Poster # 210

EFFECTS OF LONG-TERM ART ON SIVsab-INFECTED PIGTAILED MACAQUES

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Background

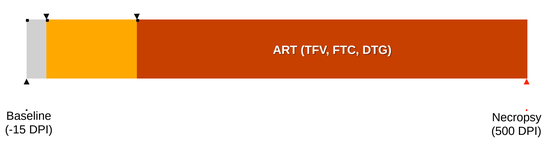
By infecting pigtailed macaques (PTMs) with SIVsab, we developed a new model of highly pathogenic SIV infection. This model is useful for HIV pathogenesis studies, as it faithfully reproduces classical features of HIV including a high degree of gut dysfunction, persistent immune activation and inflammation (IA/INFL) and high incidence of comorbidities. For model validation, it is critical to determine if available antiretroviral (ARV) therapies control virus replication at levels comparable to those in HIV-infected patients. While SIV is notoriously difficult to control with ARVs, a coformulated combination of three ARVs (reverse transcriptase inhibitors Emtricitabine [FTC] and tenofovir disoproxil fumarate [PMPA] and integrase inhibitor Dolutegravir [DTG]) induces robust virus control in SIVmac239-infected rhesus macaques.

Goals

To determine if the virological and immunological parameters of the SIVsab/ARV treated infection in PTMs are similar to those described in HIV-infected ARV-treated human subjects. This will indicate whether or not our model is useful for cure studies aimed at curbing the virus reservoir or pathogenesis studies addressing comorbidities related to ART-treated SIV/HIV infection.

Design

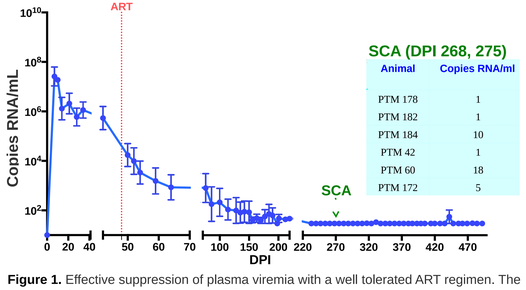
Six PTMs infected with SIVsab (300 TCID50) received ART at 48 days postinfection



Methods

- Six PTMs infected with SIVsab (300 TCID50)
- ART: coformulation of three drugs: TFV (20 mg/mL), FTC (40 mg/mL) and DTG (2.5 mg/mL). The coformulation was administered subcutaneously daily from 48 DPI, until the end of the study
- Plasma viral loads for SIVsab were quantified by qRT-PCR assay (detection limit: 30 copy/ml);
- Immunophenotyping was done on blood, intestine and lymph node, and immune cells and subsets, their immune activation and proliferation status were frequently monitored.
- ELISA assays were performed to evaluate the levels of inflammation by monitoring chemokine and metabolic markers during ART.

Results



SCA (DPI 268, 275)

Animal	Copies RNA/ml
PTM 178	1
PTM 182	1
PTM 184	10
PTM 42	1
PTM 60	18
PTM 172	5

Figure 1. Effective suppression of plasma viremia with a well tolerated ART regimen. The robust viral control was confirmed by SCA.

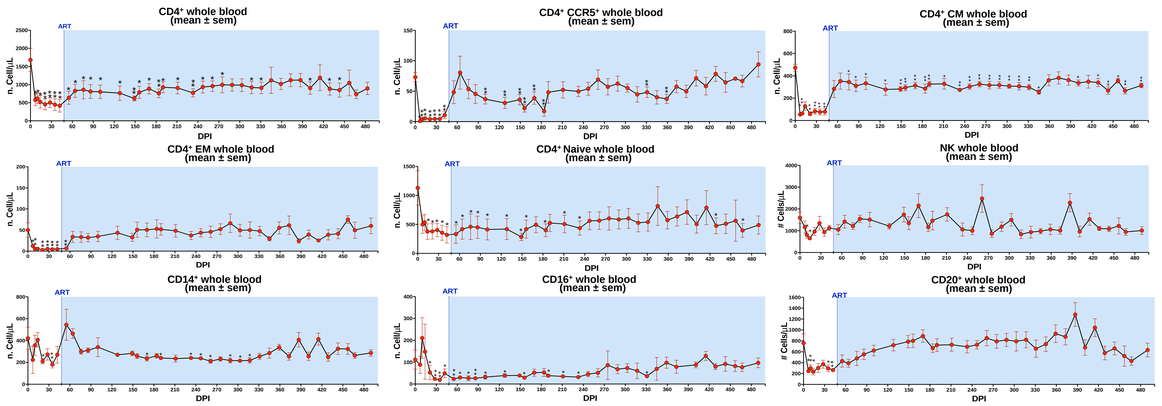


Figure 2. Immune-cell dynamics in blood of SIVsab-infected PTMs.

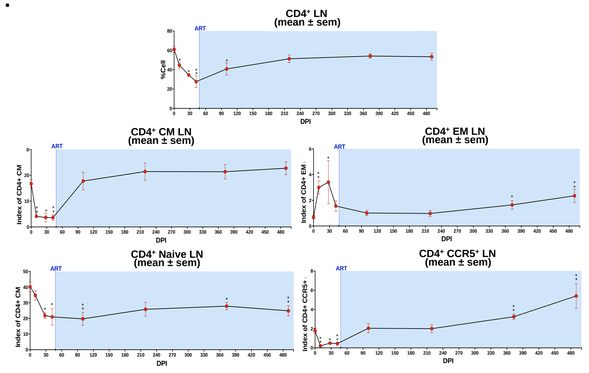


Figure 3. CD4 T cell dynamics in lymph nodes of SIVsab-infected PTMs.

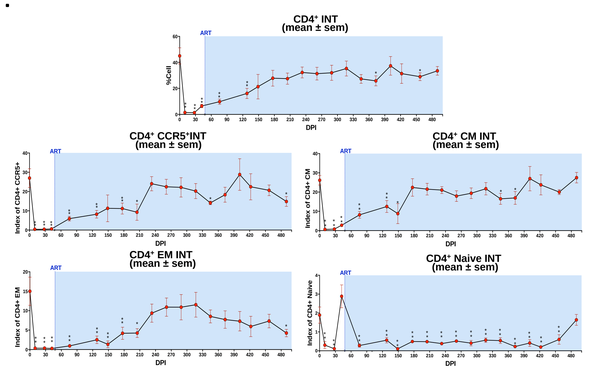


Figure 4. CD4 T cell dynamics in the intestine of SIVsab-infected PTMs.

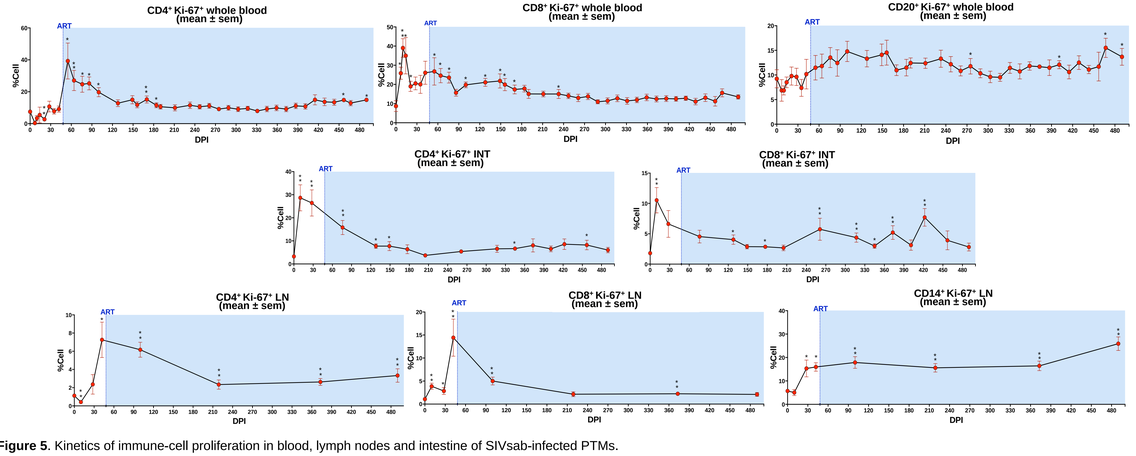


Figure 5. Kinetics of immune-cell proliferation in blood, lymph nodes and intestine of SIVsab-infected PTMs.

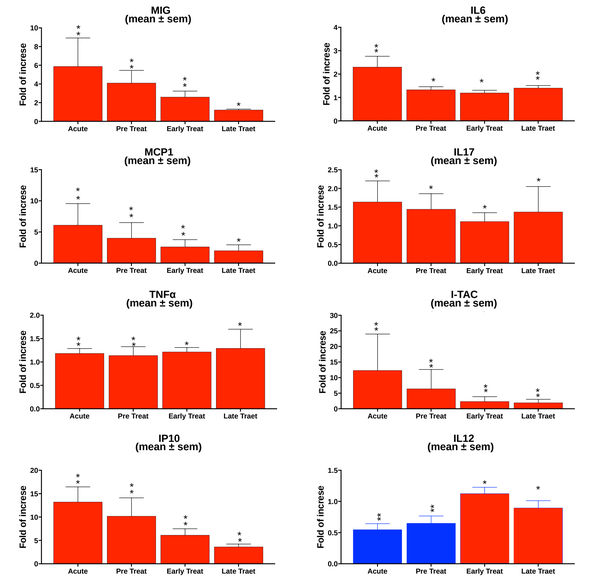


Figure 6. Assessment of changes in the levels of cytokines at different treatment stages. Shown are the average fold increases from the baseline ± standard errors of the means. Acute, acute infection; Pre Treat, pre treatment; Early Treat, early treatment; Late Treat, Late treatment. Red indicates fold of increase and blue fold of decrease.

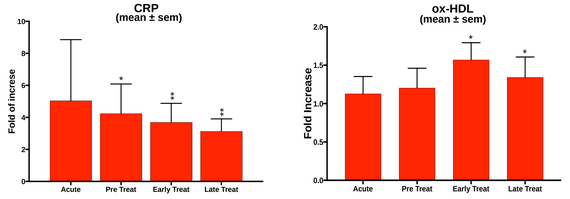


Figure 7. Assessment of changes in the levels of metabolic markers at different treatment stages. Shown are the average fold increases from the baseline ± standard errors of the means. Acute, acute infection; Pre Treat, pre treatment; Early Treat, early treatment; Late Treat, Late treatment.

Conclusion

- The long-term administration of a coformulated ARV regimen to an SIVsab/PTM model with extremely high viral loads and severe gut damage is effective in controlling virus replication and results in partial, but robust, CD4⁺ T cell restoration.
- Similar to ARV-treated HIV-infected subjects, the PTMs experience residual immune activation and inflammation and metabolic biomarker increase.
- **Our results validate the SIVsab/PTM system as an appropriate model of treated SIV infection, thus opening large avenues for its use for pathogenesis, comorbidities and cure studies involving ART.**