MONITORING THE IMPACT OF ART MODIFICATION WITH LONGITUDINAL FDG-PET IN SIV-MODEL

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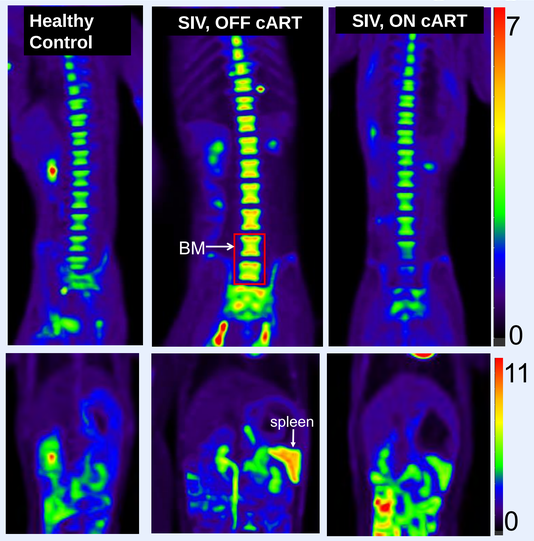
Background

The aim of this study was to assess immune activation in various organs by longitudinally measuring changes in glucose metabolism associated with initiation and interruption of combination antiretroviral therapy (cART) in SIV-infected macaques. Although some previous whole-body FDG PET studies were performed cross-sectionally in HIV/SIV infected subjects, findings mainly emphasized the lymph nodes[2,3,4]. In addition to monitoring ^{18}F-Fluorodeoxyglucose (FDG) uptake in tissues, we also studied the correlations of SUV changes with various markers of disease activity such as viral loads (VL), T and B cell counts and serum cytokines.

Methods

- Whole body FDG PET-imaging was obtained for seven infected macaques (SIVmac251 or SIVE660) and five healthy controls
- The infected macaques were imaged longitudinally at various time points within the treatment modification regimen (up to 6 months before or after cART)
- PET images were analyzed with PMOD 3.7. SUV_{max} values were obtained from manually drawn volumes of interest (VOIs) corresponding to the brain[1] and peripheral tissues: bone marrow (BM), spleen, axillary, inguinal LNs and liver
- Univariate and multivariate mixed-effect linear regression models, constructed in R, provided correlation estimates between FDG-uptake and peripheral biomarkers (blood CD4+, CD8+T cell counts, plasma viral load (PI VL) and serum cytokine levels (Il-2, Il-15, Il-1ra, Il-8, MCP-1)

FDG-Imaging



Coronal Maximum intensity projection (MIP) slices show the changes in FDG uptake in the bone marrow (upper row) and spleen (lower row). Changes between on and off therapy can be detected visually.

Results

1

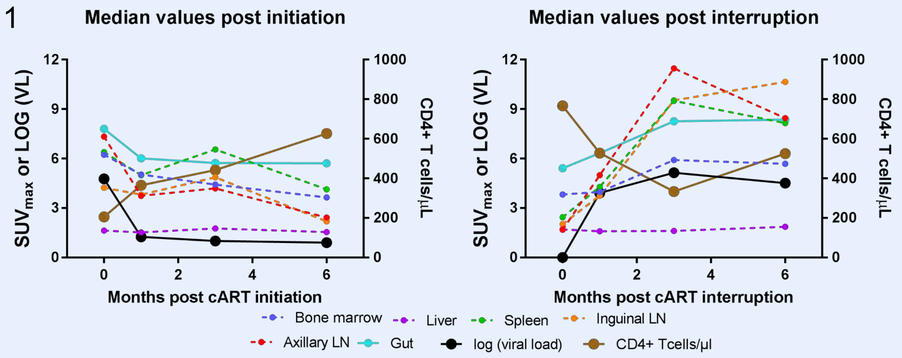


Figure 1. Graphical representation of changes in SUV_{max} and Plasma VL along with CD4+ T cell counts with initiation of cART (right) or interruption of cART (left)

- With a univariate approach, significant inverse associations of FDG uptake and CD4+ counts ($P<0.05$) and direct associations of FDG uptake and plasma VL ($P\leq0.001$) were found for all organs.
- For the group on cART therapy, univariate analysis showed a significant positive correlation between spleen SUV_{max} and the proinflammatory cytokine, Il-8 ($P<0.05$).
- In the multivariate analyses, only plasma VL remained statistically significantly associated with FDG-uptake in the lymphoid organs ($P<0.01$ for Ax LNs, Ing LNs and spleen) and the BM ($P<0.05$). There were no statistically significant correlations detected between FDG uptake and serum cytokines.
- Spearman rank correlation between BM SUV_{max} and SUV_{max} of the lymphoid organs (spleen, AxLNs and IngLNs) was highly significant ($P<0.001$).

2

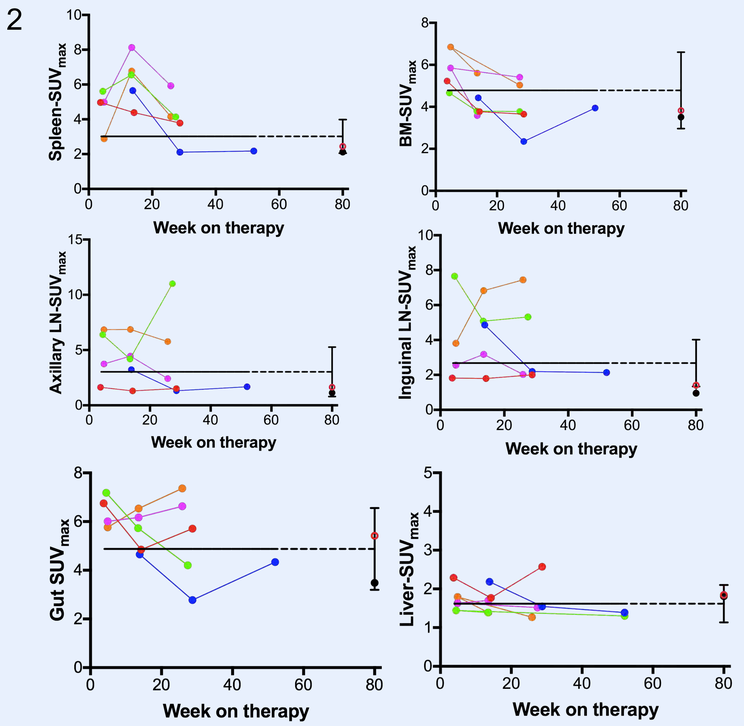


Figure 2. Limited analysis of imaging time points in cART treated subjects with suppressed plasma VL (17 scans in 7 subjects- represented with a different color) shows continued FDG normalization with treatment duration in certain tissues even when plasma VL is suppressed (<50 copies/ml). The dashed line represents the mean ± SD of SUV_{max} for the 7 healthy controls.

Conclusion

- In SIV infected animal undergoing initiation or interruption of cART, PET-FDG revealed a pattern of immune activation within the spleen, clusters of lymph nodes and bone marrow which appear to be mainly explained by changes in plasma viral load rather than changes in peripheral blood CD4+ T cell counts.
- In subjects that start antiretroviral therapy, the normalization of immune activation takes approximately 6 months (independent of the time needed to achieve plasma viral load suppression)
- These results suggest a hematopoietic and/or inflammatory reaction to viral replication that needs more investigation.

References

1. Schreiber-Stainthorp, W., et al. “Brain 18F-FDG PET of SIV-infected macaques after treatment interruption or initiation”. CROI 2018, Poster #429
2. Scharko, Alexander M., et al. "Whole-body positron emission tomography in patients with HIV-1 infection." *The Lancet* 362.9388 (2003): 959-961.
3. Iyengar, S, et al. "Anatomical loci of HIV-associated immune activation and association with viraemia. *The Lancet* 362.(2003): 945-950
4. Scharko, Alexander M., et al. "Whole body positron emission tomography imaging of simian immunodeficiency virus-infected rhesus macaques." *Proceedings of the National Academy of Sciences* 93.13 (1996): 6425-6430.