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Multi-dose Romidepsin in SIV-infected RMs Reactivates Latent Virus in Absence of ART

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Background

Persistent viral reservoirs represent a major obstacle in eliminating HIV-1 from infected individuals, even with antiretroviral therapy (ART). The difficulty in studying such reservoirs in humans stresses the need for animal models of HIV/SIV control with conventional ART. A reservoir reactivation strategy is the "shock and kill" approach, in which latent virus is reactivated [i.e., with histone deacetylase inhibitors (HDACis)] and eliminated through effective cytotoxic T lymphocyte responses. A recent study reported no effect of HDACi in reactivating the virus *in vitro*. Another study reported that HDACi hinder the cytolytic capabilities of CTLs *ex vivo*. It is currently unknown whether the reactivating virus is replication competent.

Hypothesis

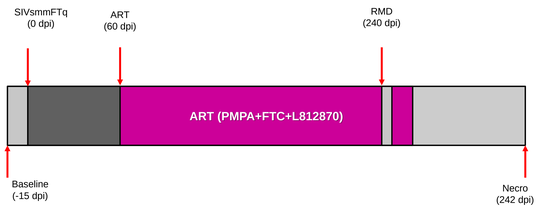
Administration of the HDACi romidepsin to our RM model of viral control will result in reactivation of replication-competent SIV.

Goals

- Develop a non-human primate model of SIV control with conventional ART
- Assess the HDACi romidepsin's (Istodax) ability to reactivate SIV in controller RMs
- Develop monitoring capabilities for reactivation studies

Design

- **4 Indian RMs (3 TFP/TFP; 1 TFP/Cyp)**



Methods

- **ART: SubQ: PMPA (20 mg/kg/day) FTC (40 mg/kg/day); P.O.: L-812 (20 mg/kg, b.i.d.)**
- **VLs-SCA for FTq; Reservoir monitoring at the necropsy (cell-associated RNA; proviral DNA; 2-LTR)**
- **Immunophenotyping;**
- **SMART biomarkers.**

Results

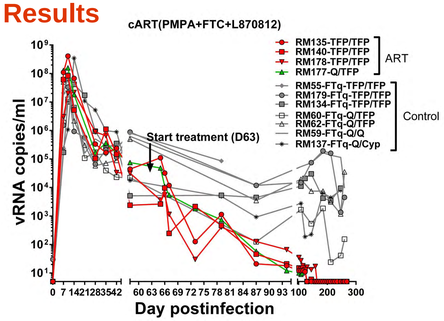


Figure 1. Effective suppression of plasma viremia with a well tolerated ART regimen

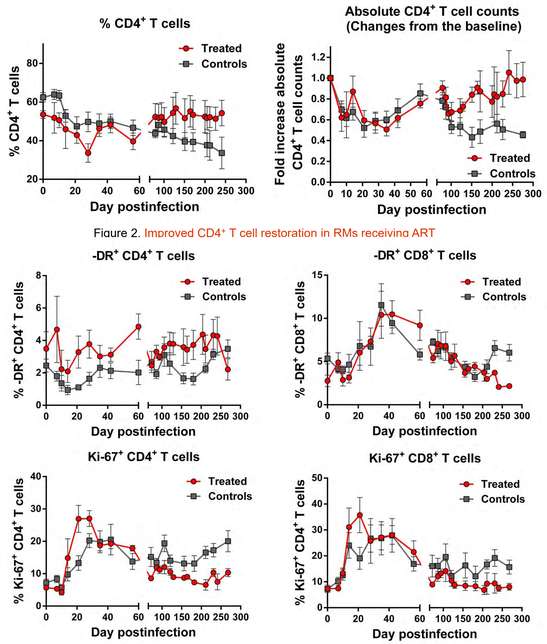


Figure 2. Improved CD4+ T cell restoration in RMs receiving ART

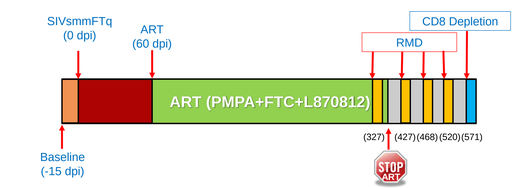
Figure 3. Normalization of T cell immune activation in RMs receiving ART

Conclusions (1)

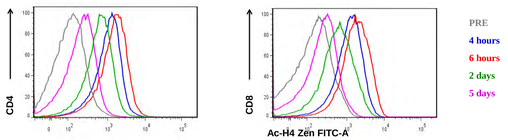
- **New SIVsmm strains show significant promise for cure research in NHPs**
- **These viruses can be controlled to <10 copies/ml with conventional ART**
- **During the follow-up, suppression was robust, with no blip (testing: every week)**
- **SIVsmmFTq-specific assays (both SCA/other virus quantification assays and ISH) are available**

Virus Reactivation with RMD/CD8 Depleting Antibody

- **3 Indian RMs (3 TFP/TFP)**



- **RMD in slow perfusion (4 hours) at a dose of 7 mg/m²**
- **CD8 Depleting antibody (M-T870R1) at a dose of 50mg/kg**



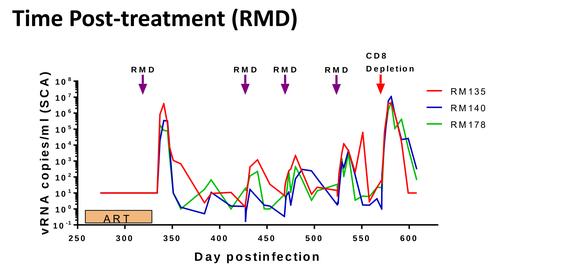


Figure 4. RMD and CD8 depleting antibody administration can reactivate SIV *in vivo* in untreated RMs

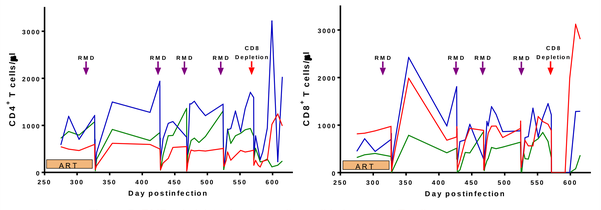


Figure 5. RMD administration has a discernible impact on T cells

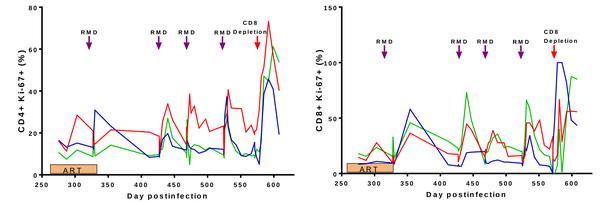


Figure 6. Massive increase in T cell proliferation after RMD and CD8 Depletion administration

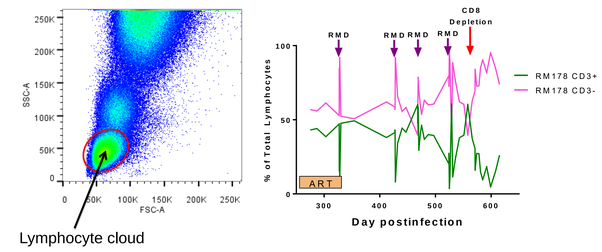


Figure 7. RMD administration transiently downregulates surface markers on lymphocytes

Conclusions

- RMD is well tolerated in RMs at doses that induce a significant increase in histone acetylation
- Following RMD administration, a significant increase in the proliferation levels of T cells is associated with a detectable virus rebound in RMs not treated with ART
- Repeated administration of RMD resulted in a accumulated rebound, suggesting that the reactivated virus is replication-competent.
- RMD shows a transient effect on CTL function, based on production of cytokines
- RMD administration in presence of ART needed to conclude effect on viral reservoir (ART will prevent reseeding of reservoir)

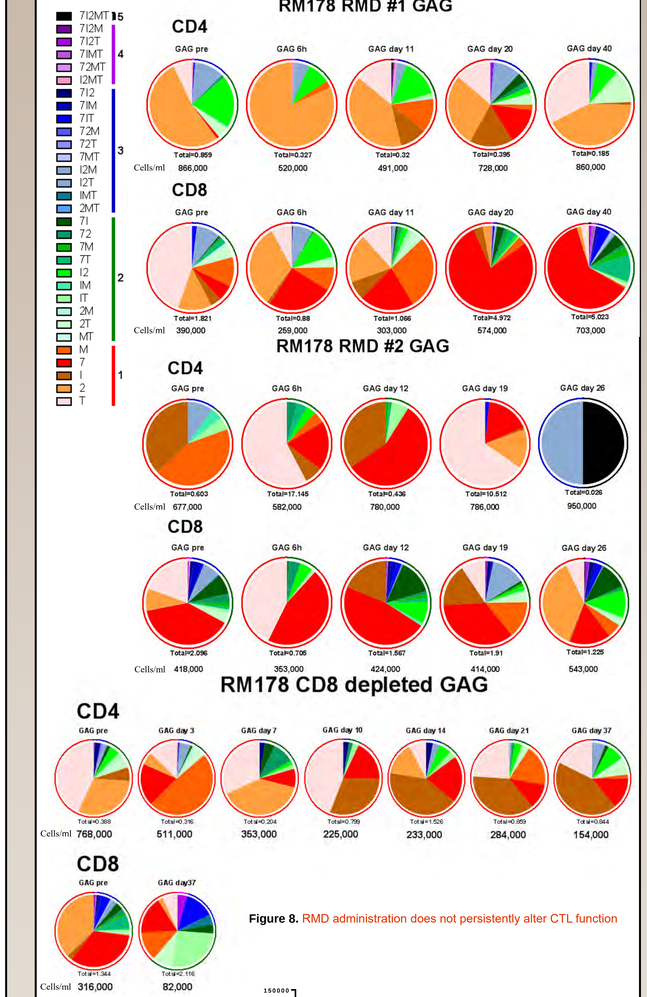


Figure 8. RMD administration does not persistently alter CTL function

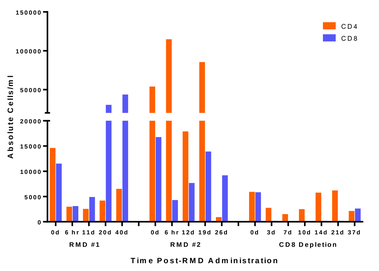


Figure 9. Absolute Gag and Env-specific CD4+ and CD8+ CTLs for RM178