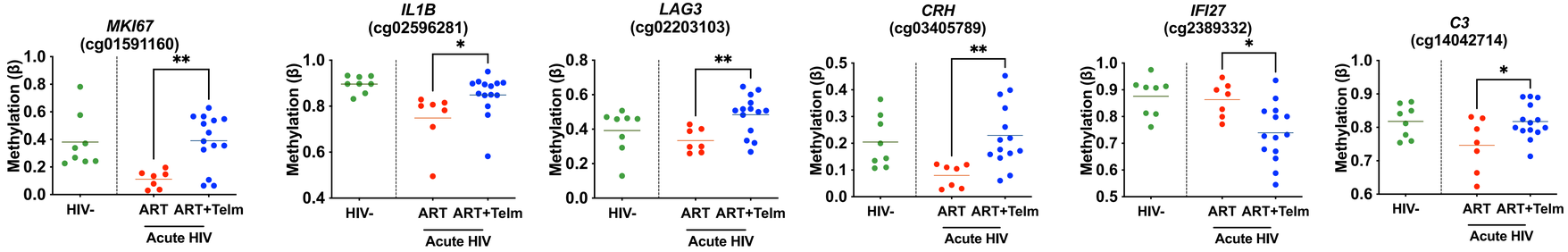


Figure 3. Cerebrospinal fluid cells DNA methylation states at Week 48 for participants randomized to telmisartan + ART or ART alone. HIV- participants cerebrospinal fluid cell DNA methylation states presented as a reference. Notably, DNAm levels of marker of proliferation Ki-67 *MKI67*, inflammatory gene *IL1B*, immune checkpoint receptor gene *LAG3*, central regulator of stress response gene CRH, and interferon stimulated gene *IFI27* were significantly altered in CSF cells of participants receiving ART+ telmisartan versus ART only for 48 weeks.

CONCLUSIONS

- We observed no significant changes in soluble makers of CNS inflammation or injury markers due to telmisartan.
- Notably, DNAm levels of marker of proliferation Ki-67 *MKI67*, inflammatory gene *IL1B*, immune checkpoint receptor gene *LAG3*, central regulator of stress response gene *CRH*, and interferon stimulated gene *IFI27* were significantly altered in CSF cells of participants receiving ART+ telmisartan versus ART only.
- Telmisartan's effects upon long-term epigenetic reprogramming of CNS cells and CNS outcomes warrants further investigation.

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