

Entinostat is a histone deacetylase (HDAC) inhibitor selective for class 1 HDACs and activates HIV production from latently infected primary T-cells

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Background: Combination antiretroviral therapy (cART) is unable to eradicate HIV due to the persistence of latently infected resting T-cells. One approach to eliminate latency is to stimulate virus production from latently infected cells using compounds such as histone deacetylase inhibitors (HDACi). Recent clinical trials of the HDACi vorinostat in HIV-infected patients on cART confirmed that vorinostat can activate virus transcription in resting CD4+ T-cells in vivo. Evaluation of newer HDACi is critical to identify more potent, less toxic and more selective compounds. In this study, we aimed to determine the relative potency and toxicity of a panel of HDACi in clinical development in latently infected cell lines and a primary T-cell model of latency. In addition, we sought to demonstrate which HDACs were expressed and were critical for maintenance of latency in resting CD4 T-cells.

Methods: Latently infected CCL19-treated CD4+ T-cells and latently infected cell lines ACH2 and J-Lat were treated with a panel of HDACi including entinostat, vorinostat, panobinostat and MCT3. Viral production and cell viability were compared. Expression of cellular HDACs was measured by western blot and PCR. Association of HDACs with the HIV long terminal repeat (LTR) using latently infected CCL19-treated primary CD4+ T-cells in the presence and absence of specific HDACi was determined by chromatin immunoprecipitation (ChIP).

Results: We demonstrated considerable variation in the potency and toxicity of HDACi in latently infected primary CD4 T-cells and cell lines. All HDACi tested activated HIV production in latently infected primary T-cells with greatest potency demonstrated with entinostat and vorinostat and greatest toxicity with panobinostat. Following addition of HDACi in vitro, there were no changes in markers of T-cell activation or expression of the HIV co-receptors CXCR4 or CCR5. ChIP analysis of latently infected CCL19-treated primary CD4 T-cells showed binding by HDAC1, 2 and 3 to the LTR with removal of HDAC1 and 2 following treatment with the HDACi vorinostat and HDAC1 only following treatment with entinostat.

Conclusion: The HDACi entinostat, selective for inhibition of class I HDACs, induced virus expression in latently infected primary CD4 T-cells making this compound an attractive novel option for future clinical trials.