

# Latency Reversal Agent (LRA) Romidepsin Reactivates Latent Virus in Two Rhesus Macaque (RM) Models of Controlled SIV Infection in the Absence of Antiretroviral Therapy (ART)



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# Background

- “Shock and kill”
  - Use of latency reversing agents (LRAs) to increase HIV-1 gene expression in latently infected cells
  - If administered to patients on ART, no risk that released virus would infect new cells
  - Cells with reactivated virus die from viral cytopathic effects or virus-specific CTL lysis

# Background

- **Limitations of “shock and kill”**
  - CTLs are exhausted in HIV-infected patients and they fail to eliminate the reactivated virus (Shan et al., 2012)
  - Histone deacetylase inhibitors were reported to impair the elimination of HIV-infected cells by CTLs (Jones et al., 2014)
  - It is not yet clear that infected cells will die after the reversal of latency, particularly when latency-reversal strategies do not induce T-cell activation or high levels of virus gene expression
  - Latency reversing agents are ineffective in reactivating the latent virus (Bullen et al., 2014), but combination of LRAs might be effective (Laird et al., 2015)



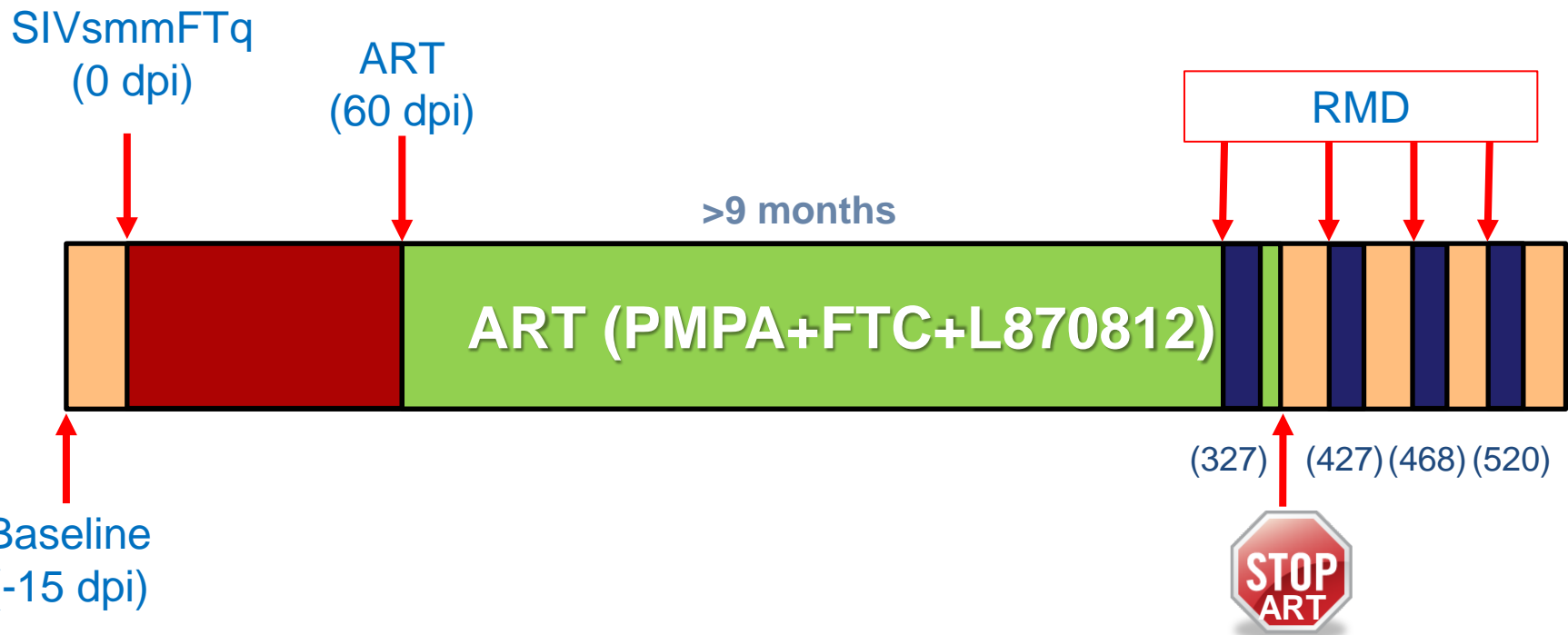
# Goal

- Evaluate the ability of HDACi Romidepsin (RMD) to reactivate SIV from the latent reservoir

# Study Design - SIVsmmFTq

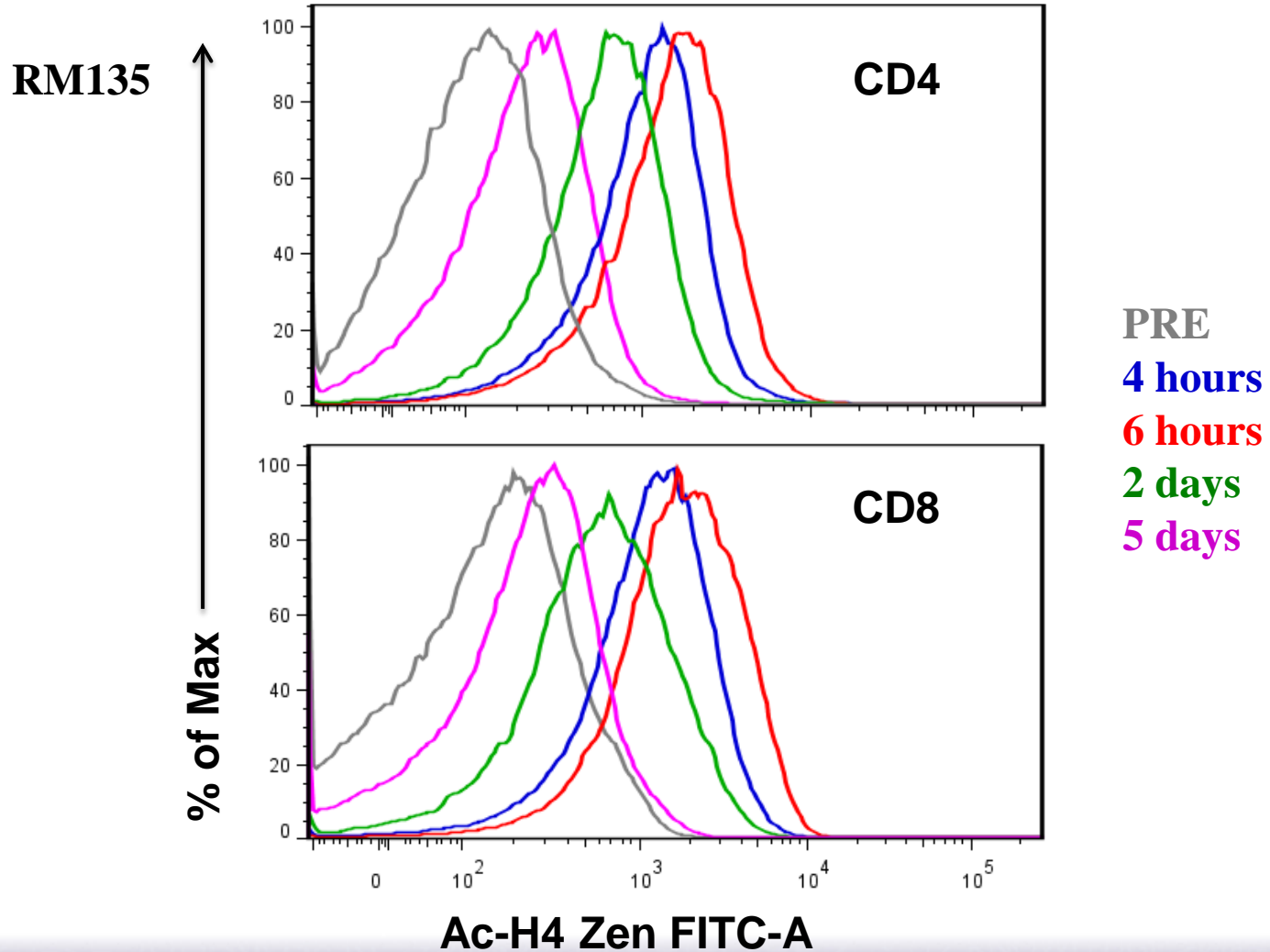
**SIVsmmFTq/RM** – a model of posttreatment control of viral replication (received ART for >9 months starting at D60 pi)

- 3 Indian RMs (TFP/TFP)

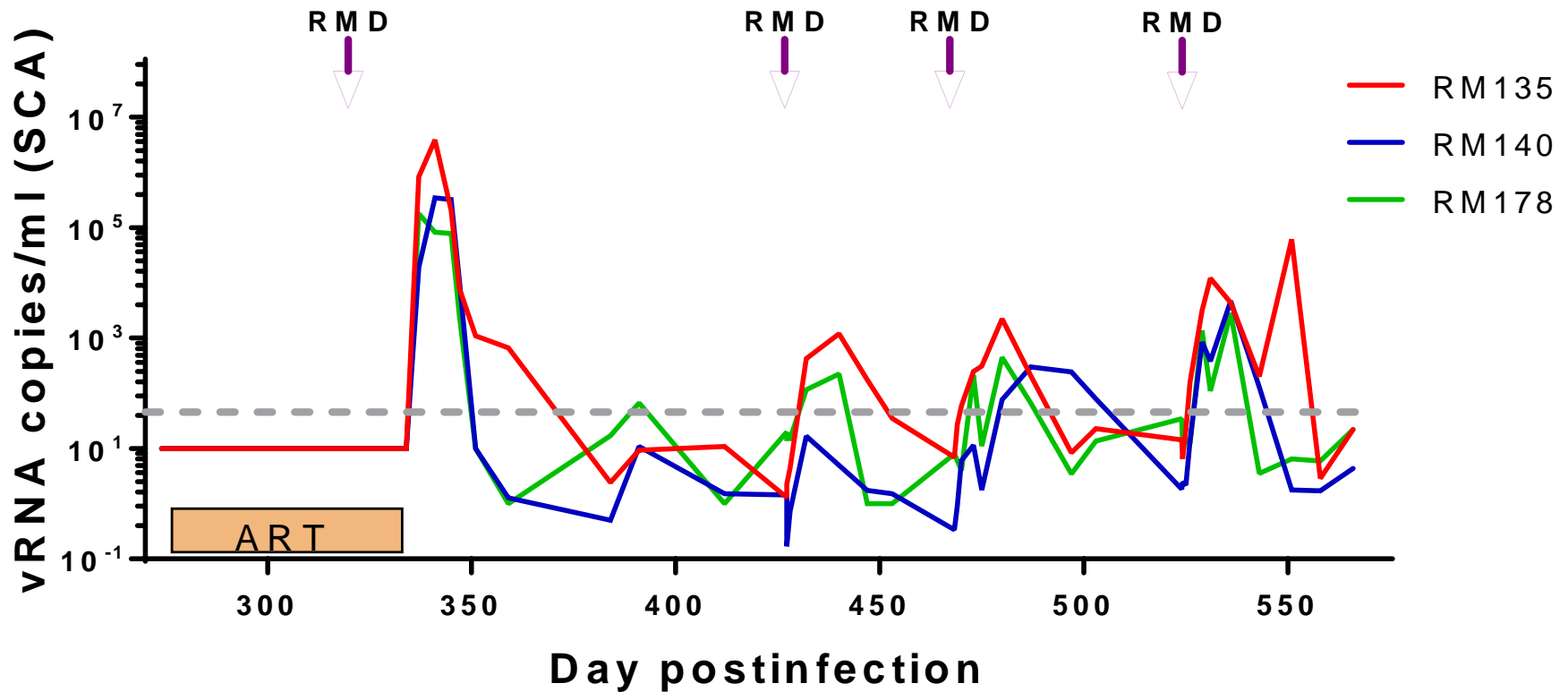


**RMD administered at 7mg/m<sup>2</sup> over 4 hours**

# RMD Administration *in vivo* Increases Histone Acetylation

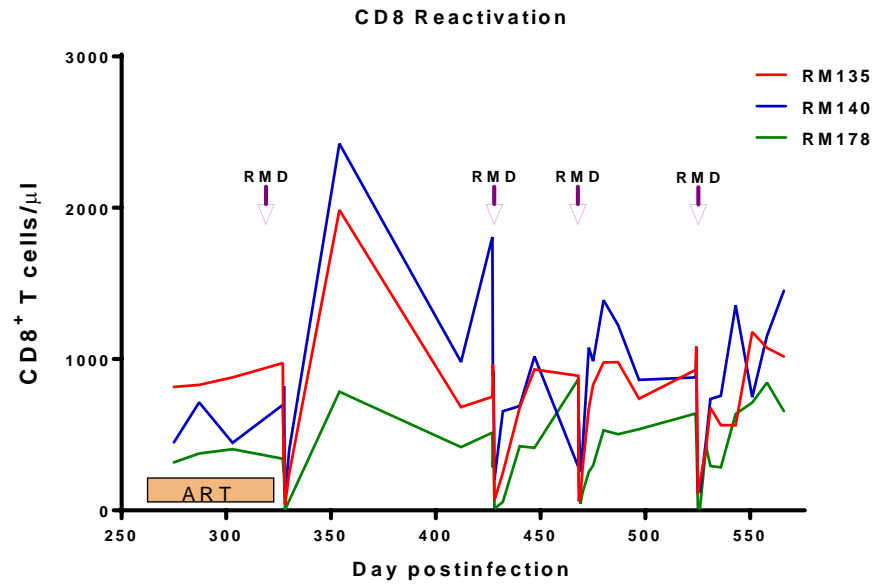
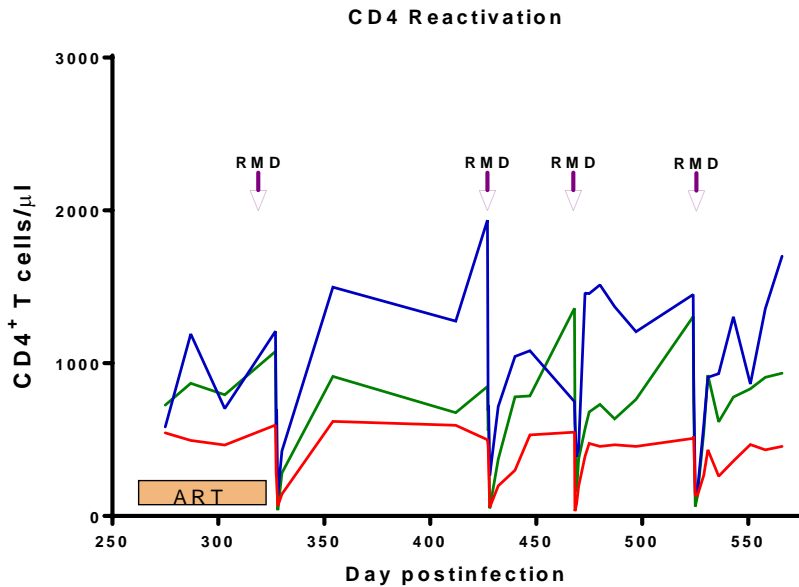


# RMD Administration Reactivates SIV *in vivo*

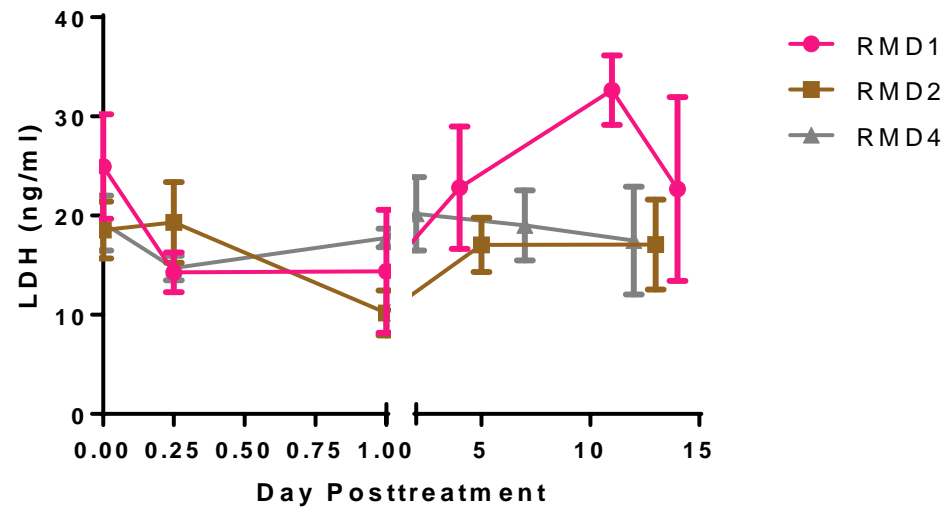


LoD of conventional PCR assays = 30 copies/ml

# RMD Administration Has a Discernible Impact on T Cell Counts



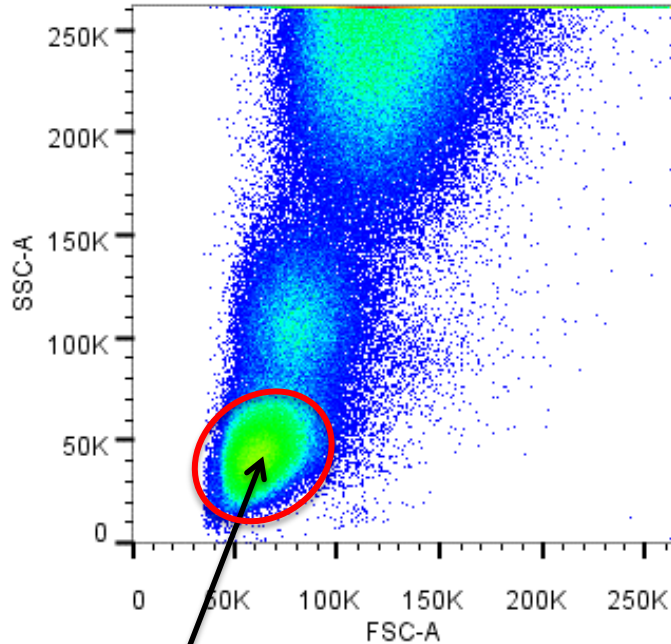
No major liver toxicity of RMD in RMs (chemistry)



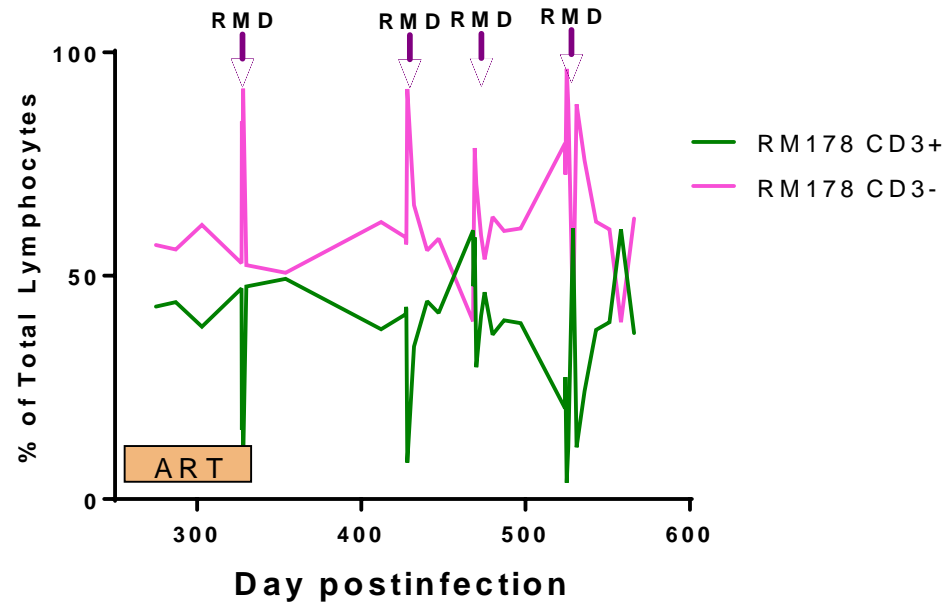
LDH = lactate dehydrogenase



# Downregulation of Surface Markers Occurs After RMD



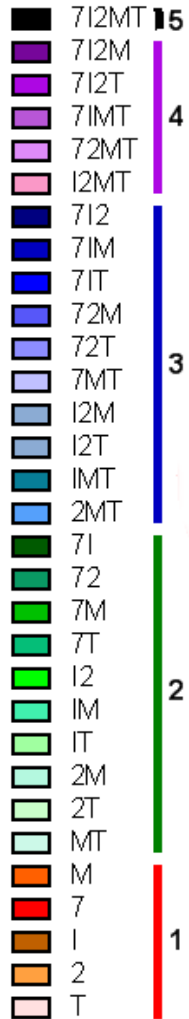
Lymphocyte cloud  
(contains the CD3 cells)



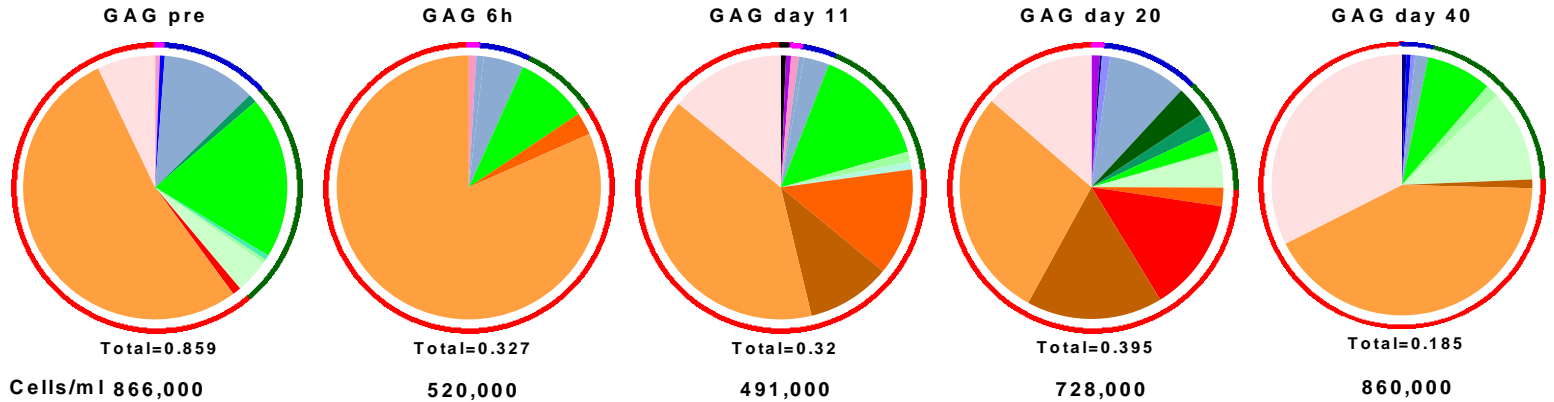


# RMD Shows Transient Effect on CTLs

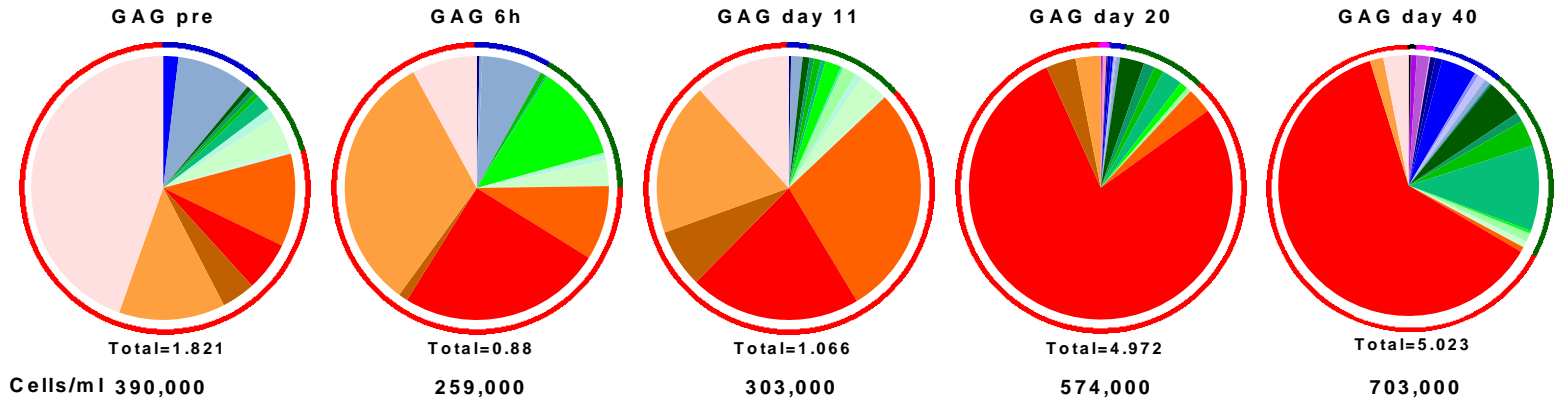
RM178 RMD #1 GAG (125 peptide pool, SIVmac239)



## CD4



## CD8

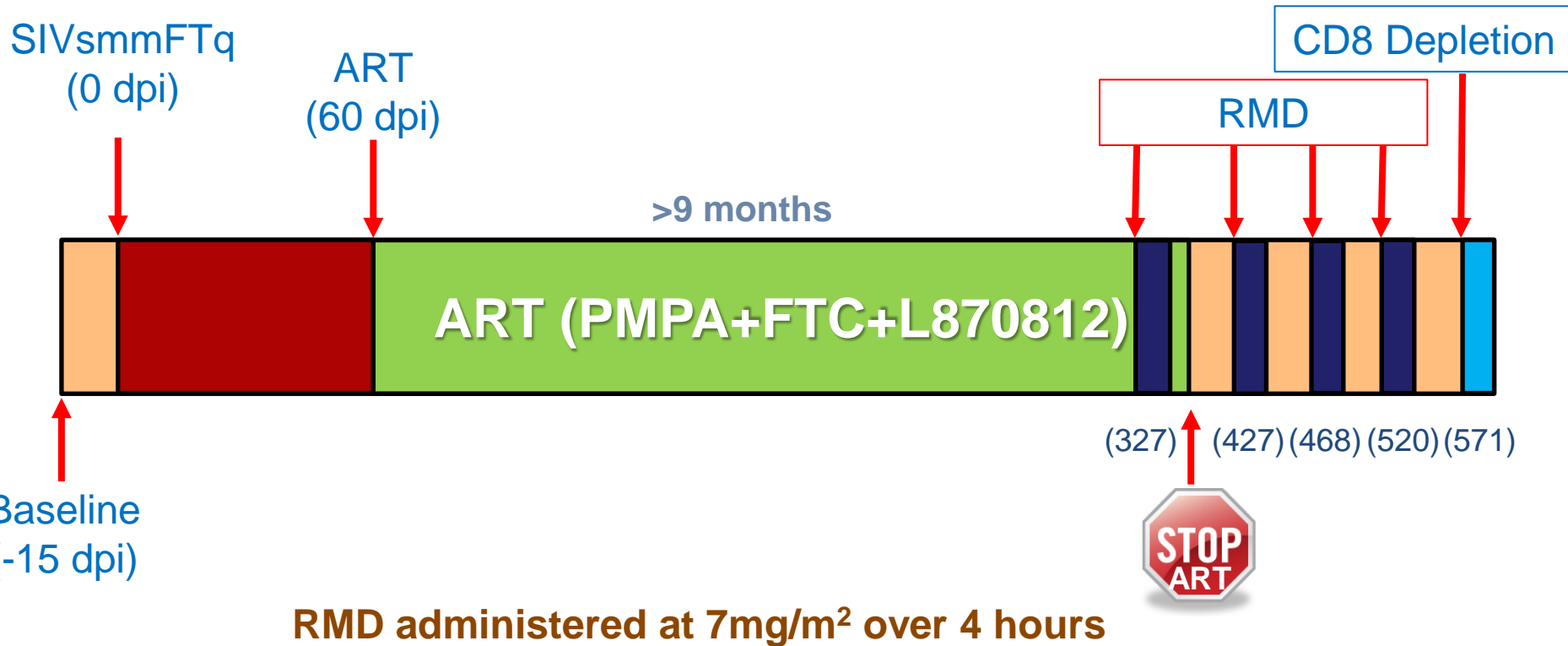


M=MIP-1B; 7=CD107a; I=IFN-g; 2=IL-2; T=TNF-a

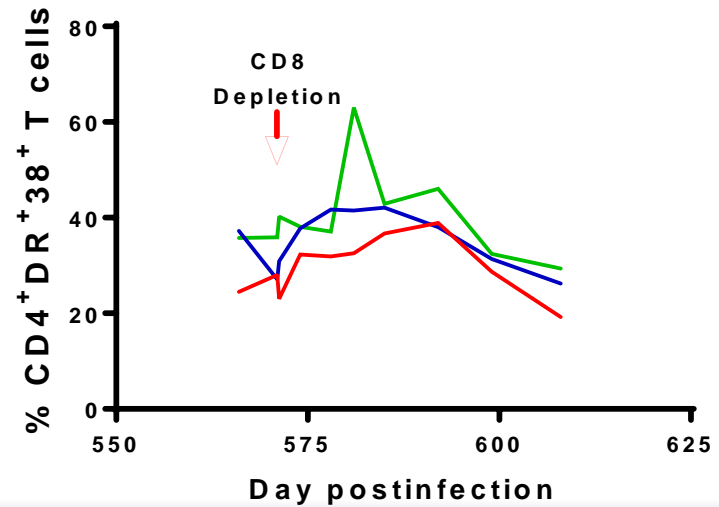
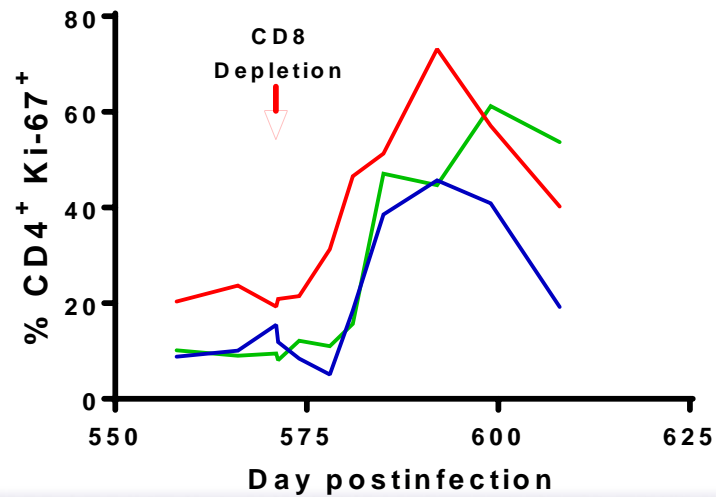
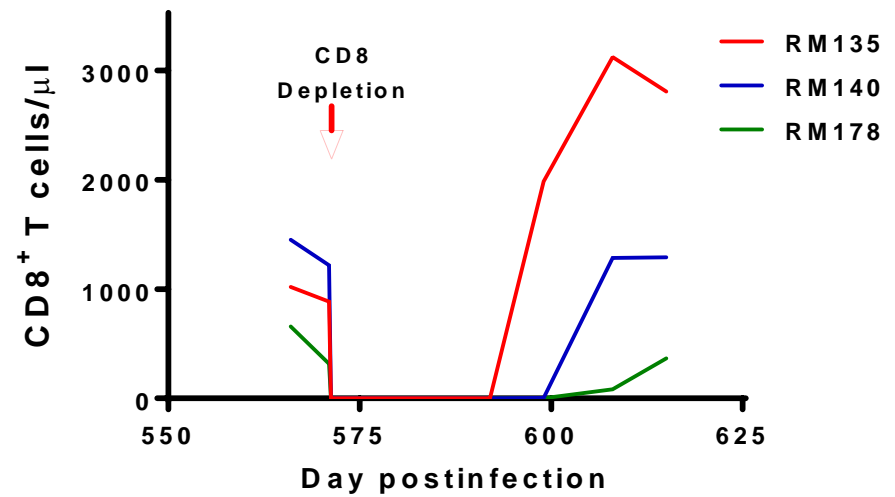
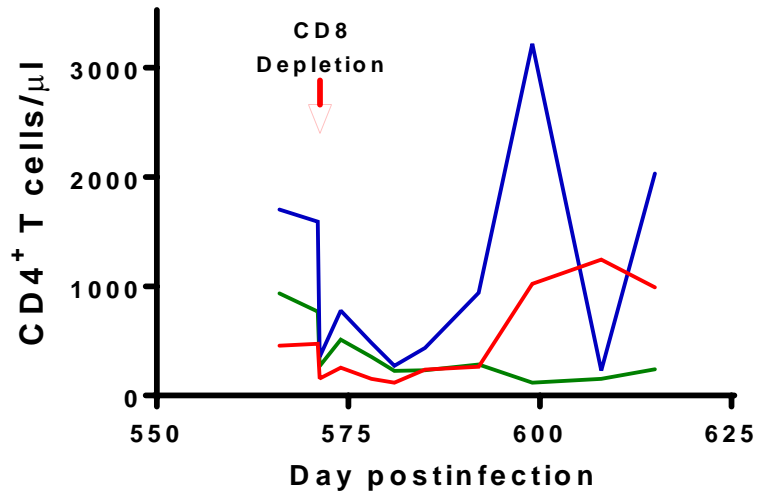
# Study Design - SIVsmmFTq

Since we did not gather significant data supporting a major impact of the RMD on the CTLs, we wanted to model CTL ablation by performing an experimental CD8 depletion.

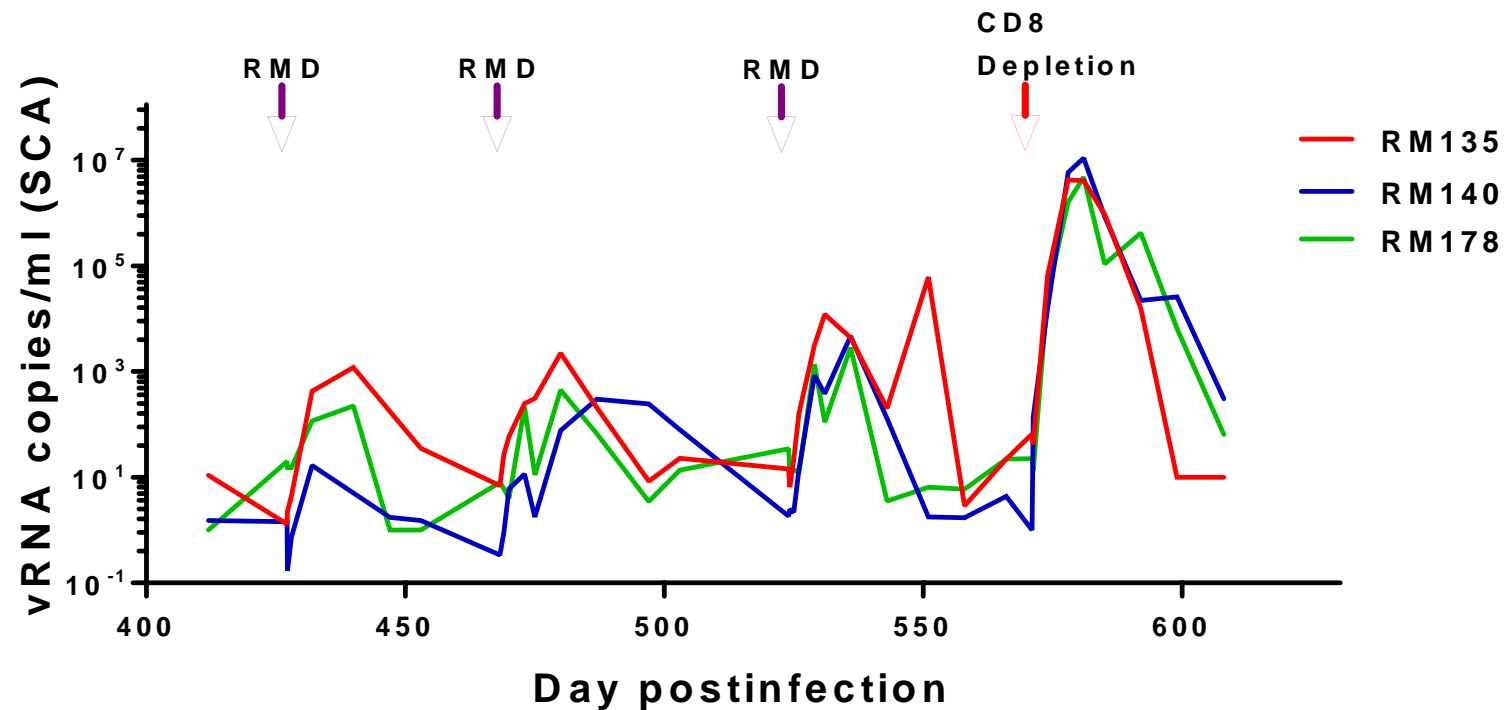
- 3 Indian RMs (TFP/TFP)



# CD8 Depletion Induces Activation of CD4 Cells



# Virus Rebounds to Acute Levels upon CD8 Depletion



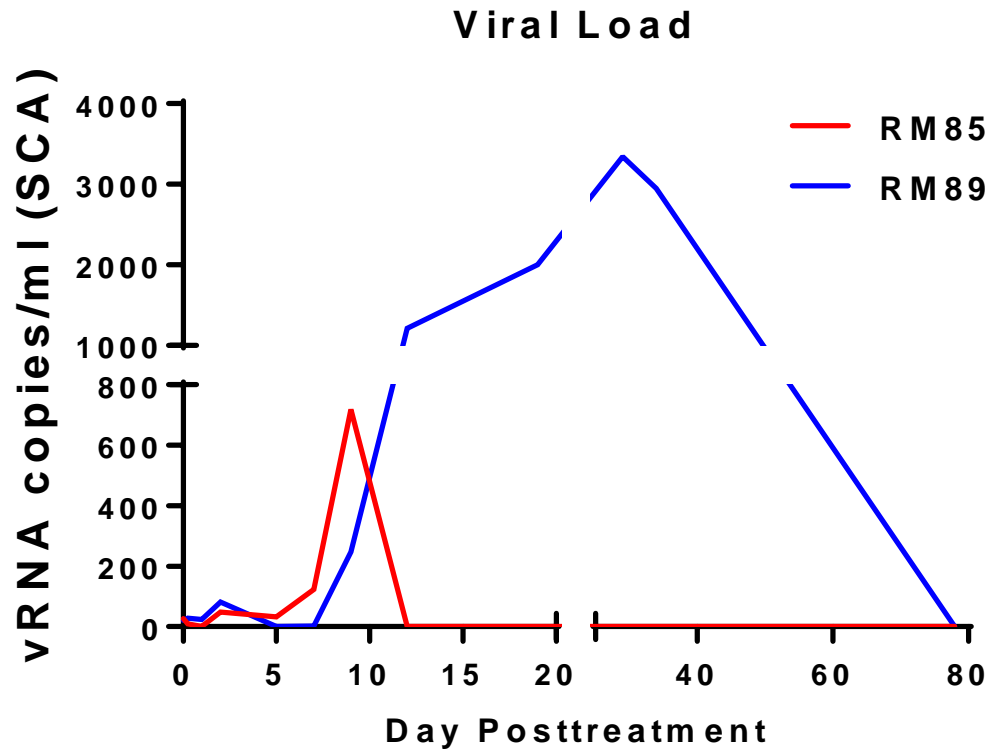
# Study Design - SIVagmSab

**SIVagmSab/RM** – a model of spontaneous superelite control (control of both viral replication to  $<3$  copies/ml and of the residual immune activation)

- 2 Indian RMs

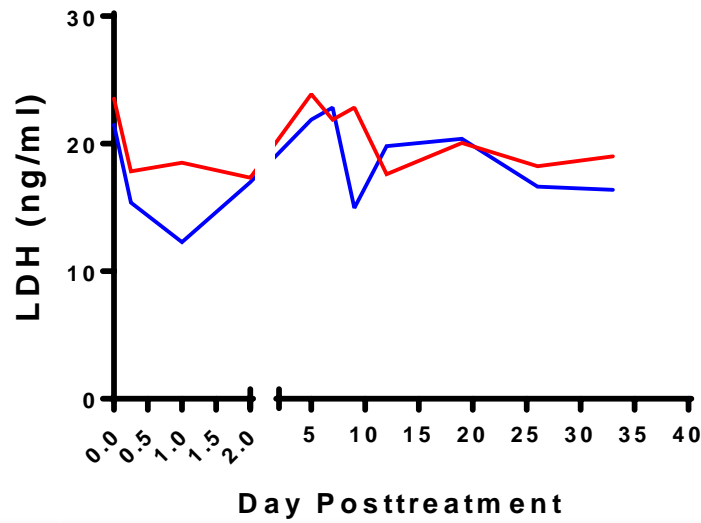
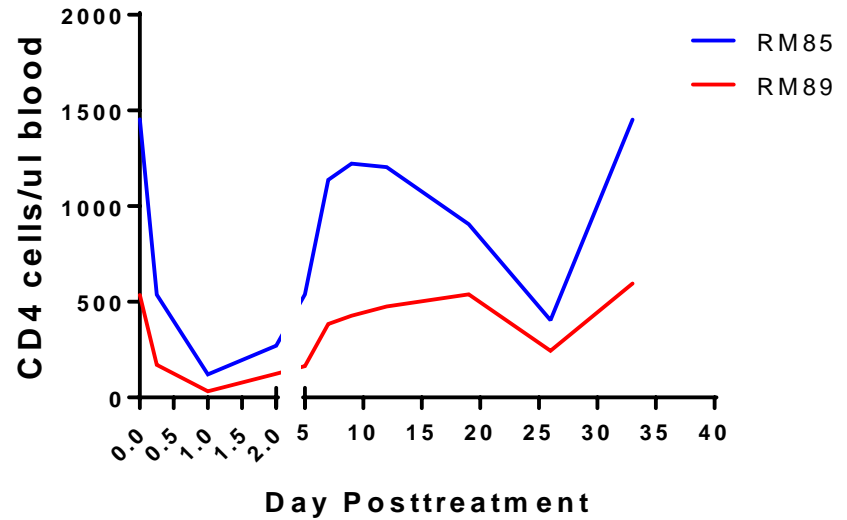
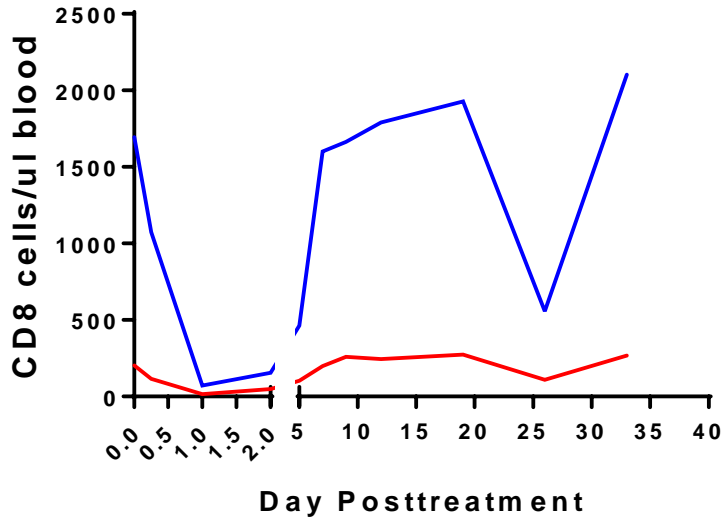


# RMD Administration Reactivates SIVsab in RM Controllers

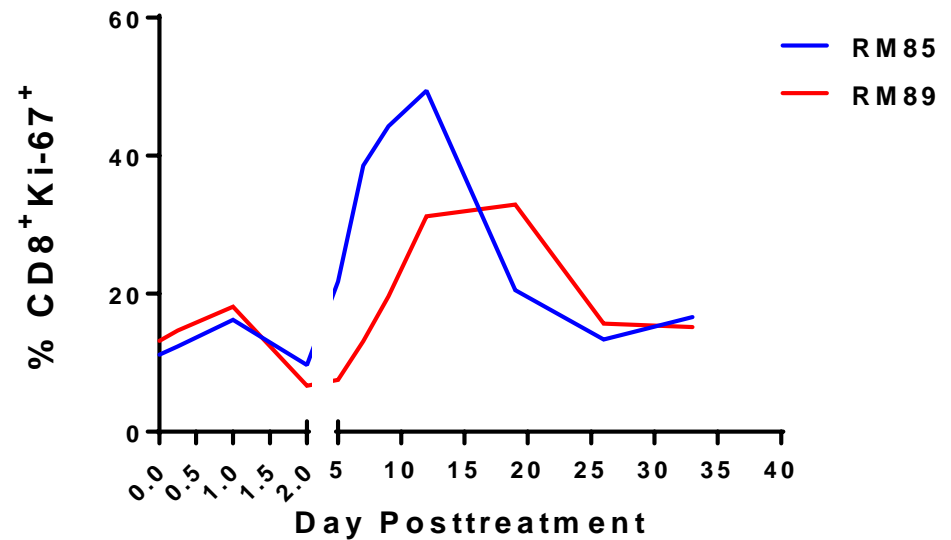
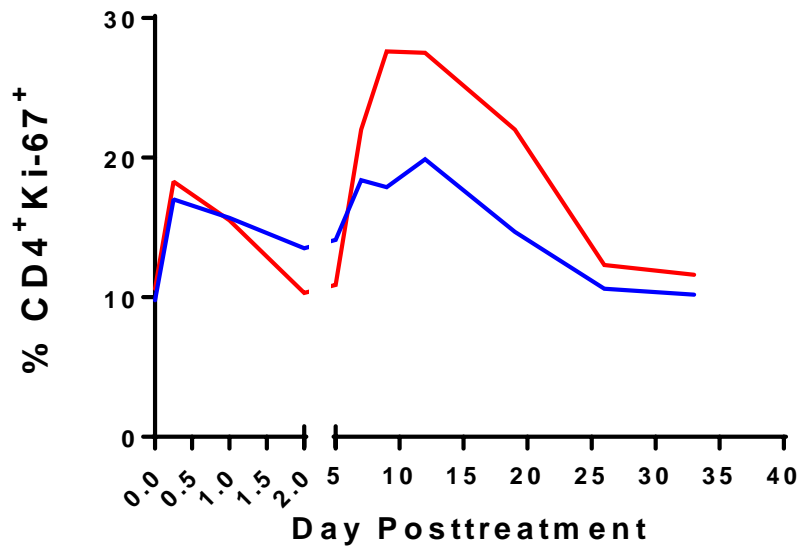




# RMD Administration Reactivates SIVsab in RM Controllers

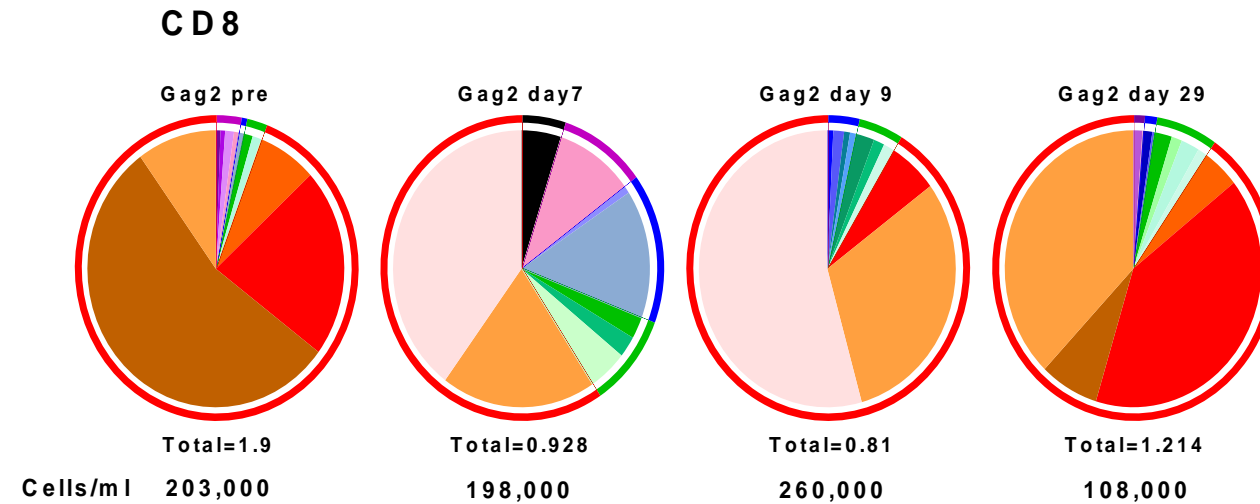
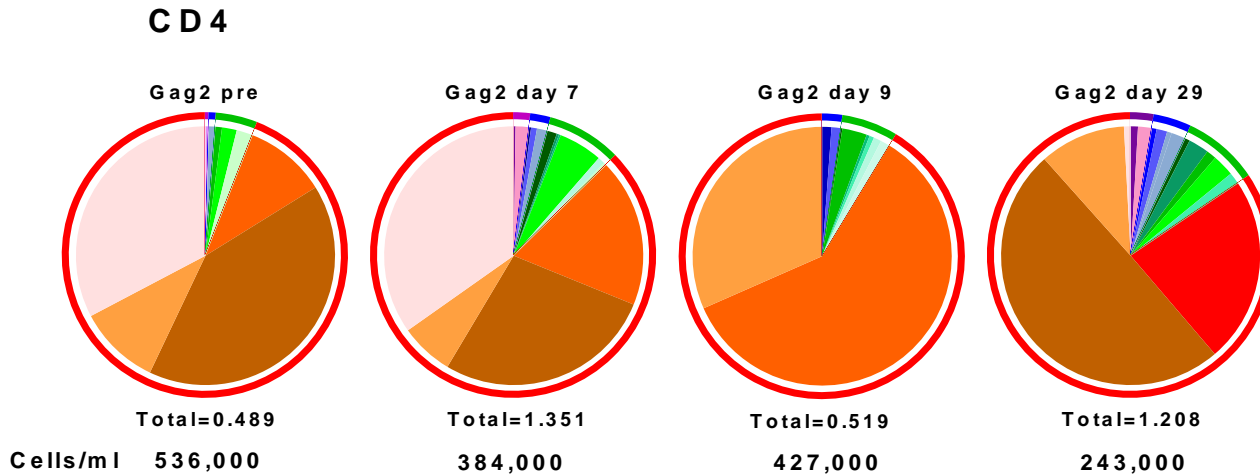
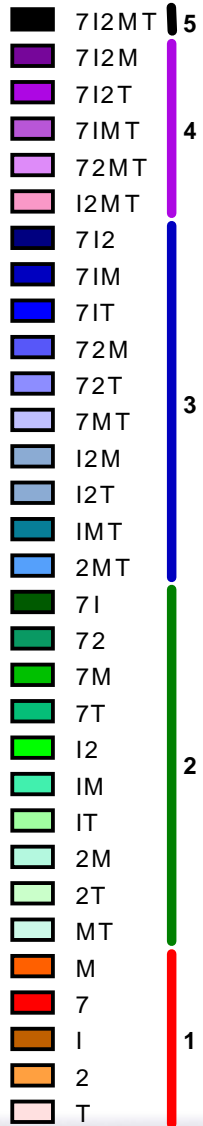


# T cell Activation Occurs in RM Controllers Following RMD Administration



# RMD Shows Transient Effect on CTLs


## RM89 RMD GAG2 (pool of 68 peptides, SIVagm Sab)



M=MIP-1B; 7=CD107a; I=IFN-g; 2=IL-2; T=TNF-a



# Conclusions

- RMD is well tolerated in RMs at doses that induce an increase in histone acetylation
  - Repeated administration of RMD did not result in increased toxicity
  - RMD successfully reactivated virus from the reservoir in posttreatment and spontaneous RM controllers
  - The delay of virus rebound (in the absence of ART) suggests that the reactivated virus is replication competent
  - RMD administration *in vivo* results in increased T cell activation and proliferation
  - RMD has only a transient effect on CTL function; furthermore, virus reactivation is associated with increased CTL polyfunctionality
  - RMD administration combined with ART is needed to conclude the effect on the reservoir
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