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

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Disclosure

- None

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 in to 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)

Methods

- **Outcome:**
- Absolute _change_ in CD4 count during the follow-up from (re)start of ART (visit 0) to 24 months post-ART.
  o Calculated by subtracting CD4 count at each follow-up visit from that at ART initiation

Methods

- **Main covariates:**
  - **C-reactive protein (CRP) and interleukin-6 (IL-6)**
  - **D-dimer**
  - **'Inflammation score'** generated by adding the rank of the 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 naïve)
  - 425 from FIRST
- Total 8264 CD4 count measurements

Results

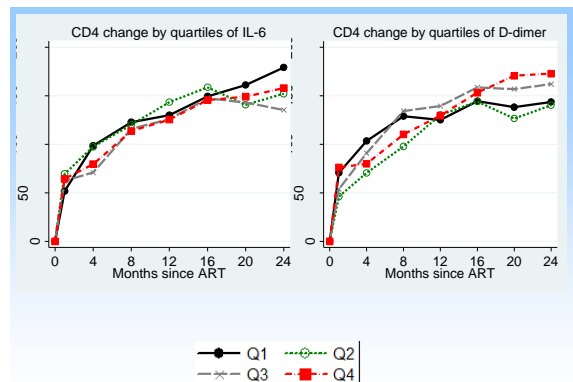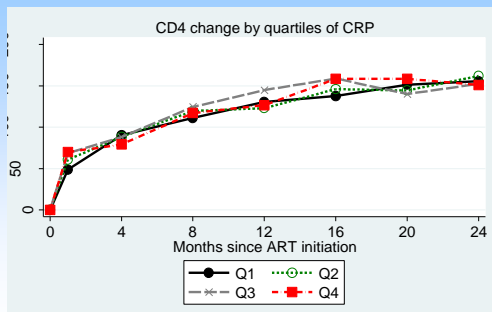| Characteristics	SMART	FIRST	Total
Male	466(70.7)	352 (82.8)	818 (75.5)
Age Mean(SD)	42.4(9.2)	40.7 (8.8)	41.9 (9.1)
Black race (%)	266(40.4)	244 (57.4)	510 (47.1)
IDU mode of transmission	88(13.3)	157 (36.9)	245 (22.6)
CD4 count Median (IQR)	416(350-530)	100 (22-300)	360 (165-473)
Hepatitis B positive (%)	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 (1.50-3.63)	3.5 (2.00-6.21)	2.59 (1.63-4.45)

Results

- **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)

Results

CD4 change by quartiles of CRP

CD4 change by quartiles of IL-6 | CD4 change by quartiles of D-dimer

Results
Adjusted* models

Covariate	Difference in mean CD4 count change relative to reference (95% CI), P-value			
Quartiles of Biomarker	IL-6	CRP	D-dimer	Inflammation Rank-score
1	Reference	Reference	Reference	Reference
2	-2.7 (-21.9, 16.5)	1.0 (-18.3, 20.3)	-20.4 (-39.9, -0.8)	0.2 (-19.4, 19.8)
3	-5.1 (-25.1, 14.9)	3.7 (-16.2, 23.6)	-7.5 (-27.4, 12.5)	7.3 (-12.8, 27.5)
4	-11.9 (-32.4, 8.6)	-0.9 (-21.0, 19.1)	-16.3 (-37.1, 4.5)	-10.9 (-31.8, 9.9)
P for trend	0.25	0.97	0.29	0.44

*Adjusted 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

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Acknowledgements