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

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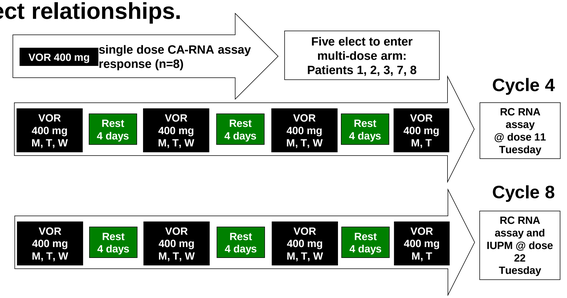
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BACKGROUND

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.

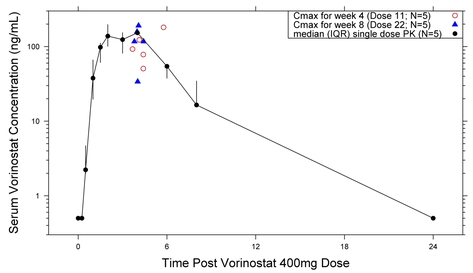
METHODS

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 4-8 week rest period by another 4 weekly cycles (dosing schema below). VOR serum concentrations ([VOR]), measurements of histone acetylation within PBMCs, rc-RNA, total cellular HIV DNA, 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 with NONMEM 7.2. The model was used to predict individual [VOR] at the time of leukapheresis and perform exploratory exposure-effect relationships.

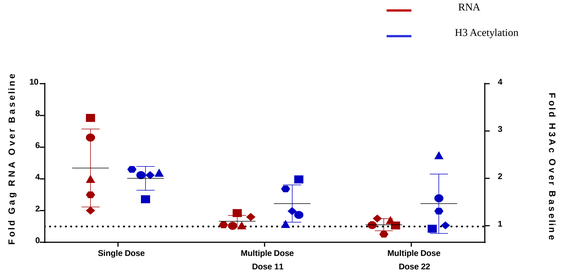


RESULTS

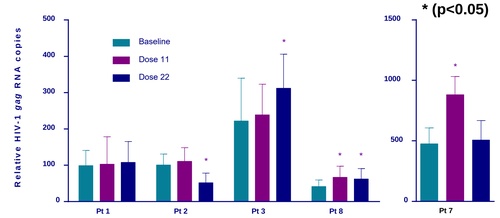
1 Repeat Dose Exposure Similar to Single Dose



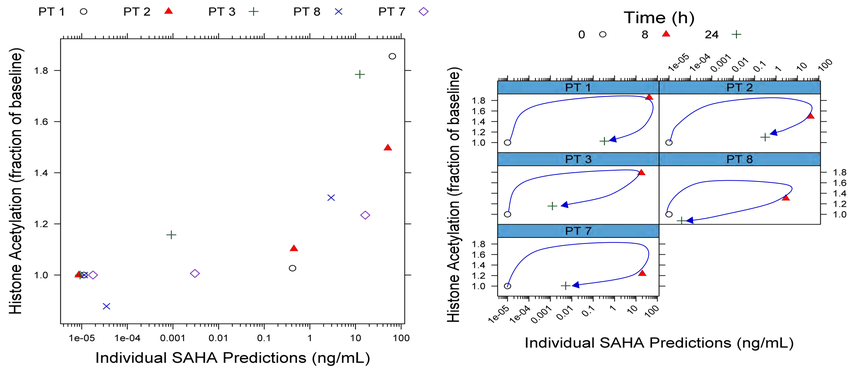
2 H3 Acetylation Little Increased from Baseline After Multiple Dosing



3 Cell associated HIV RNA modestly increased In only some patients



4 Clock-wise hysteresis, with the exposure-effect curve changing during drug absorption vs. elimination, suggest tolerance to VOR



CONCLUSIONS

- HIV latency is disrupted by an initial VOR dose, but a refractory period[1] 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.

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