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Vorinostat, panobinostat and romidepsin nonselectively activate transcription from quiescent HIV-1 proviruses in HIV-infected individuals on long-term suppressive anti-retroviral therapy

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Background: Clinical trials in HIV-infected individuals on long-term anti-retroviral therapy (ART) using histone deacetylase inhibitors (HDACis) to reverse HIV-1 latency have demonstrated a measurable increase in HIV-1 transcription in CD4 T cells in blood. However, for effective viral clearance, it is important that these compounds activate transcription from a broad range of integrated proviruses. In this study, we used sequencing to determine whether vorinostat, panobinostat, and romidepsin selectively or nonselectively target HIV-1 proviruses.

Methods: CD4 T cells were obtained from 36 participants before, during, and after HDACi treatment using vorinostat (n=15), panobinostat (n=15), and romidepsin (n=6). We used single-proviral/genome sequencing to characterize the genetic composition of the env region of cell-associated HIV-1 DNA and RNA to determine which HIV-1 proviruses were being transcribed in response to HDACi therapy within CD4 T cells. Additionally, for the panobinostat trial, we sequenced plasma HIV-1 RNA from samples collected during a post-HDACi ART interruption. Maximum-likelihood trees were constructed for each participant and the average-pairwise distance of the sequences was calculated using MEGA 6.0.

Results: The average-pairwise distance of the cell-associated HIV-1 RNA that was detected following administration of the HDACis was not significantly different from that of the cell-associated HIV-1 DNA (2.9% vs. 3.1%, p=0.79). Furthermore, upon phylogenetic analysis, the HIV-1 RNA sequences intermingled with the HIV-1 DNA sequences throughout the phylogenetic trees, supporting a broad and nonselective activation of HIV-1 proviruses. The plasma-derived sequences from the ART interruption samples contained expansions of identical sequences, which in three cases were identical to cell-associated DNA sequences. Additionally, cell-associated HIV-1 RNA had a significantly higher percentage of dead-end virus (hypermutated and/or containing stop codons) than the cell-associated HIV-1 DNA (40.1% vs. 7.8%, p=0.0004).

Conclusions: We found that vorinostat, panobinostat, and romidepsin nonselectively induce transcription from HIV-1 proviruses in HIV-infected individuals on long-term suppressive therapy, which is promising for the development of future therapies that aim to activate quiescent HIV-1 proviruses as part of an eradication strategy. Although, a large amount of cell-associated HIV-1 RNA was replication incompetent, we did identify cell-associated HIV-1 DNA that contributed to rebound virus during a post-HDACi ART interruption.

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