Central nervous system impact of vorinostat, hydroxychloroquine and maraviroc combination therapy followed by treatment interruption in individuals treated during acute HIV infection (SEARCH 026)

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Background:

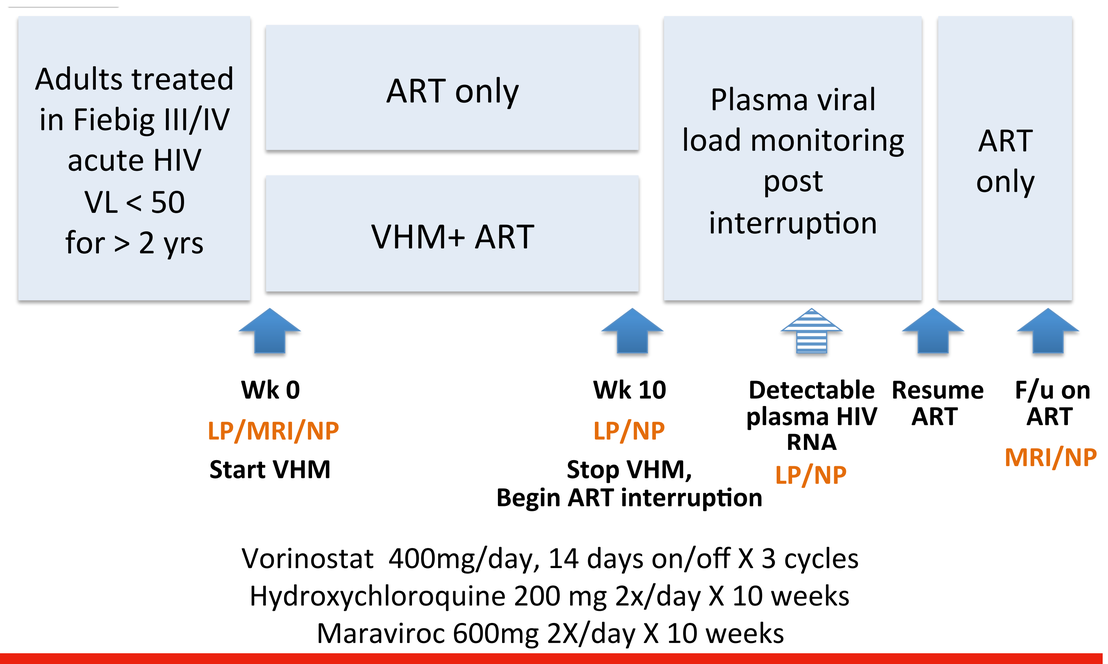
- Strategies to reactivate the HIV reservoir and analytic treatment interruption (ATI) could each have adverse consequences on the central nervous system (CNS) through induction of neuroinflammation or viral escape.
- We performed a CNS study in parallel with a systemic study of vorinostat/hydroxychloroquine/maraviroc (VHM) followed by ATI *(study SEARCH 019, abstract TUAX0101LB, late breaker, 19 July 2016, 13.00, session room 6).*

Methods:

Study participants and intervention design:

- Acutely treated participants with >48 weeks viral suppression and CD4 ≥450 cells/mm^3
- Randomization to 10 weeks of oral VHM (see **Figure 1** for dose/schedule) + ART (n=10) vs. ART alone (n=5), followed by ATI with ART resumption at plasma HIV RNA>1,000 copies/ml.

Figure 1. Study Design



Optional CNS sub-study:

- Lumbar puncture (**LP**) for cerebrospinal fluid (CSF) sampling at Wk 0 prior to intervention, Wk 10, and during ATI at first plasma HIV RNA >20 copies/ml. CSF HIV RNA was measured by standard assays as well as a single copy assay with a lower limit of detection of 0.27 copies/ml.
- Neuropsychological (**NP**) testing composed of 13 tests (summarized as NPZ Global) at Wk 0, Wk10, during ATI, and after resuming ART.
- 3T brain magnetic resonance imaging/spectroscopy (**MRI**/MRS) at Wk 0 and 6-8 weeks after ART resumption (see **Figure 1**).

Results:

Ten SEARCH 019 participants enrolled in the CNS sub-study (VHM+ART=8, ART=2); one withdrew due to adverse VHM effects, and one ART-only participant did not have LPs. Baseline demographics are shown as median (range) in **Table 1.**

Table 1. Demographics of Study Participants	VHM+ART (n=8)	ART (n=2)
HIV duration prior to ART, days	16 (12-27)	27 (21-32)
Age, years	30 (22-51)	32 (30-34)
Male:Female	7:1	1:1
ART duration, weeks	224 (79-294)	203 (111-295)
CD4 count, cells/mm^3	623 (501-1106)	1461 (1311-1612)
Plasma VL, copies/ml	<20	<20

Results (continued):

*In all graphs, Wk 10 VHM denotes visit during VHM randomization phase; symbols indicate participants receiving **VHM+ART** (red) or **ART** alone (blue).*

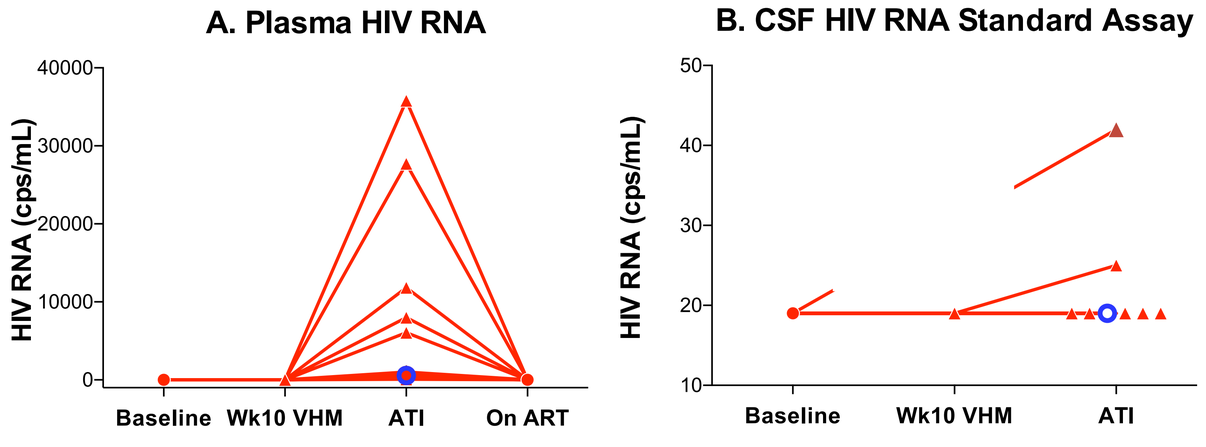
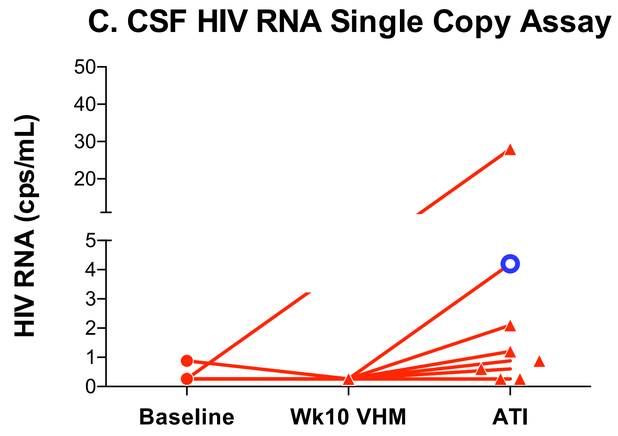


Figure 2. CSF HIV RNA with ART +/- VHM and ATI. CSF HIV RNA was <20 cps/ml or <0.27 cps/ml at Wk 0 and Wk 10 in all participants. 3-4 weeks after ATI, CSF HIV was detected in two VHM +ART participants by standard assay (25 and 42 cps/ml with corresponding plasma HIV of 35,796 and 329 cps/ml) (**A & B**). CSF HIV RNA was detected by single copy assay (≥ 0.27 cps/ml) in 6/8 participants (75%) during ATI (**C**).



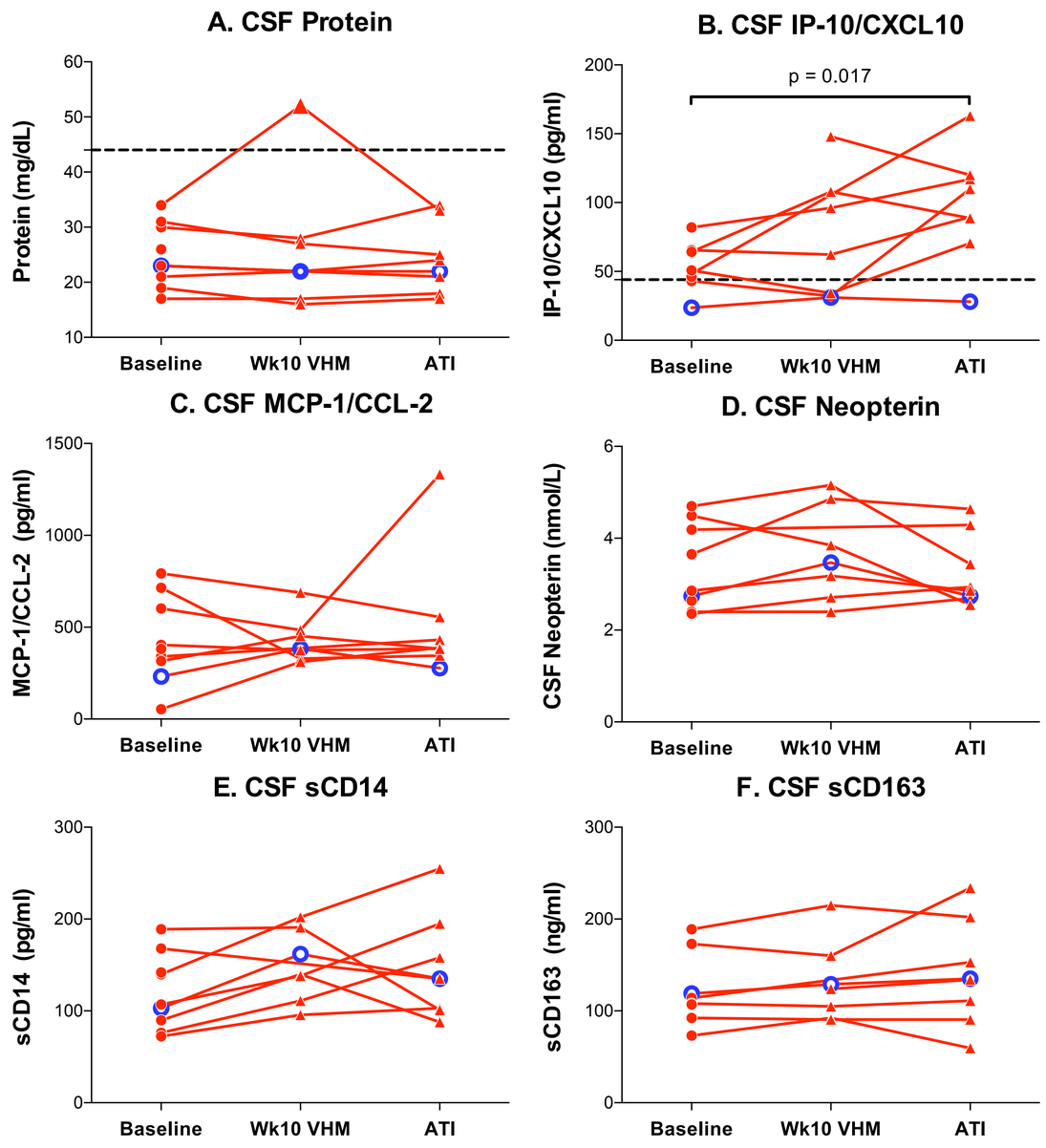


Figure 3. CSF immune activation with ART +/- VHM and ATI. CSF protein, a marker of blood-brain-barrier disruption, rose above the upper limit of normal (dashed line) during VHM in one participant (**A**). CSF IP-10/CXCL10, a lymphocyte chemokine, rose after ATI (**B**). CSF markers of monocyte/macrophage chemo-attraction and activation did not significantly change (**C-F**).

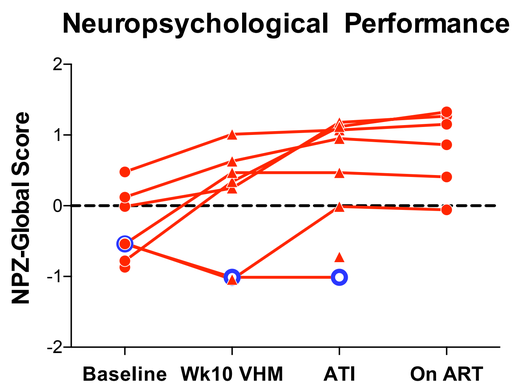


Figure 4. Neuropsychological performance improved with repeated testing in all but one VHM participant whose z scores declined at the Wk 10 VHM visit. Brain MRS in 6 participants at Wk 0 and after ART resumption revealed no significant changes in neuronal or inflammatory measures (not shown).

Conclusions:

- VHM, a latency reactivating intervention, did not lead to detectable CSF HIV RNA nor evidence of persistent adverse outcomes based on CSF inflammatory measures, neuropsychological testing performance, or brain MRS.
- Monitored ATI was associated with CNS immune activation and HIV RNA in CSF as detected by standard (in VHM+ART participants) and single copy assays (in both groups), though CSF rebound levels were lower than in blood.

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