Persistent HIV-1 in People Living with HIV on Antiretroviral Therapy

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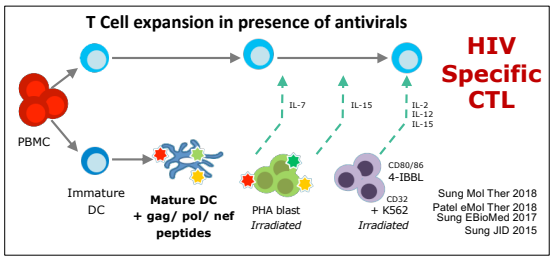
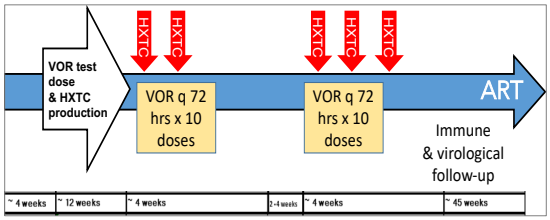
Background: One approach to eradicate HIV is to interfere with mechanisms that maintain latency, and simultaneously enhance the clearance of infected cells without interrupting antiretroviral therapy (ART). The histone deacetylase (HDAC) inhibitor, vorinostat (VOR), can repeatedly induce the expression of latent HIV-1 in vivo and allow clearance of infected cells in vitro. However, when paired with HIV vaccines or antibodies, this approach has not yielded substantial depletion of the latent reservoir in vivo. Adoptive T cell therapy has had dramatic success in the treatment of virus-related malignancies and infections following hematopoietic stem cell transplantation and has been adapted to produce ex-vivo expanded HIV-specific T cells (HXTCs) and other antiviral cell therapy products.

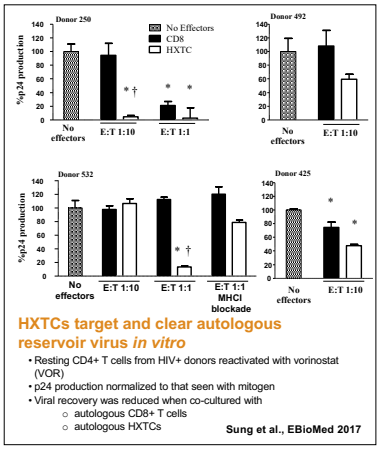


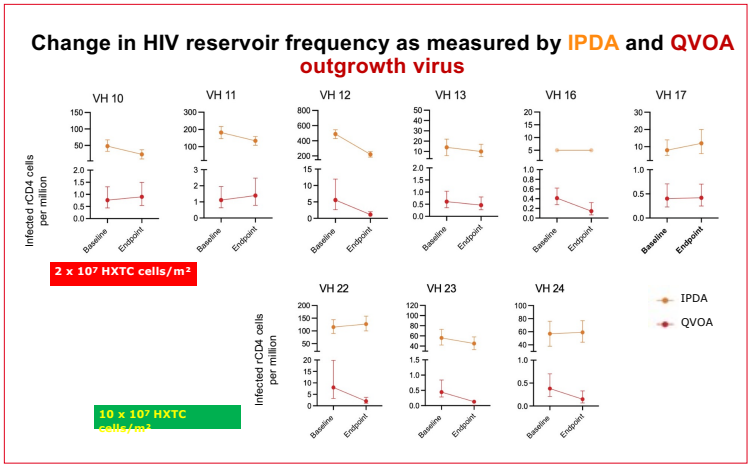


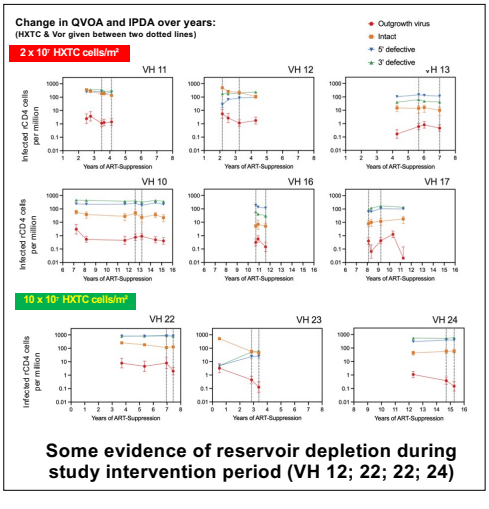
Initial pilot cohort N= 6 — **2 x 10⁷ HXTC cells/m²**
Study Extension N=3 — **10 x 10⁷ HXTC cells/m²**

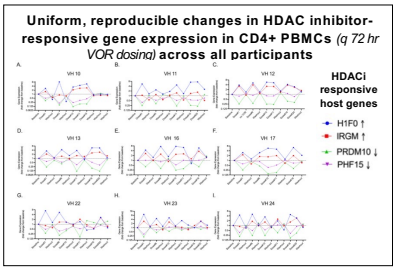
Results:

- Overall, PWH tolerated VOR and HXTCs, with only transient Grade 1 AEs related to study products.
- Biomarkers of serial VOR effect were detected in PBMCs, but evidence of enhanced antiviral activity in the total pool of circulating cells was not detected.
- One of 6 PWH exhibited a decrease in measures of persistent HIV after 2 x 10^7 HXTCs/m² infusions with VOR
- All three PWH exhibited such declines when 10 x10^7 HXTCs/m² were given.
- However, QVOA declines did not exceed 6-fold, a threshold required to definitively ($p > 0.05$) attribute QVOA decline to the study intervention, rather than assay variation.









Methods: In this pilot study we administered VOR and HXTCs to antiretroviral (ART)-suppressed people with HIV (PWH). Six PWH received five infusions of 2 x10^7 HXTCs/m² with VOR 400 mg every three days. Three PWH received five infusions of 10 x 10^7 HXTCs/m² with VOR. Leukapheresis was performed at baseline and after final HXTC infusion to measure the frequency of persistent HIV by Quantitative Viral Outgrowth Assay (QVOA) of resting CD4+ cells, cell-associated HIV RNA (rcaRNA), and intact HIV provirus assay (IPDA).

Clinical Characteristics at entry

Study ID	Age	Sex	Race/ Ethnicity	Stage ART initiated	CD4 nadir	CD4 at study entry	Years on ART	QVOA (infectious units per million rCD4+ cells)
VH-10	57	M	Caucasian	Chronic	195	701	30	0.761
VH-11	54	M	Caucasian	Chronic	174	785	4	1.112
VH-12	25	M	Caucasian	Chronic	323	740	2	5.576
VH-13	30	M	Black/ African American	Chronic	467	642	6	0.608
VH-16	55	M	Caucasian	Chronic	n.a.	923	14	0.309
VH-17	51	M	Black/ African American	Chronic	335	661	8	0.403
VH-22	63	M	Black/ African American	Chronic	352	927	28	8.010
VH-23	33	M	Black/ African American	Acute	795	1012	3	0.442
VH-24	52	M	Hispanic	Chronic	13	461	16	0.381

Conclusions:

- **These findings provide some support for the therapeutic strategy of HIV latency reversal and enhanced reservoir clearance**
- **However, the modest effects seen highlight the need for more effective latency reversal agents and clearance approaches that can be repeatedly employed to achieve the profound depletion of persistent HIV needed for clinical benefit.**

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