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 \textit{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) $T_{1/2}$~4 hrs
- However, *ex vivo* viral outgrowth data question the ability of HDACi (incl. RMD) to reverse latency *in vivo*
Trial design

• Non-randomized interventional trial

• Romidepsin (5 mg/m²) 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 2\(^{nd} \) 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

Days post first infusion

- Leucocytes $10^7$/L
- Neutrophils $10^7$/L
- Trombocytes $10^9$/L
- CD4+ $10^6$/L
- CD8+ $10^6$/L
Lymphocyte histone H3 acetylation

Days post first infusion

Median fluorescence intensity (MFI)
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.

CD69 expression in CD4 T cell memory subsets

%CD4 T cells expressing CD69

PD-1 on CD4 and CD8 T cells

% T cells expressing PD-1
Total HIV-1 DNA in CD4+ T cells

[Graph showing HIV DNA copies in CD4+ T cells over time from Day 0 to Day 21 for different patients]

[Graph showing fold change in proviral HIV DNA for different patients over time from Day 0 to Day 21]
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
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THE STUDY PARTICIPANTS

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