HIV-1 Expression within Resting CD4 T-Cells Following Multiple Doses of Vorinostat In Vivo

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BACKGROUND

A single dose of the potent class I histone deacetylase inhibitor (HDACi), vorinostat (VOR), upregulates HIV RNA expression within the resting CD4+ T cells of antiretroviral (ART)-treated, aviremic HIV+ patients (Archin, Nature 2012). The ability of VOR to repeatedly disrupt latency is unproven, the optimal dosing schema unknown, and effect of repeated VOR exposure on host mechanisms that contribute to viral expression is uncertain.

METHODS

Following a single VOR 400 mg dose, an increase in resting CD4+ T cell-associated HIV RNA (rc-RNA) was measured in all patients (Archin, Nature 2012), and consenting patients later received VOR 400 mg daily Monday-Wednesday for 4 weekly cycles, followed after a 4-week rest period by another 4 weekly cycles (dosing schema below). VOR serum concentrations (VOR), measurements of histone acetylation within PBMCs, and quantitative viral outgrowth assays (QVOA) from resting CD4+ T cells were obtained. A population PK model was built from all available VOR data using nonlinear mixed effects modeling (NONMEM 7.2). The model was used to predict individual VOR exposure and effect curve changing during drug absorption vs. elimination, suggest tolerance to VOR.

RESULTS

1. Repeat Dose Exposure Similar to Single Dose

![Graph showing repeat dose exposure similar to single dose](image1)

2. H3 Acetylation Little Increased from Baseline After Multiple Dosing

![Graph showing H3 acetylation little increased from baseline](image2)

3. Cell associated HIV RNA modestly increased in only some patients

![Graph showing cell associated HIV RNA](image3)

CONCLUSIONS

- HIV latency is disrupted by an initial VOR dose, but a refractory period of more than 24 hours ensues, which may reduce the responsiveness of the viral promoter to HDACi induction.
- Latent resting CD4+ T cell infection as measured by QVOA was not significantly reduced.
- Attempts to use HDACis to deplete persistent HIV infection will require a detailed understanding of the kinetic effects of HDACis on host cellular functions.
- Gene expression analysis to understand the complex cascade of events that follow VOR exposure in vivo is ongoing.