Effect of vorinostat, hydroxychloroquine and maraviroc combination therapy on viremia following treatment interruption in individuals treated during acute HIV infection

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The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense or other institutions involved.
Conflict of Interest

- JA has received travel support from Cooper Human Systems, honoraria from ViiV Healthcare and Merck
- KE, HY, KC and MdS are employees of Cooper Human Systems
- The presentation will include discussion of off-label products
Background

• Multifaceted approach using drugs with different modes of action informed by mathematical modelling
  – Vorinostat: Latency reversal
  – Maraviroc: Entry inhibitor
  – Hydroxychloroquine: Immune modulator

• Acutely treated participants with low HIV reservoir size

• Objective
  – Frequency of participants with VL < 50 copies/ml at 24 weeks post treatment interruption with VHM+ART vs. ART alone
Study Design

Adults treated in Fiebig III/IV acute HIV
VL < 50 for > 2 yrs

<table>
<thead>
<tr>
<th>ART only (n=5)</th>
<th>ART if VL &gt; 1000</th>
<th>Weekly VL monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHM+ ART (n=10)</td>
<td>ART if VL &gt; 1000</td>
<td></td>
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</tbody>
</table>

Viral load post interruption

Wk 0
start VHM

Wk 10
Stop VHM, Begin interruption

Wk 34
End of study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>400mg/day</td>
<td>14 days on/off</td>
<td>3 cycles (10 weeks)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200mg/dose</td>
<td>2 times/day</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>600mg/dose</td>
<td>2 times/day</td>
<td>10 weeks</td>
</tr>
</tbody>
</table>
### Characteristics

**At Acute HIV Infection Diagnosis/ART initiation**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VHM+ART</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiebig stage</td>
<td>8 Fiebig III/2 Fiebig IV</td>
<td>5 Fiebig III</td>
</tr>
<tr>
<td>Viral load</td>
<td>6.1 (4.7 – 7.5)</td>
<td>5.6 (3.1 – 7.1)</td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>397 (132 – 574)</td>
<td>532 (213 – 740)</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>0.4 (0.3 – 2.1)</td>
<td>0.8 (0.6 – 1.0)</td>
</tr>
<tr>
<td>Total HIV DNA in PBMC, c/10⁶ cells</td>
<td>837 (0 – 2323)</td>
<td>594 (19 – 1878)</td>
</tr>
</tbody>
</table>

**At randomization**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VHM+ART</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28 (22-51)</td>
<td>26 (24-34)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>9:1</td>
<td>4:1</td>
</tr>
<tr>
<td>ART duration, weeks</td>
<td>224 (79-294)</td>
<td>155 (100-295)</td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>634 (501-1106)</td>
<td>1079 (537-1612)</td>
</tr>
<tr>
<td>Total HIV DNA in PBMC, c/10⁶ cells</td>
<td>44 (0 – 93)</td>
<td>27 (3 – 86)</td>
</tr>
</tbody>
</table>

*P > 0.05 for all*
Safety

- Two participants with serious adverse events in the VHM arm
  - One discontinued the study from renal insufficiency and low platelets from VHM
  - One with diarrhea possibly from food poisoning/VHM

- Non-serious adverse events
  - 81 events in 10 VHM vs. 37 events in 5 ART participants
  - Significantly more participants in VHM vs. control with thrombocytopenia (7 vs. 0) and high creatinine (7 vs. 0)

- Treatment interruption
  - No acute retroviral syndrome
  - No new resistance mutations by genotyping
  - No virological failure after ART resumption
Viral Load after ART Interruption

Median time to first VL detection: 22 days (range 14 to 77 days)

Two of 8 had detected CSF VL during plasma viremia post interruption (Kroon, Valcour, Spudich, Abstract 10588)
### Post-treatment Interruption

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>VHM+ART</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from treatment interruption to VL detection, weeks</td>
<td>3 (2 – 5)</td>
<td>3.1 (3 -11)</td>
</tr>
<tr>
<td>VL levels at first detection, c/ml</td>
<td>222 (33 – 41822)</td>
<td>156 (52 – 395)</td>
</tr>
<tr>
<td>Peak VL levels, c/ml</td>
<td>10797 (2823 – 75084)</td>
<td>4717 (1614 – 31264)</td>
</tr>
<tr>
<td>Time from first VL detection to ART resumption, weeks</td>
<td>1 (0.1 – 4.1)</td>
<td>2 (1 – 5.3)</td>
</tr>
<tr>
<td>Time from ART resumption to VL suppression, weeks</td>
<td>2.9 (0.9 – 10.9)</td>
<td>2 (1.9 – 3.9)</td>
</tr>
<tr>
<td>CD4 change from pre interruption to ART resumption, cells/mm³</td>
<td>2 (-376 to 549)</td>
<td>16 (-284 to 474)</td>
</tr>
</tbody>
</table>
No Changes in Total HIV DNA in PBMCs

No significant changes in total HIV DNA in PBMCs from week 34 to week 0
- VHM: median -4 (range -49 to 0)
- ART: median -1 (range -19 to 0)

Amélie Pagliuzza, Nicolas Chomont (U Montreal)
VHM Induces Low Level Plasma Viremia

Assay cut-off = 0.5 copies/ml

Frank Maldarelli (NCI), Robert Gorelick, Jeff Lifson (ACVP, Leidos Biomed Res)
No Changes in Immune Activation Markers

No changes in frequencies of activated CD4+ and CD8+ T cells
No changes in IP10, MCP1, sCD14, sCD163

Serena Spudich (Yale), Lydie Trautmann (MHRP)
Summary

• Proof-of-concept study of vorinostat/hydroxychloroquine/maraviroc + ART vs. ART alone in treated acutely infected persons
  – Closely monitored treatment interruption was safe
  – VHM
    • Well tolerated in the majority
    • No changes in total HIV DNA in PBMCs
    • Increases low level plasma viremia in some participants
    • No changes in T cell and soluble immune activation markers

• All Fiebig III/IV treated individuals had viral rebound after ATI
  – Time to VL rebound did not differ significantly to published chronic HIV cohorts
  – In this small study, ART duration, total HIV DNA in PBMCs, single copy VL, CD4/CD8 ratio did not predict time to viral rebound
Conclusion

• Treatment in Fiebig III/IV with or without VHM did not result in delayed time to viral rebound

• Alternative strategies to reduce or eliminate HIV reservoirs are needed
Acknowledgements

The SEARCH 019 and RV254 study participants

Thai Red Cross
James Fletcher
Donn Colby
Carlo Sacdalan
Thidarat Jupimai

Chulalongkorn
Kiat Ruxrunghtham
Sukalya Lerdlum
Sunee Sirivichayakul

U Montréal
Amelie Pagliuza
Remi Fromentin

U Melbourne
Ajantha Rhodes
J. Judy Chang

The Westmead Institute/ U Syd
Vincent Morcilla

UNC
Gail Henderson
Jean Cadigan

RTI
Holly Peay

U Minnesota
Timothy Schacker

Kapson Analytics
John Kapson

U Pittsburgh
John Mellors

MHRP
Nelson Michael
Merlin Robb
Hiroshi Takata
Supranee Buranapraditkun
Julie Mitchell

AFRIMS
Alexandra Schuetz
Yuwadee Phuang-ngern
Rapee Trichavaroj
Siriwat Akapirat

NIAD
Irini Sereti
Daniel Douek

NCI
Frank Maldarelli

ACVP, Leidos Biomed Res
Jacob Estes
Claire Deleage
Robert Gorelick
Robin Dewar
Jeff Lifson

UCSF
Victor Valcour
Joanna Hellmuth

Yale
Serena Spudich
Leah Le

Thai GPO
ViiV Healthcare
Gilead
Merck
Monogram