INDUCIBLE RESERVOIR IN TISSUES, BUT NOT IN PERIPHERY, PREDICTS FUNCTIONAL CURE OF SIV - #354

Adam J. Kleinman1, Sindhuja Sivanandham1, Ranjit Sivanandham1, Paola Sette1, Benjamin B. Policicchio1, Cuiling Xu2, Quentin Le Hingrat1, Egidio Brocca-Cofano1, Dongzhu Ma2, Ivona Pandrea2, Cristian Apetrei1

[1]University of Pittsburgh, Department of Medicine, Pittsburgh, USA; [2] University of Pittsburgh, Department of Pathology, Pittsburgh, USA

BACKGROUND

Several strategies are being studied towards the aims of both sterilizing and functional cures of HIV. One of the largest emphasis has been placed on the "shock and kill" strategy; the administration of latency reversing agents (LRAs), such as histone deacetylase inhibitors (HDACi), to induce the reactivation of latent proviruses, with subsequent clearance of the reactivated, infected cells by the cell-mediated immune response and viral cytolytic effects. Yet, multiple studies have shown that LRAs do not reactivate a large enough portion of the reservoir for significant changes in reservoir size to occur and, even more daunting, treatment with HDACi may impair the function of HIV/SIV-specific immune responses.

GOALS

- To assess the ability of the HDACi, romidepsin (RMD), to reactivate SIV from viral reservoirs with repeated doses in infected rhesus macaques
- To assess the effect of RMD on SIV-specific immune responses
- To assess adverse effects of repeated RMD administrations
- To assess the efficacy of "double dose" treatments

METHODS

- We utilized our nonhuman primate model of SIVsab infection of rhesus macaques, in which spontaneous complete immune control of SIV occurs in the context of healthy cellular immune responses without antiretroviral therapy (ART).
- 5 RMs were inoculated intravenously with 300 TCID50 of SIVagm.sab92018.
- Plasma viral loads became undetectable (<30 vRNA copies/mL) at approximately 72 days postinfection (dpi). After 200 days of complete control, 3 rounds of RMD administration (7 mg/m^2 via slow perfusion over 4 hours) were performed every 2 months.
- After 3 rounds of RMD administration, two RMs (RM85 and RM89) did not reactivate virus. Thus, experimental CD8$^+$ T-cell depletion with monoclonal antibody M-T807R1 was performed in the 2 RMs.
- In the remaining 3 RMs, 3 additional rounds of RMD, given as "double doses" (7 mg/m^2, two days apart), were performed two months apart.

RESULTS

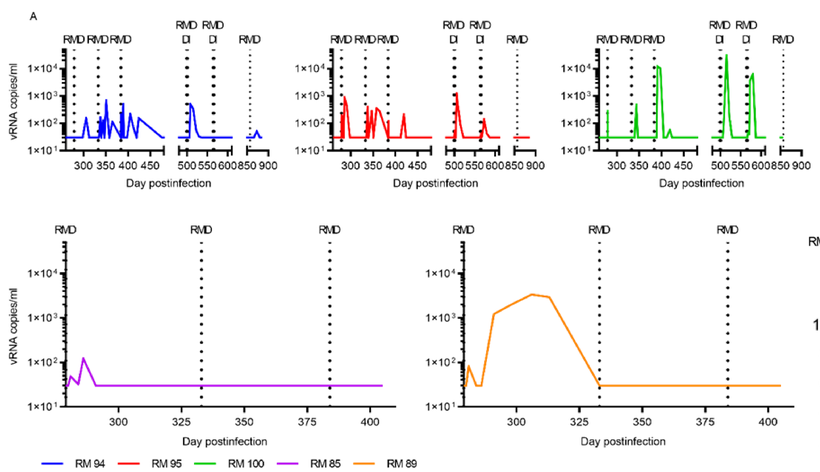

Figure 1. Plasma viral loads after Romidepsin (RMD) treatments

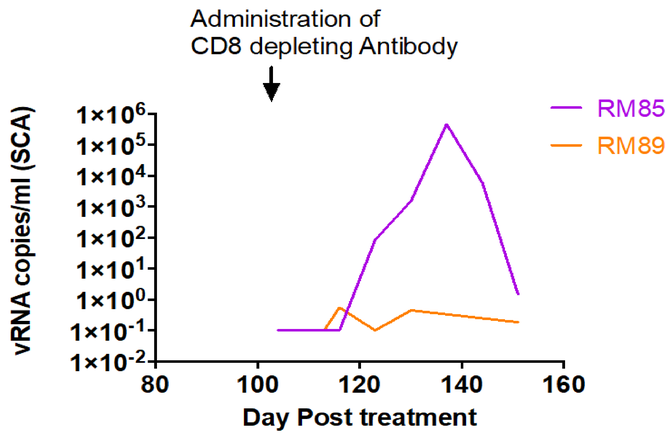

Figure 2. Plasma viral loads after CD8-depletion

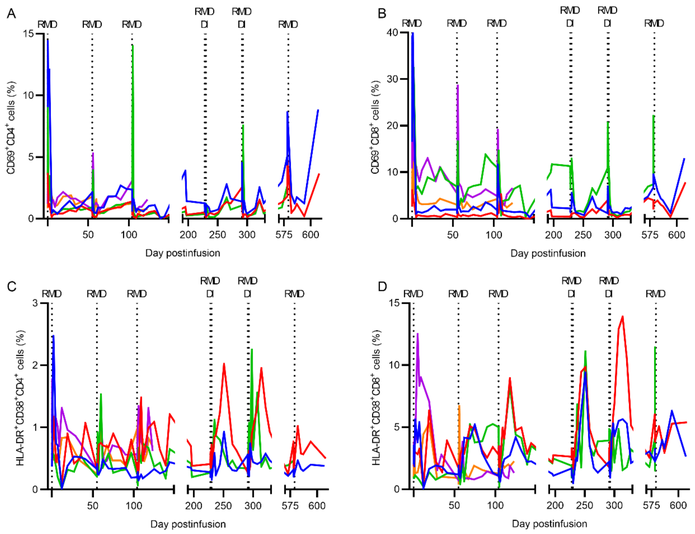

Figure 3. Immune activation of CD4 and CD8 T cells after RMD treatment

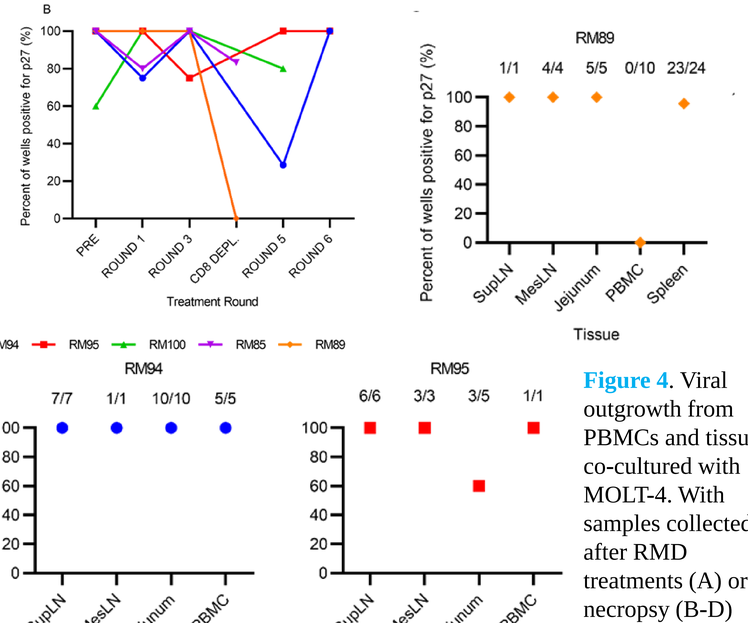

Figure 4. Viral outgrowth from PBMCs and tissues co-cultured with MOLT-4. With samples collected after RMD treatments (A) or at necropsy (B-D)

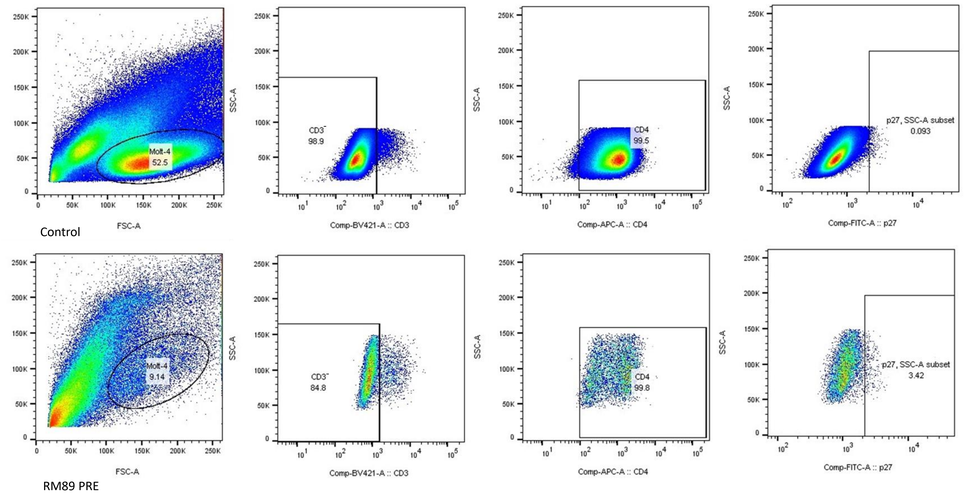

Figure 5. Gating strategy for selection of MOLT-4 cells (CD3$^-$CD4^{variable}) and p27 positivity

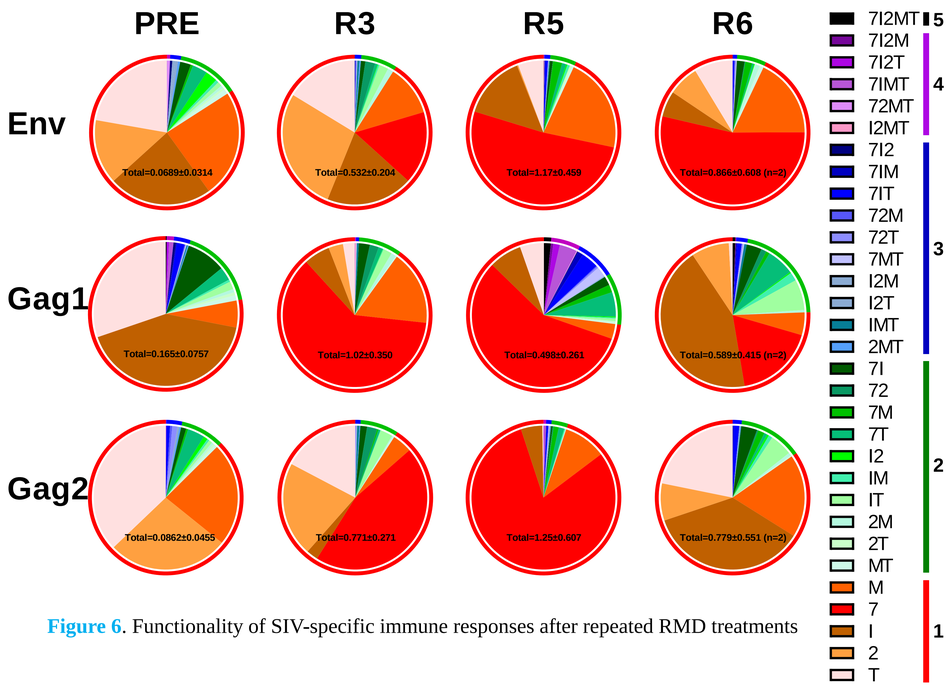

Figure 6. Functionality of SIV-specific immune responses after repeated RMD treatments

CONCLUSIONS

- In the context of a healthy immune response, RMD treatments led to reactivation in SIVsab-infected rhesus macaques;
- "Double doses" increased viral reactivation relative to single doses
- RMD treatments bolstered the SIV-specific immune response
- Our intervention has likely impacted the viral reservoir as evidenced by: (i) the repeated treatments resulted in longitudinally decreased viral reactivation, (ii) lack of reactivation in RM89 after CD8 depletion, and (iii) decreased viral outgrowth after round 5 in RM94 and no outgrowth from RM89 after CD8 depletion, correlating with lack of viral reactivation in plasma.
- It is possible that the conflicting results between what is seen in this study and the human studies is due to the context of a healthy immune response that occurs with our spontaneous elite controller model. Thus, correcting the abhorrent immune dynamics during HIV infection may be greatly beneficial for the various cure strategies being investigated, HDACi included.

ACKNOWLEDGEMENTS

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