Online Expert Poster Review and Discussion

ARV Therapies and Therapeutic Strategies

Reporting From

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Administration of Vorinostat Disrupts HIV-1 Latency in Patients on ART

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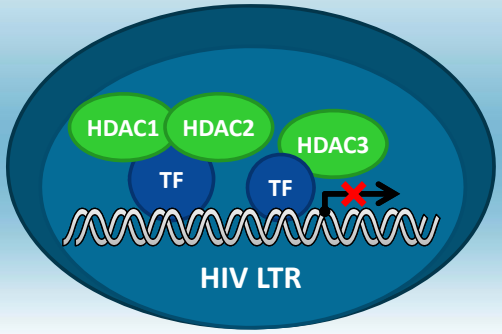
Abstract # 157LB

Research Leading to a Cure for HIV/AIDS

- Resting $CD4^+$ cell infection is extremely stable despite ART and is primary reservoir of persistent HIV infection
- Histone Deacetylases (HDACs) contribute to the maintenance of latency of HIV integrated into the genome of CD4+ T cells
- The class I HDACs --- HDAC 1, 2 and 3 --- are the primary enzymes that drive this effect at the HIV LTR in CD4+ T cells



Archin 2009; Keedy 2009

Vorinostat
Suberoylanilide Hydroxamic Acid (SAHA)

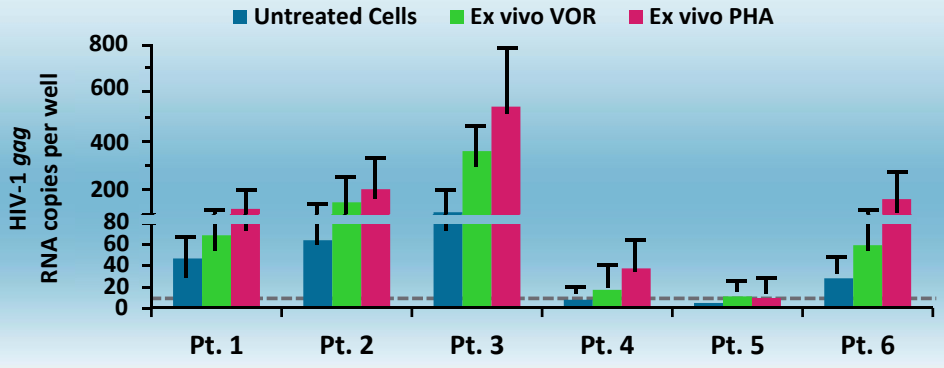
- Potent oral HDAC inhibitor
- Licensed for treatment of cutaneous lymphoma, Ames test +
- Selective inhibitor of HDACs 1, 2, 3
- Induces expression of latent HIV from the resting CD4 cells of HIV+ patients ***ex vivo***

Single does, proof-of-concept:
Can VOR disrupt latency in resting CD4+ T cells *in vivo*?

Archin 2009; Keedy 2009

Step 1

- Harvest resting CD+ T cells, establish baseline resting cell HIV RNA, and demonstrate that a change is detectable after a physiological exposure to VOR



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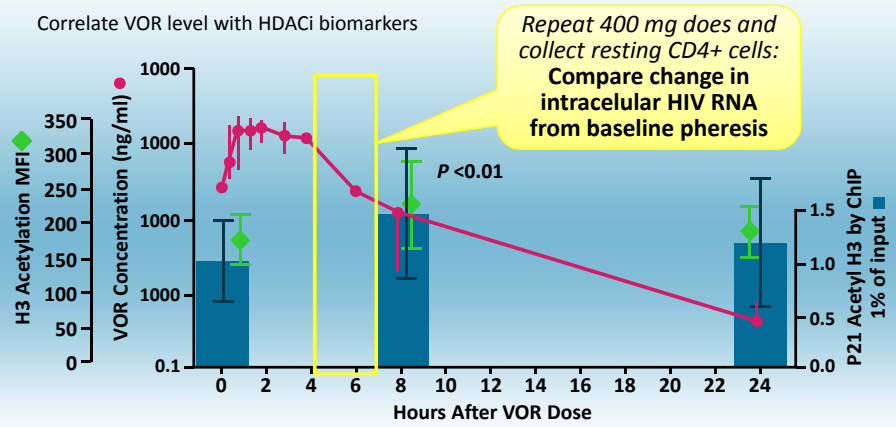
Step 2

- **Single 400 mg VOR Dose:** 12 hr VOR PK and cellular biomarkers of HDACi effect: Total cell histone acetylation and histone acetylation at human p21 gene

Correlate VOR level with HDACi biomarkers



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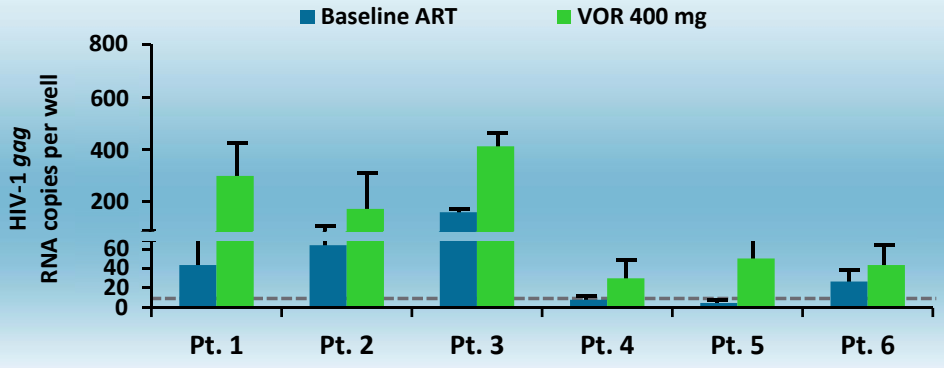
Step 3

- Mean 4.8-fold induction (range 1.5- to 10-fold)
- **All increases significant (*P* <0.01)**
- No AE >Grade I
- No AE due to VOR



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Single-copy Plasma HIV RNA

		200 mg			400 mg			400 mg		
	Screen	0 hr	8 hr	24 hr	0 hr	8 hr	24 hr	0 hr	8 hr	24 hr
Pt. 1	20	8	10	26	23	16	30	5	14	3
Pt. 2	<1	<1	1	1	<1	<1	<1	<1	<1	3
Pt. 3	1	1	2	<1	2	1	1	NA	<1	NA
Pt. 4	<1	<1	1	<1	<1	<1	<1	NA	<1	NA
Pt. 5	2.8	5	1	NA	2	NA	6	NA	NA	NA
Pt. 6	<1	<1	<1	<1	1	<1	<1	<1	1	5

No Significant Changes

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Summary

- A single dose of VOR induces expression of full-length HIV RNA within latently infected resting CD4+ T cells
- This is the first direct measurement of disruption of latent HIV infection *in vivo*
- A change in single-copy viremia could not be observed after a single dose of VOE
- Real-time measures of resting CD4+ T cells-associated HIV RNA could prove useful in the evaluation of eradication strategies
- The optimal dosing schedule of VOR, and its ability to deplete latent infection, remains to be established

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