Pre-therapy inflammation and long-term CD4 response to antiretroviral therapy

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INTRODUCTION

• CD4 count response to ART is an important determinant of serious outcomes in HIV-positive individuals
• Pre-ART levels of inflammation and coagulation markers are associated with the risk of long-term outcomes
• It is unknown whether pre-ART inflammation predicts long-term CD4 count response to ART initiation
  – High pre-ART immune-activation could potentially result in attenuated gain in CD4 count
• Exploring this relationship could provide a mechanistic insight into the process of how inflammation relates to clinical outcomes

Kalayjian RC et al, J Infect Dis. 2010; 201(12); Boulware D et al, J Infect Dis. 2011; 203(11); Tenorio et al, J Infect Dis. 2014; 210(8)

Study aim

• To investigate whether pre-ART inflammation and coagulation activation predict CD4 count response to ART in HIV-positive patients (re)initiating ART at a wide range of baseline CD4+ cell counts.

Methods

• Study cohort nested in two large trials:
  – SMART trial: A multi-national trial investigating continuous (VS) vs interrupted (DC) ART
  o Selected: ART naive or off ART at randomisation, subsequently (re)initiated ART and had biomarkers measured at randomisation
  – FIRST trial: Investigating three first-line ART regimens with >=2 classes of drugs
  o Selected: who had biomarkers measured at randomisation as the part of previous case-control studies
  – Follow-up commenced at the (re)initiation of ART

El-Sadr WM et al, N Engl J Med. 2006; 355(22); SMART Study group, J Infect Dis. 2008; 197(8); Andrade BB et al, J Infect Dis. 2013; 207(9)

Disclosure

• None
Methods

- **Main covariates:**
  - C-reactive protein (CRP) and interleukin-6 (IL-6)
  - D-dimer
  - ‘Inflammation score’ generated by adding the rank of each patient according to the level of each of the markers.
    - Higher score reflects high immune activation/inflammation and coagulation activation.
  - All markers measured at randomisation (pre-ART) and analysed as quartiles.

- **Statistical methods:** Random effects linear models to model change in CD4 count. Adjusted for time (as visits at months 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24), baseline CD4 count and key confounders.

Results

- **Total N= 1084 participants**
  - 659 patients were from SMART (26% ART naive)
  - 425 from FIRST
- **Total 8264 CD4 count measurements**

Characteristics | SMART | FIRST | Total
--- | --- | --- | ---
Male | 466 (70.7) | 352 (82.8) | 818 (75.5)
Age Mean (SD) | 42.4 (9.2) | 40.7 (8.8) | 41.9 (9.1)
Black race (%) | 266 (40.4) | 244 (57.4) | 510 (47.1)
IDU mode of transmission | 88 (13.3) | 157 (36.9) | 245 (22.6)
CD4 count Median (IQR) | 410 (350-530) | 100 (22-300) | 360 (165-473)
Hepatitis B positive (%) | 25 (3.8) | 79 (18.6) | 104 (9.6)
Hepatitis C positive (%) | 125 (19.0) | 230 (54.1) | 355 (32.8)
D-dimer µg/mL Median (IQR) | 0.34 (0.22-0.63) | 0.60 (0.37-1.16) | 0.43 (0.25-0.81)
CRP µg/mL Median (IQR) | 1.61 (0.68-3.58) | 1.87 (0.69-5.11) | 1.69 (0.69-4.12)
IL-6 pg/mL Median (IQR) | 2.23 (1.50-6.63) | 3.5 (2.00-6.21) | 2.39 (1.63-4.45)

- All of the markers showed an inverse correlation with the baseline CD4+ cell count, largely driven by a strong correlation in the FIRST cohort (P<0.05 for interaction between baseline CD4 count and the study).
- In FIRST, the coefficient for each marker (95% CI) per 100 cell increment in baseline CD4 count were:
  - D-dimer: -0.11 (-0.16, -0.06)
  - IL6: -1.11 (-2.03, -0.18)
  - CRP: -1.30 (-2.24, -0.37)

CD4 change by quartiles of CRP

CD4 change by quartiles of IL-6

CD4 change by quartiles of D-dimer
Results

Adjusted* models

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Inflammation Rank-score</th>
<th>CRP</th>
<th>D-dimer</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartiles of Biomarker</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>1</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>2</td>
<td>-1.1 (-25.1, 14.9)</td>
<td>3.7 (-16.2, 23.6)</td>
<td>7.5 (-27.4, 12.5)</td>
<td>7.3 (-12.8, 27.5)</td>
</tr>
<tr>
<td>3</td>
<td>-11.9 (-32.4, 8.6)</td>
<td>-0.9 (-21.0, 19.3)</td>
<td>-16.3 (-37.1, 4.5)</td>
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</table>

P for trend 0.25 0.97 0.29 0.44

*SAdjusted for the following baseline (at ART initiation) variables: age, CD4 count, sex, race, mode of transmission, hepatitis B and C status, body mass index, history and duration of any prior ART (if any), duration or date of HIV infection (if known), treatment arm and of viral load.

Sensitivity analyses

- Analyse by trial
- Analyse only FIRST participants included in Andrade et al [as they were not selected on case-control status] and SMART VS arm [as the DC arm had a greater time gap between biomarker measurement and start of ART]
- Analyse following alternative outcomes:
  - percent change in absolute CD4 count;
  - change in CD4 percentage;
  - change in CD4:CD8 ratio, (only available in SMART cohort)

Conclusions

- Pre-ART immune-activation/inflammation and coagulation activation levels do not predict CD4+ cell count response to ART
  - Note we did not investigate effects of ongoing inflammation on CD4
- They likely influence the risk of clinical outcomes through mechanisms independent of blunting the long-term CD4 count gain.
- Findings imply that the potential benefit of suppressing pre-ART immune-activation/inflammation (e.g. by anti-inflammatory agents) may not be apparent in the CD4+ cell count trajectory over time

Acknowledgements

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