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 ≥ 250 cells/mm³.
  - 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 >20 copies/ml. Baseline LPs were performed in all participants.

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 copies/ml or <0.27 copies/ml at Wk 0 and Wk 10 in all participants. 3-4 weeks after ATI, CSF HIV was detected in two VHM+ART participants (13.1 copies/ml vs. 25 and 42 copies/ml with corresponding plasma HIV RNA of 35,706 and 329 copies/ml (A & B). CSF HIV RNA was detected by single copy assay (≥ 0.27 copies/ml) in 6/8 participants (75%) during ATI (C).

Optional CNS sub-study:
- Lumbar puncture (LP) for cerebrospinal fluid (CSF) sampling at Wk 0 prior to treatment, 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

<table>
<thead>
<tr>
<th>Group</th>
<th>VHM+ART  (n=8)</th>
<th>ART  (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV duration prior to ART, days</td>
<td>16 (12-27)</td>
<td>27 (21-32)</td>
</tr>
<tr>
<td>Age, years</td>
<td>30 (22-51)</td>
<td>32 (30-40)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>7:1</td>
<td>1:1</td>
</tr>
<tr>
<td>ART duration, weeks</td>
<td>224 (79-294)</td>
<td>203 (111-295)</td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>623 (501-1106)</td>
<td>1461 (1311-1612)</td>
</tr>
<tr>
<td>Plasma VL, copies/ml</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

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 HIV rebound levels were lower than in blood.

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