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Impact of maraviroc-intensification on immunisation and T-cell activation: A phase IV randomised double-blinded placebo-controlled study

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Objectives

- HIV-1 entry blockade by CCR5-antagonists potentiates immunomodulation.

- We hypothesised that maraviroc-intensification favourably impacts
  - Response to immunisation
  - T-cell phenotype and function
  - Delayed-type hypersensitivity (DTH) in HIV-1+ subjects.

Study Design
Referral, Screening and Randomisation

- **157 referred**
- **90 declined consent**
- **67 screened**
- **47 randomised**
- **20 excluded**

**24 assigned to placebo + background therapy**
- Week 24: 17 attended, 6 LTFU, 1 DO
- Week 16: 18 attended, 1 DNA, 5 LTFU, 1 DO
- Week 12: 18 attended, 5 LTFU, 1 DO
- Week 4: 20 attended, 3 LTFU, 1 DO

**24 were included in ITT analysis**

**23 assigned to MVC + background therapy**
- Week 24: 20 attended, 1 LTFU, 2 DO
- Week 16: 19 attended, 1 DNA, 1 LTFU, 2 DO
- Week 12: 20 attended, 1 LTFU, 2 DO
- Week 4: 21 attended, 1 LTFU, 1 DO

**23 were included in ITT analysis**

**Methods**

- **Clinical Care**
- ** Delayed Type Hypersensitivity; Mantoux skin test**
- **Detailed Immunology**
  - **T-cell Phenotype;** surface markers of differentiation, activation, senescence, exhaustion, co-stimulation and co-inhibition
  - **T-cell Function;** IFN-γ, IL-2, perforin and proliferation in response to HIV-1 Gag peptides, CMV and TTox
  - **Humoral Immunity;** anti-tetanus, -MenC and -cholera antibody titres
Methods

- Statistical Methods
  - Linear mixed model (SAS v9.1.3) compared between group data collected over time to derive time-weighted differences from baseline to each time-point.
  - Point estimates and 95% CI of changes from baseline are presented.

Adverse Events and Clinical Parameters

<table>
<thead>
<tr>
<th>Grade 1 &amp; 2</th>
<th>Oral MVC</th>
<th>System</th>
<th>Placebo</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly</td>
<td>49</td>
<td>GI, CNS, MS, Psych, ENT</td>
<td>36</td>
<td>4 Gi, CNS, Skin</td>
</tr>
<tr>
<td>Probably</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Definitely</td>
<td>0</td>
<td></td>
<td>1</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Oral MVC</th>
<th>System</th>
<th>Placebo</th>
<th>System</th>
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<tbody>
<tr>
<td>Possibly</td>
<td>0</td>
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<td>Probably</td>
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<tr>
<td>Definitely</td>
<td>0</td>
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<td>0</td>
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</tbody>
</table>

No clinically relevant changes in:
- Lymphocyte subsets
- Viral load
- Haematology
- Biochemistry
### Delayed Type Hypersensitivity

<table>
<thead>
<tr>
<th></th>
<th>Oral MVC n=23</th>
<th>Placebo n=24</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Pre baseline reaction results (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Negative (&lt; 5mm induration)</td>
<td>22 (95.7)</td>
<td>21 (87.5)</td>
<td>0.632</td>
</tr>
<tr>
<td>Positive (= 5mm induration)</td>
<td>1 (4.4)</td>
<td>3 (12.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 24 reaction results (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt; 5mm induration)</td>
<td>15 (75.0)</td>
<td>11 (64.7)</td>
<td>0.909</td>
</tr>
<tr>
<td>Positive (= 5mm induration)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>5 (25.0)</td>
<td>5 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Not applicable as not administered</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Agreement baseline to week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K )</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(78-100)</td>
<td>(74-100)</td>
<td></td>
</tr>
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### T-cell Phenotype

**CD4 T cells**
- Late (CD28-CD27-)
- Costimulation (CD28+)
- Coinhibition (CTLA-4)
- Activated (CD38+HLA-DR+)
- MHC II (CD38+HLA-DR+)

**CD8 T cells**
- Early (CD28+CD27+)
- Intermediate (CD28-CD27+)
- Late (CD28-CD27-)
- CD27+
- Coinhibition (CTLA-4)
T-cell Function

HIV-1-specific anti-viral function
TTox immunisation-specific function

Humoral Responses to Immunisation
Response to TTox significantly increased in both groups
Response to MenC enhanced by MVC
Response to Cholera dampened by MVC
### Summary

- No excess of AE or clinically relevant changes (VL, LSS, Chem, Haem)
- No change in DTH
- **Reduced CD4 T-cell activation**
- Increased number of MHC-II expressing and late-stage CD4 T cells
- **Normalisation of CD8 T-cell skewing** towards early and intermediate
- Less expression of co-stimulatory and more co-inhibitory molecules
- **Improved anti-Gag and anti-Ttox T-cell function** and expedited proliferation to Tetanus boost
- **Enhanced humoral neo-response** to MenC immunisation, however **reduced humoral neo-response** to Cholera immunisation
- **No effect on recall humoral response** to Tetanus boost

### Conclusion

Maraviroc-intensification favourably influences immune profiles of HIV-1\(^+\) patients, supporting immunomodulatory use in HIV-1 infection and potentially other immunologically relevant settings.
**Acknowledgements**

*Patients and Staff of the St Stephen’s Centre*

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