**INTRODUCTION**

- CD4+ cell 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 gain in CD4+ cell count post ART initiation.
- High pre-ART immune-activation could potentially result in attenuated gain in CD4+ cell count.
- Exploring this relationship could provide a mechanistic insight into the process of how inflammation relates to clinical outcomes.

**STUDY AIM**

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

**METHODS**

- **Study population:** SMART study participants who were ART naïve or off ART at randomisation, subsequently initiated ART and had biomarkers measured at randomisation.
- **Outcome:** Absolute change in CD4+ cell count during the follow-up from (re)initiation of ART (visit 0) to 24 months post-ART. The CD4+ cell count change was calculated by subtracting CD4+ cell count at each follow-up visit from that at ART initiation.
- **Main covariates:** Biomarkers of immune-activation: inflammation (C-reactive protein (CRP) and Interleukin-6 (IL-6)), Biomarker of Bimorbidity D-dimer. Inflammation score generated by adding the rank of the each participant according to the level of each of the markers. Thus a higher score reflects high immune activations/inflammation and coagulation activation.
- **Statistical methods:** Follow-up commenced at the (re)initiation of ART. We plotted mean change in CD4+ cell count at each visit by the quartiles of each baseline biomarker. We then fitted random effects linear models to model change in CD4+ cell count. Model was timed as visits at months 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24.
- Models were adjusted for the following baseline (at ART initiation) variables: age, CD4+ cell count, sex, race, mode of transmission, hepatitis B and C status, body mass index, history and duration of any prior ART (if any), duration and date of HIV infection (if known), treatment arm, and log(base10) of viral load copies/mL.

**RESULTS**

- A total of 1084 participants with 6264 CD4+ cell count dataset were included in this analysis. Of these, 659 patients were from SMART (26% ART naïve) and 425 from FIRST.
- 75% were male with the mean age of 42 years. 47% were Black, 22% reported IDM as mode of transmission, and 9.6% and 32.8%, respectively, were known to be hepatitis B and C positive.
- The medians (inter-quartile ranges) (IQRs) of key variables at ART (initiation) were as follows: CD4+ cell count: 360 (265-473), D-dimer: 0.43 (0.25-0.81) μg/mL, CRP: 1.69 (0.69-4.12) μg/mL and IL-6: 2.59 (1.63-4.45) pM/mL.
- The median (IQR) CD4+ cell count in SMART and FIRST was 416 (350-530) and 100 (22-300) cells/mm2, respectively.
- All of the markers showed an inverse correlation with the baseline CD4+ cell count, largely driven by a strong correlation in the FIRST cohort (R=0.05 for interaction between baseline CD4 count and the study). In FIRST, the coefficient for each marker (95% confidence interval) per 100 cell increase in baseline CD4 count was: D-dimer: 0.11 (0.06, 0.16), IL-6: 1.11 (2.03, -0.18) and CRP: 1.30 (2.24, -0.37).
- Figure 1 shows the mean CD4+ cell count change by the quartile (Q1 to Q4) of each biomarker at baseline, overall and separately for each trial.
- Table 1 provides the adjusted mean difference in CD4+ cell count change across all visits for quartiles of each biomarker from random effect models. Each model was adjusted for visits (time) and covariates mentioned above.
- There did not appear to be any relationship between baseline biomarker levels and mean change in CD4+ cell count post ART initiation.

**CONCLUSIONS**

- Pre-ART immune-activation/inflammation and coagulation activation levels do not predict CD4+ cell count response to ART.
- They likely influence the risk of clinical outcomes through mechanisms independent of blunting the long-term CD4+ cell gain.
- Findings indirectly 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.

**REFERENCES**


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