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The HDAC Inhibitor Romidepsin is Safe and Effectively Reverses HIV-1 latency in vivo as Measured by Standard Clinical Assays

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Background: In a recently published *ex vivo* study, the latency reversing agent (LRA) romidepsin induced HIV expression in resting CD4+ T cells isolated from patients undergoing combination antiretroviral treatment (cART). In light of this exciting finding, we evaluated the effects of romidepsin on measures of viral transcription and plasma viremia *in vivo*.

Methods: In a phase I/II clinical trial, six aviremic HIV-infected adults received intravenous romidepsin (5 mg/m^2) once weekly for 3 weeks while maintaining cART. We used flow cytometry to determine H3 histone acetylation levels in lymphocytes as a cellular measure of the pharmacodynamic response to romidepsin. Changes in intracellular viral transcription were quantitated by cell-associated unspliced HIV-1-RNA (CA-US HIV-1-RNA) using digital droplet PCR in unfractionated CD4+ T cells. Plasma HIV-1-RNA was analyzed by a standard clinical viral load assay (Cobas Taqman) and a transcription-mediated amplification (TMA) assay (Procleix Ultrio Plus). Safety was evaluated at each study visit. Baseline values were compared with post-infusion values using Wilcoxon signed-rank tests. Binary outcomes were analyzed using two-sided binomial exact tests.

Results: All 6 patients (5 males, 1 female) completed three romidepsin infusions. H3 histone acetylation increased rapidly (max 17.7 fold relative to baseline) within the first hours following each romidepsin administration and then decreased between day 3 and 7 day post-infusion. Concurrently, CA-US HIV-1-RNA levels increased significantly from baseline during treatment (2.1-3.9 fold after 2nd infusion; p=0.03). Importantly, viral load increased from "undetectable" at baseline to readily quantifiable levels at multiple post-infusion timepoints in 5 of 6 patients (range 46-103 copies/mL after 2nd infusion, p=0.007). Plasma HIV-1-RNA was also detected by TMA more frequently at post-infusion timepoints vs. baseline (p=0.03 after 2nd infusion). Furthermore, the emergence of quantifiable plasma HIV-1-RNA corresponded directly with the cyclic romidepsin infusions. Adverse events (all grade 1-2) were consistent with the known side effects of romidepsin and HDAC inhibitors in general.

Conclusions: Romidepsin safely induced HIV-1 transcription resulting in plasma viremia that was readily quantified with standard commercial assays. Our data show that potent *in vivo* latency reversal is possible with a single LRA. A trial combining romidepsin and therapeutic vaccination is ongoing.