# The HDAC inhibitor romidepsin is safe and effectively reverses HIV-1 latency in vivo as measured by standard clinical assays

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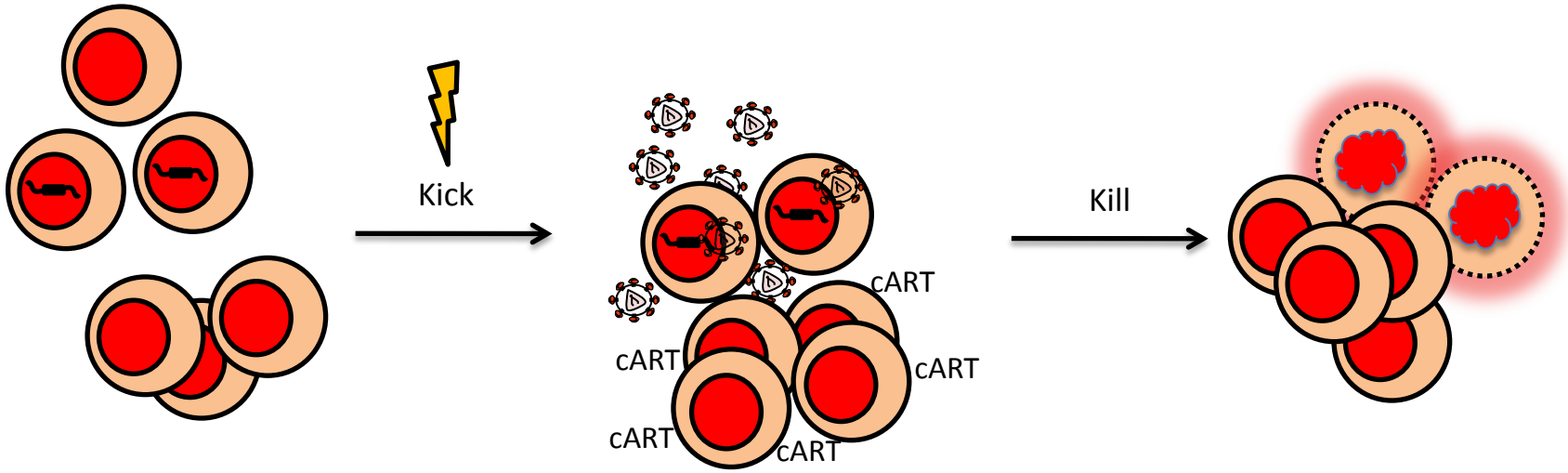
# The “kick and kill” approach to cure HIV

**Reactivate latent viral expression**

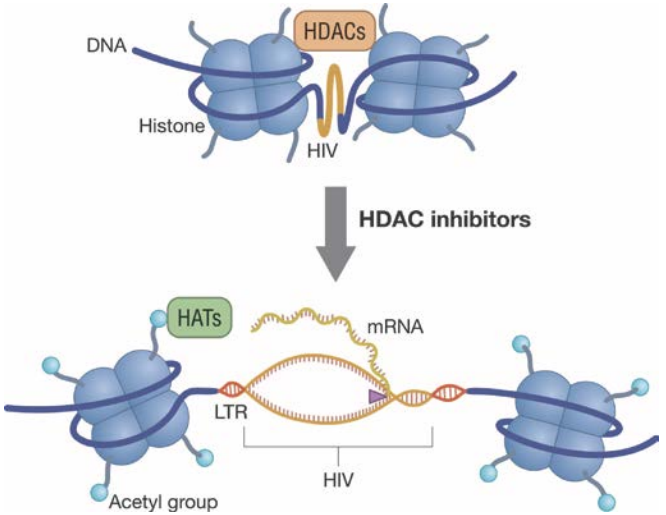
- HDAC inhibitors, PKC activators, BET bromodomain inhibitors, etc.

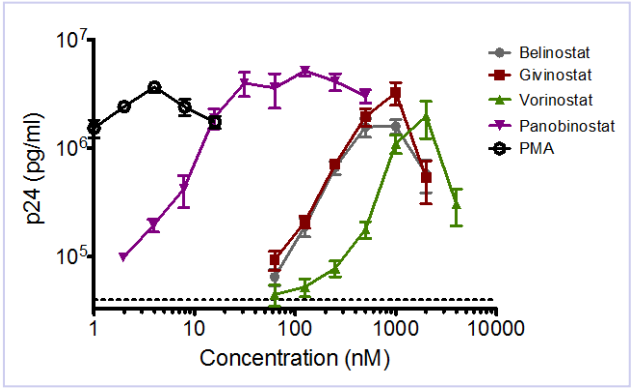



Deeks *S.* Nature 2012

# HDAC inhibitors

- Induce HIV mRNA transcription in latently infected resting CD4 cells *in vivo*
- Considerable variability in potency between HDACis
- Ultimately, HDACis should induce virion release to allow for immune-mediated killing of infected cells



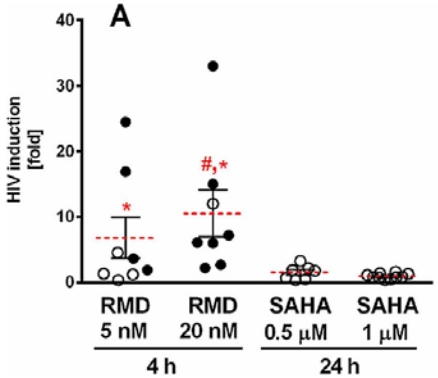






Archin Nature 2012; Lewin CROI 2013; Rasmussen HVIT 2013

# Romidepsin

- Licensed in the US for treatment of PTCL and CTCL
- Increase extracellular RNA release from memory and resting CD4+ T cells in patients on cART *ex vivo*
- $EC_{50}$ for RMD approx. 4.5 nM compared with 3,950 nM for SAHA in a primary T cell model
- RMD (IV) T½~4 hrs
- However, *ex vivo* viral outgrowth data question the ability of HDACi (incl. RMD) to reverse latency *in vivo*




| Patient | DMSO control | Vorinostat | Romidepsin | Panobinostat | Disulfiram | Bryostatin-1 | PMA + ionomycin | IUPM |
|---|---|---|---|---|---|---|---|---|
| S2 | − | − | − | − | − | − | + | 0.220 |
| S3 | − | − | − | − | − | − | + | 0.220 |
| S6 | − | − | − | − | − | − | + | 8.079 |
| S7 | − | − | − | − | − | − | + | 1.108 |
| S14 | − | − | − | − | − | − | + | Not measured |
| S15 | − | − | − | − | − | − | + | Not measured |
| S17 | − | − | − | − | − | − | + | 1.610 |
| S26 | − | − | − | − | − | − | − | <0.220 |
| S27 | − | − | − | − | − | − | + | 1.108 |
| S28 | − | − | − | − | − | − | + | 0.511 |
| S29 | − | − | − | − | − | − | + | 16.248 |
| S30 | − | − | − | − | − | − | + | 0.220 |
| S31 | − | − | − | − | − | − | − | <0.220 |



Wei PLoS Path 2014, Bullen Nature Med 2014

# Trial design

- Non-randomized interventional trial
- Romidepsin (5 mg/m$^2$) IV day 0, 7, and 14
- Primary endpoints: **Safety** as well as **activation of HIV-1 from latency** as determined by plasma HIV-1 RNA and cell-associated unspliced HIV-1 RNA in total CD4+ cells
- Secondary endpoints: H3 acetylation, HIV-1 DNA, T cell activation
- HIV-1 patients on cART
  - Age >18 years
  - CD4 >500 cells/µL
  - VL <50 copies/mL for >1 year
  - No HBV/HCV infection
  - No significant cardiac disease

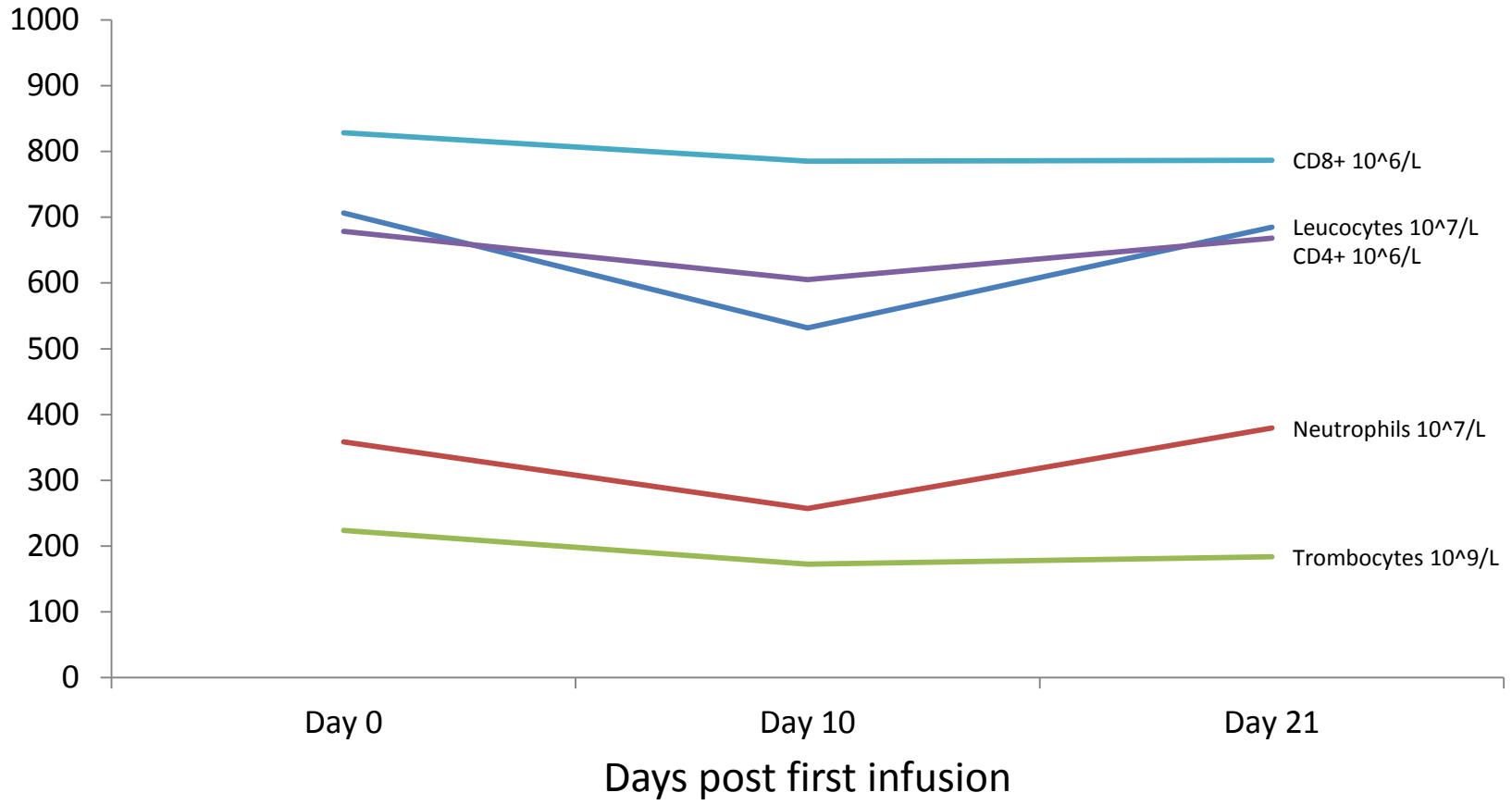
# Patient characteristics

- N=6, 5 males and 1 female (caucasian)
- Median
  - CD4+ cell count: 760 (range 510-1000)
  - age: 54 years (range 37-60)
  - duration of cART: 9.5 years (range 4.2-14.5)
- None started cART during PHI
- ART regimens: PI+2NRTIs (n=3), NNRTI+2NRTIs (n=2), INT+2NRTIs (n=1)

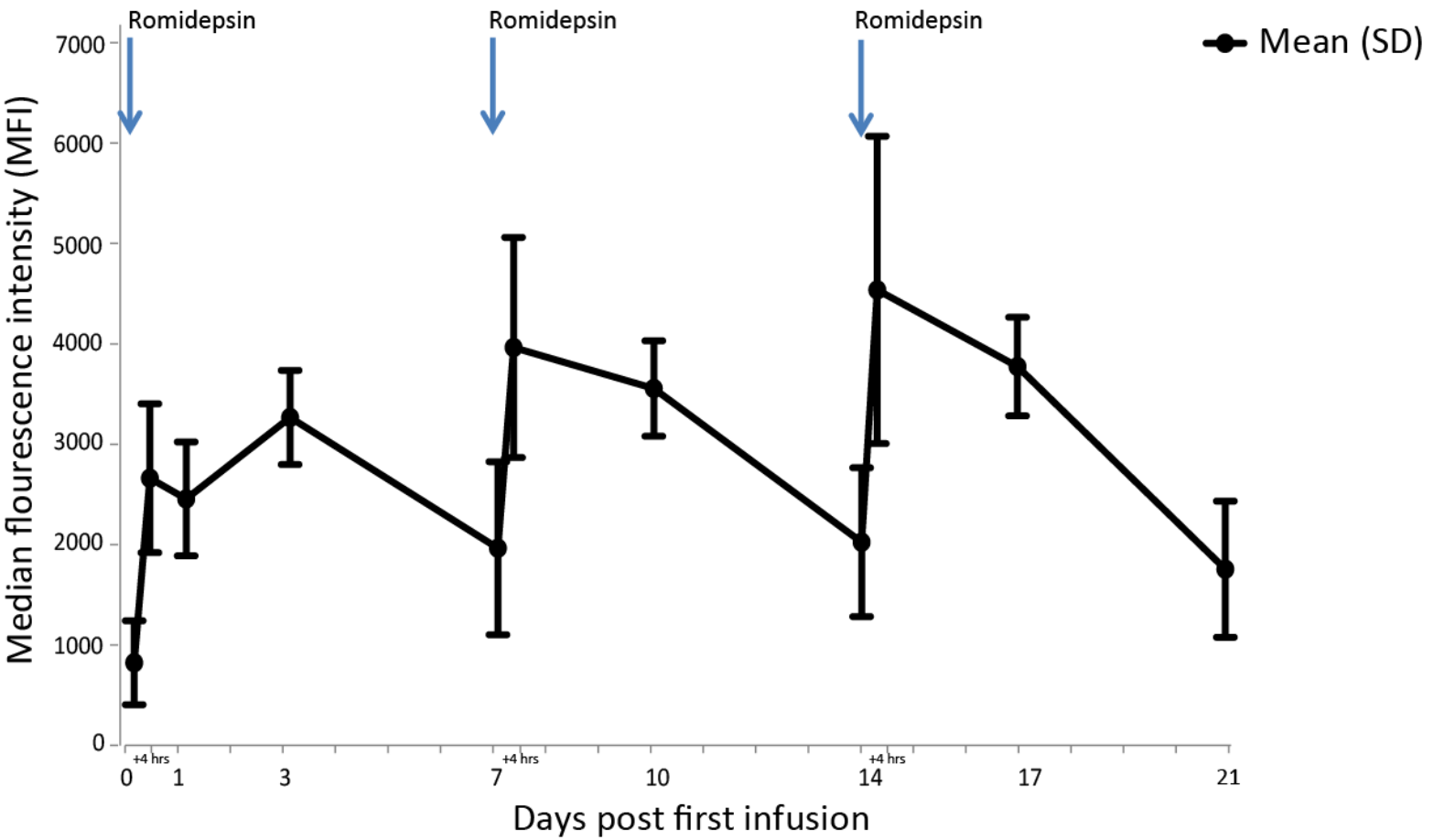
# Self-reported AEs

- 40 adverse events (AE) were registered – 36 AEs were considered to be related to the study drug
- Most AEs were mild (grade 1, n=38) and resolved spontaneously within a few days
- Two AEs were grade 2 (fatigue and fever in one individual after the 2nd infusion)
- The number of AEs reported by each study participant during follow-up ranged from 1 to 13 (up to day 21)
- The most common AEs were abdominal symptoms such as nausea (n=12), borborygmia (n=4), abdominal pain (n=2), diarrhea (n=1), and vomiting (n=1) and fatigue (n=5).

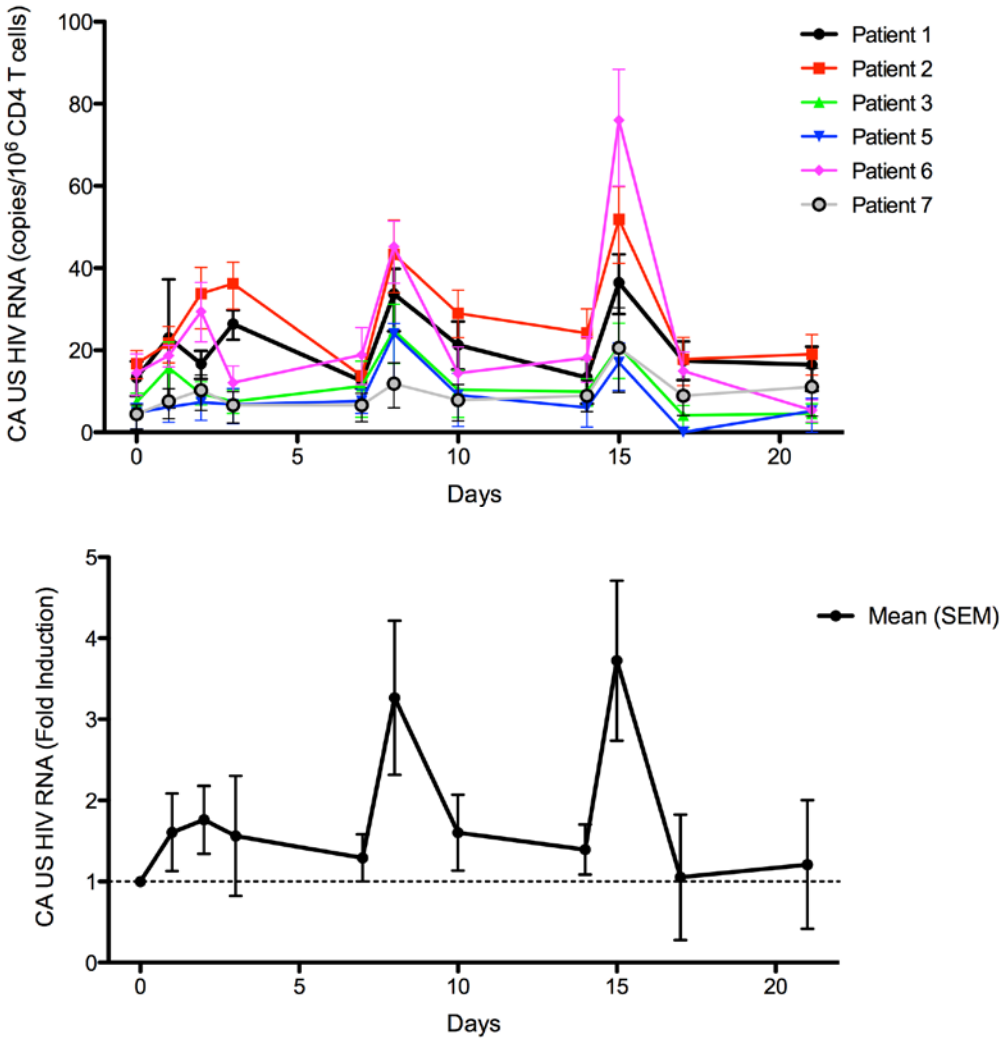
# Biochemistry



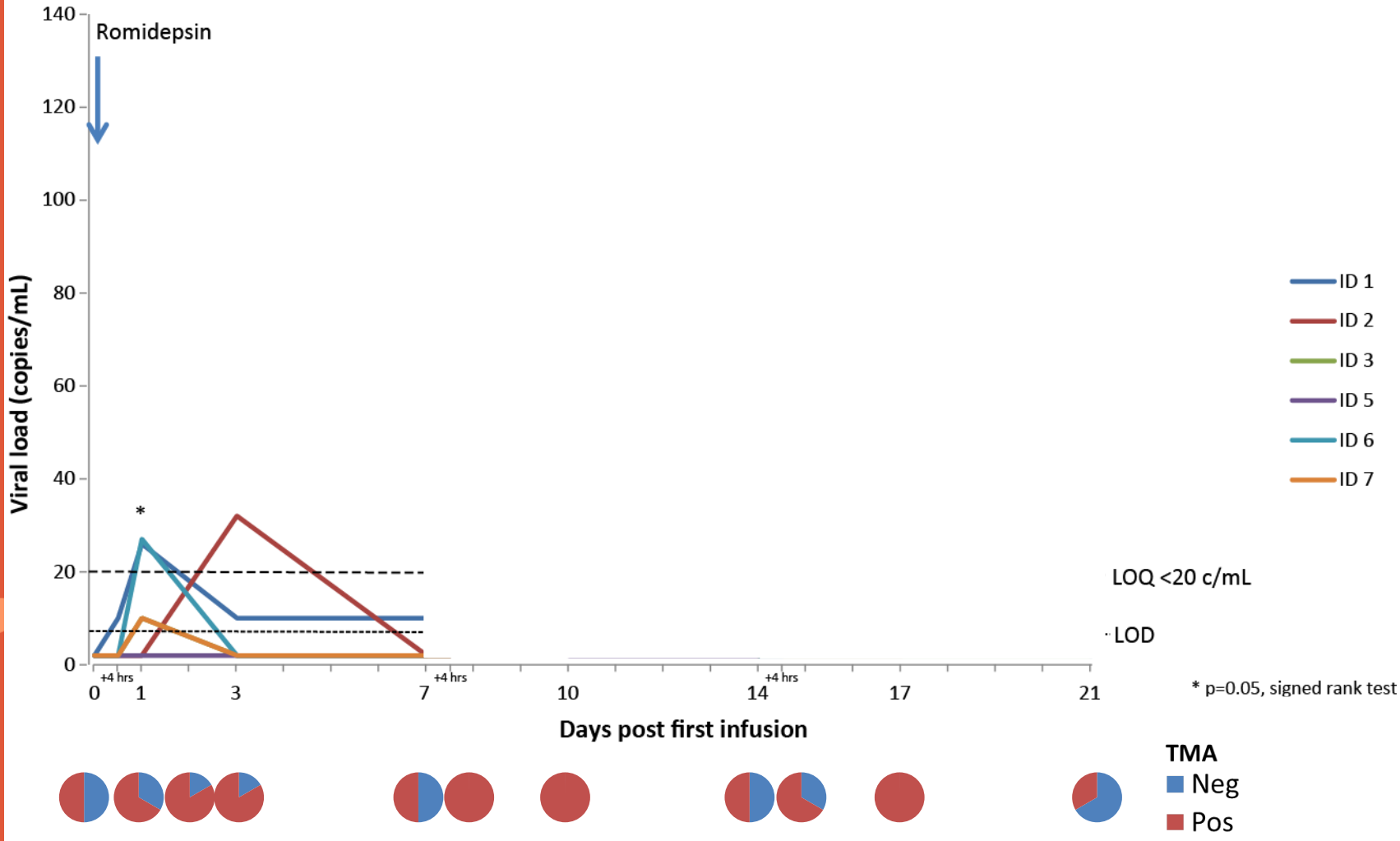
# Lymphocyte histone H3 acetylation



# Cell-associated unspliced HIV-1 RNA

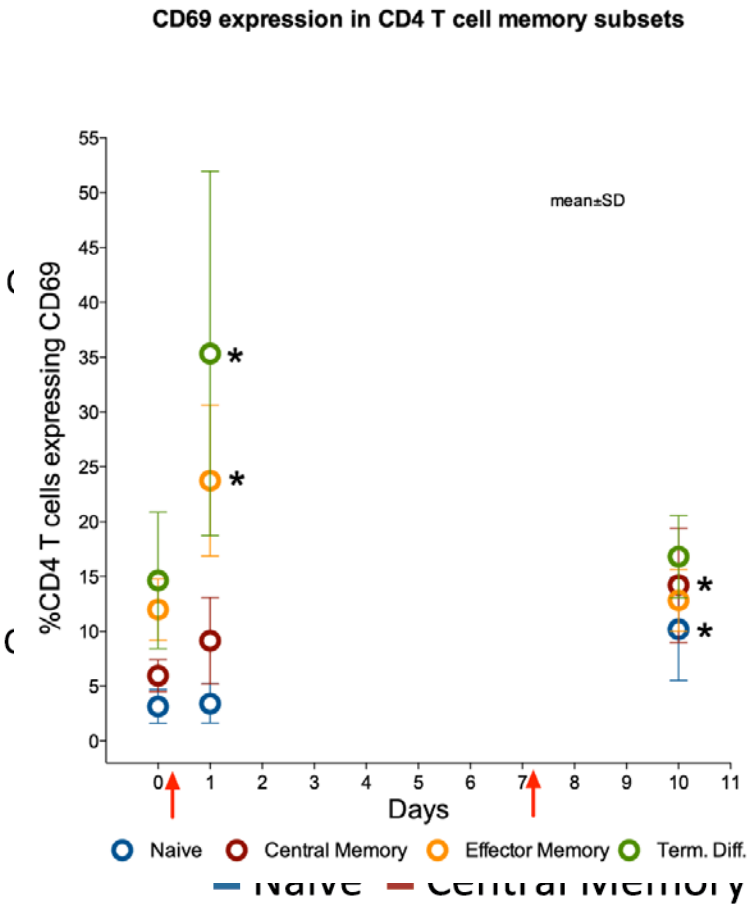


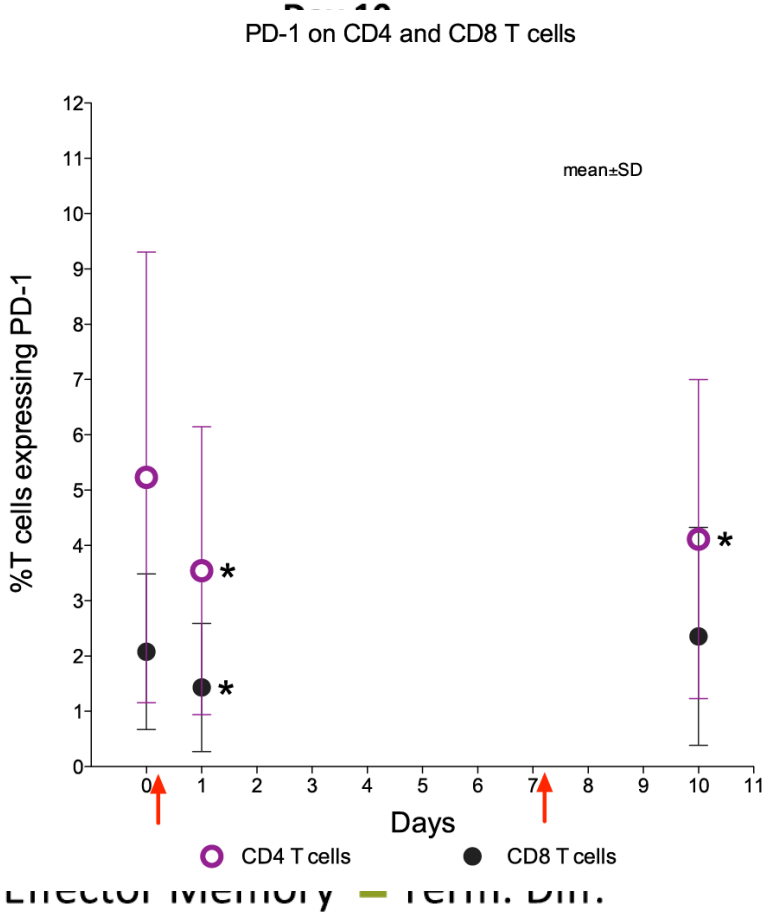
# Plasma HIV-1 RNA



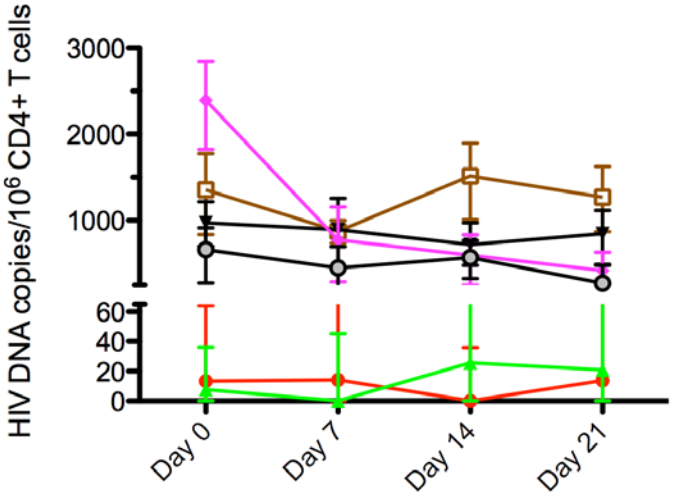

Viral load: COBAS® TaqMan® HIV-1 Test, v2.0
TMA: Qualitative NAT screening system (PROCLEIX ULTRIO Plus, Genprobe)

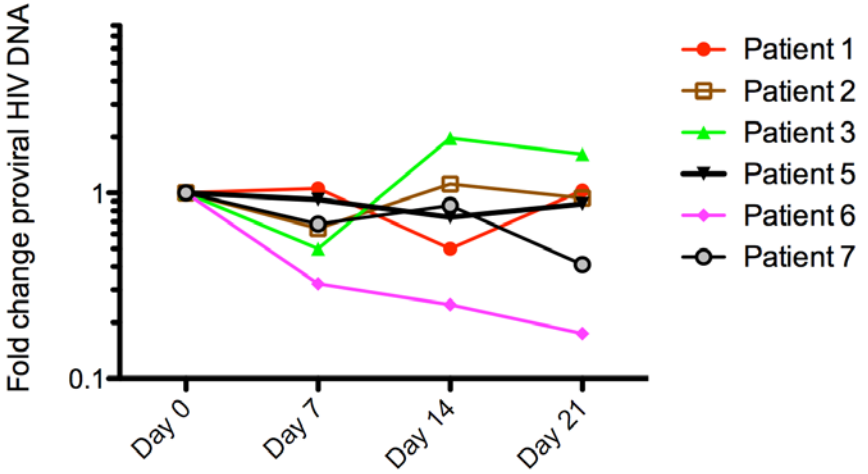
# T cell subsets, activation and PD-1 expr.



# Total HIV-1 DNA in CD4+ T cells



# Conclusions

- RMD safely activated latently infected cells and induced transient quantifiable plasma viremia
- Phenotypic changes occurred in the T cell compartment during RMD treatment
- The HIV-1 reservoir was not significantly reduced by RMD (as measured by HIV-1 DNA)
- A clinical trial combining a therapeutic HIV vaccine (Vacc-4x) and RMD is ongoing

# Acknowledgments

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