THE SYSTEMIC INFLAMMATORY PROFILE DIFFERS ACCORDING TO THE MECHANISM OF HIV CONTROL

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I. Background

- Elite controllers (EC) are an exceptional group of people living with HIV (PLWH) able to control HIV replication without antiretroviral therapy and have been proposed as a model of functional HIV cure.
- However, significant evidence suggests that despite viral control, EC subjects may have altered levels of activation and systemic inflammation.
- We have characterized the systemic inflammation profile in EC compared to non-controllers PLWH with ART-mediated control of viral replication.

II. Methods

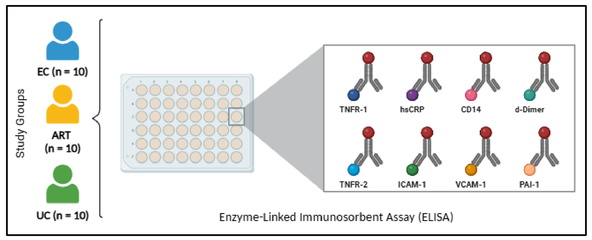


Figure 1. General outline of the methodology. Three study groups were included: 10 EC, 10 non-controllers PLWH on ART (ART), and 10 uninfected controls (UC) as reference. Plasmatic levels of markers of inflammation (sTNFR1, sTNF2, hsCRP), endothelial activation (sICAM1, sVCAM1), monocyte activation (sCD14), intestinal barrier permeability (FABP2), and coagulopathy (d-Dimer, PAI-1), were assessed using enzyme-linked immunosorbent assay (ELISA). Inter-group differences were tested by nonparametric tests (Kruskall-Wallis; Mann-Whitney) and a discriminant analysis was employed to ascertain the markers involved in discriminating between pairs of study groups.

III. Results

- The baseline clinical and demographic characteristics of EC, ART, and UC groups are shown in **Table 1**. UC group was matched for age and sex with PLWH groups. There were no significant differences between PLWH participants for age, sex, transmission route, CD4 counts, plasma HIV load, years of infection, and years on ART.
- The profile of alterations (tacking UC group as a reference) of the plasma markers analyzed was different between EC and ART groups (**Figures 1-4**).

Table 1. Characteristics of study groups.

Characteristics	EC group (n=10)	ART group (n=10)	UC (n=10)	*p*-value
Age (years)	56 [45 - 61]	55 [47 - 60]	51 [45 - 57]	0.702
Sex (% of males)	60	60	60	1.0
Transmission route (% of sexually transmitted)	60	70	NA	0.405
CD4 count (cells/ µL)	869 [514 - 1200]	993 [655 - 1120]	NA	0.529
Plasma HIV load (copies/ mL)	20 [20 - 23]	20 [20 - 20]	NA	0.481
Years of infection	19 [11 - 24]	13 [8 - 20]	NA	0.436
Years on ART	NA	7 [6 - 9]	NA	-

Data are given as median [IQR], except sex and transmission route, which are expressed as percentages. Statistical differences between the three study groups were tested by Mann-Whitney or Kruskal-Wallis tests for continuous variables and by the Chi-square test for sex and transmission route. Statistical significance was considered for p-values below 0.05. NA: not applicable.

III. Results

- The profile of alterations (taking UC group as reference) of the markers analyzed was different in the EC and the ART groups. ART group presented increased plasma levels of endothelial activation marker of sVCAM1 (714[564-890] vs. 474[332-741] ng/mL in ART and UC; p=0.086) (**Figure 1**), whereas EC group presented increased plasma levels of the monocyte activation marker of sCD14 (1210[990-1944] vs. 965[574-1140] ng/mL in EC and UC; p=0.054) (**Figure 1**). Moreover, sVCAM was increased in ART group compared to EC group (714[564-890] vs. 560[377-636] ng/mL; p=0.041) (**Figure 1**). For the other markers assessed there were no significant differences between the groups studied (**Figure 2**), although, interestingly, there was a trend towards higher plasma levels of sTNFR-2, hs-CRP and sCD14 in the PLWH groups (EC and ART) compared to uninfected controls (UC).

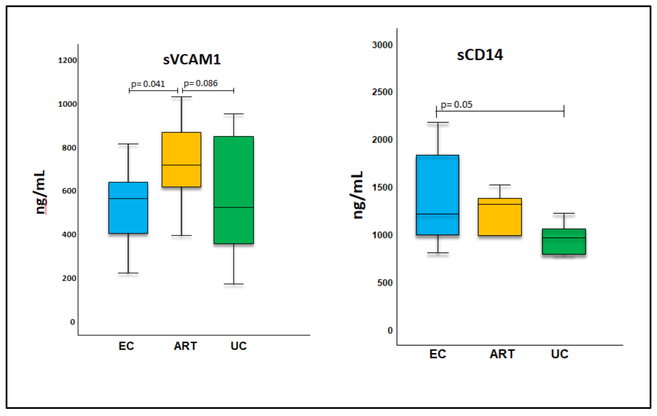


Figure 1. Box-plots graphs showing plasma levels (median ng/mL, range) of sVCAM-1 and sICAM-1 and sCD14 in EC, ART and UC groups. Pairwise comparisons between groups were made using the Mann-Whitney test.

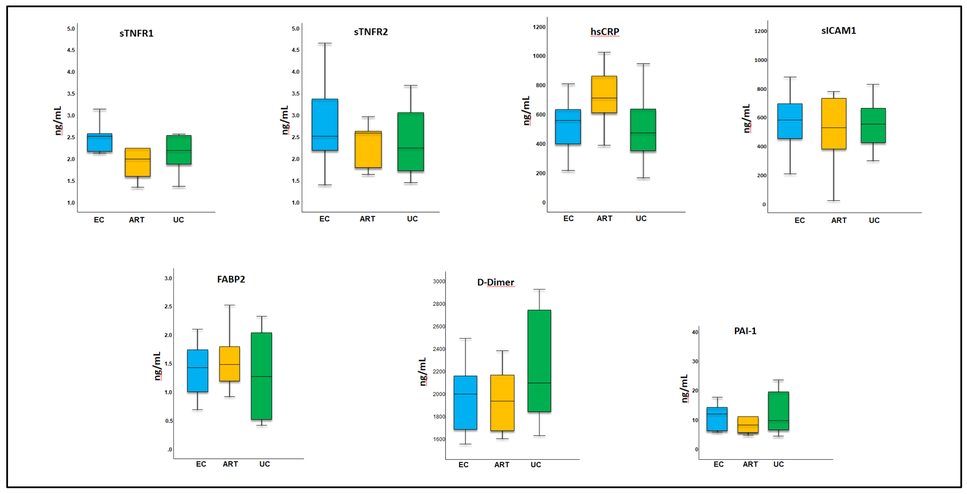


Figure 2. Box-plots graphs showing plasma levels (median ng/mL, range) of sTNFR1, sTNFR2, hsCRP, sICAM!, FABP2, D-Dimer and PAI-1 in EC, ART and UC groups. Pairwise comparisons between groups were made using the Mann-Whitney test.

- The discriminant models were able to separate between the EC and UC groups (proportion of individuals correctly classified by the model was 70% and 80% for EC and UC respectively; sCD14 was the only variable in the model) **(Figure 3)**
- The disiciriminant analysis was also able to discriminate between the EC and the ART groups (proportion of individuals correctly classified by the model was 70% and 70% for EC and ART respectively; sVCAM was the only variable in the model) **(Figure 4)**.

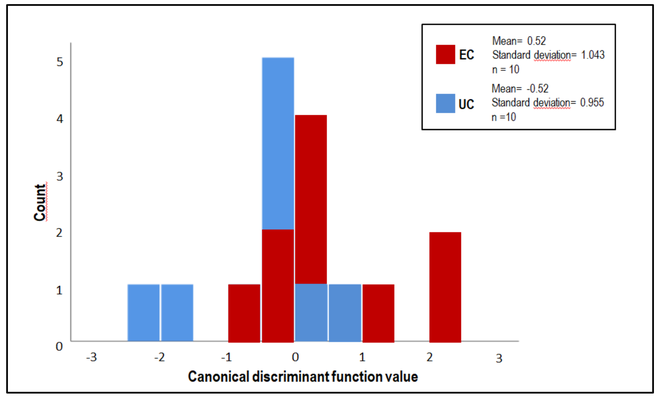


Figure 3. Canonical discriminant analysis to discriminate between EC and UC according to plasma levels of sCD14 marker. The bar graph shows the distribution of the canonical function values (x-axis) and the frequency of participants with each value (y-axis). Mean and standard deviation of the canonical function value for each group is given in the graph.

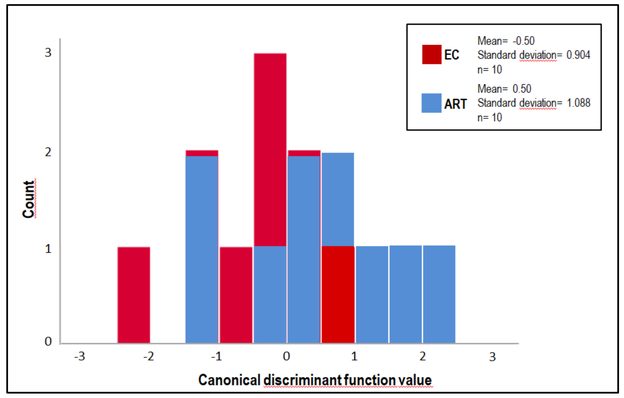


Figure 4. Canonical discriminant analysis to discriminate between EC and ART PLWH according to plasma levels of sVCAM marker. The bar graph shows the distribution of the canonical function values (x-axis) and the frequency of participants with each value (y-axis). Mean and standard deviation of the canonical function value for each group is given in the graph

V. Conclusions

- Our results show the existence of a chronic inflammatory status in people living with HIV in spite of controlled viral replication.
- Interestingly the profile of inflammation differs according to the mechanism of HIV control and points to monocyte activation as a main driver in PLWH elite controllers.
- Further studies are warranted to test the effect of different biomarkers levels on the profile of morbidities observed in PLWH with different mechanisms of viral suppression.

IV. Funding/Aknowledgements

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