HERV Associate With HIV-DNA and Immune Activation in Blood and GALT of Virologically Suppressed PLWH

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BACKGROUND: Despite effective antiretroviral therapy (ART), many people living with HIV-1 (PLWH) show persistent immune activation and harbour latent reservoirs that hinder long-term management. The gut-associated lymphoid tissue (GALT), an early-established HIV reservoir, experiences massive CD4+ T-cell loss and high viral replication. Human endogenous retroviruses (HERVs), remnants of ancient infections comprising 8% of the human genome, have been linked to chronic inflammation and HIV-1. We previously showed their association with persistent immune activation in virologically suppressed PLWH. Here, we evaluated HERV transcription, immune activation, and HIV reservoirs in blood and GALT to identify novel markers for clinical monitoring.

In people living with **HIV** who are in virological suppression, increased **HERV** expression is associated with persistent immune activation in **blood** and **GALT**, and could represent a useful **biomarker** for clinical monitoring and personalized treatment management.

METHODS: 31 HIV-1+ viral suppressed patients, and 10 Healthy Donors (HD) were enrolled. Blood and GALT HIV-DNA levels and residual plasma viremia were quantified by droplet digital-PCR system. The expression of the env gene of HERV-K113 and HERV-K111, of pHERV-W, Syncitin-1 (SYN-1) and HERV-H have been analysed from blood samples by RT-Real time PCR. The immunophenotyping have been evaluated by flow cytometry. The non-parametric Mann-Whitney test and the Spearman Correlation were used for statistical analysis.

1

Blood



Gut Associated Lymphoid Tissue (GALT)



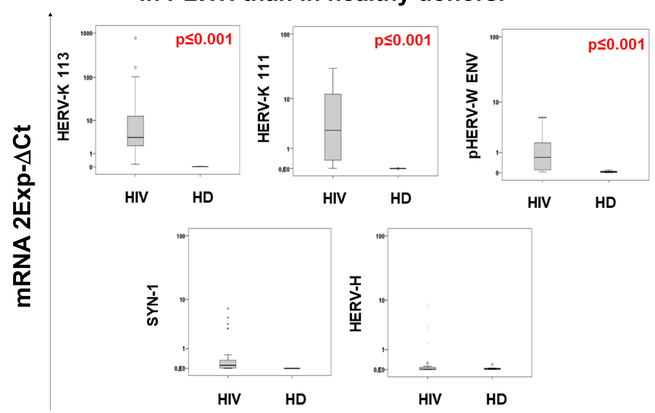
Inclusion criteria

For at least one year:
- Antiretroviral treatment
- virological suppression (HIV RNA < 20cp/ml)

	HIV individuals (n=31)	Healthy donors (n=10)
Gender M/F (ratio)	29/2(97.5%)	10/0(100%)
Median age (range)	37(32-45)	33 (30-46)
HIV RNA	3 (2-5) cp/mL	-
CD4 count	742 (553-1127) cells/µL	-

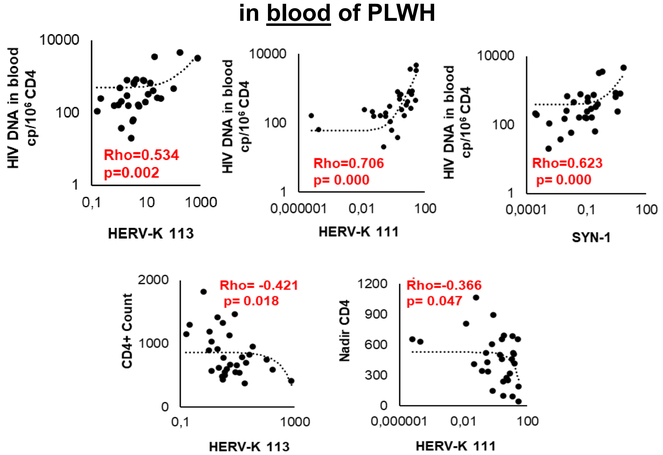
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Higher levels of HERVs expression in PLWH than in healthy donors.



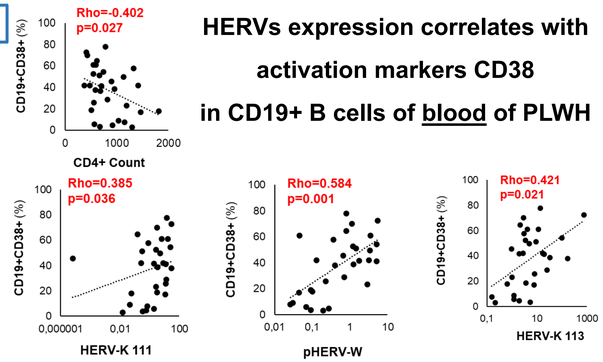
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HERV expression correlates positively with HIV reservoir, and negatively with CD4 count in blood of PLWH



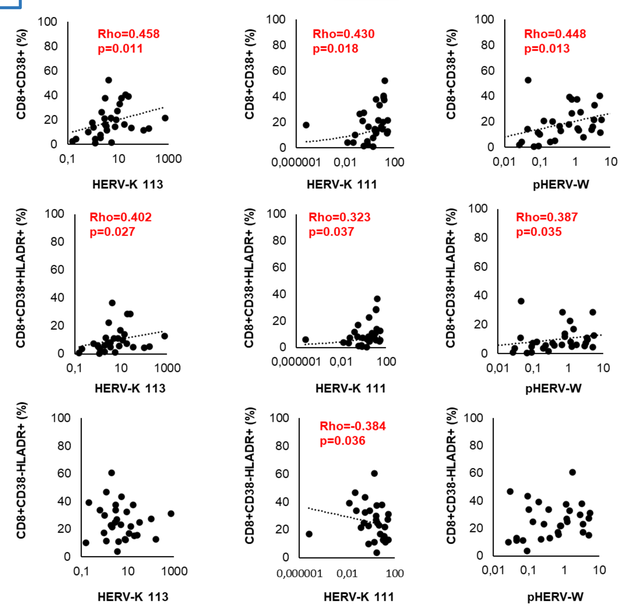
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HERVs expression correlates with activation markers CD38 in CD19+ B cells of blood of PLWH



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HERVs expression correlates with CD38 and HLADR in CD8+ T cells of blood samples.



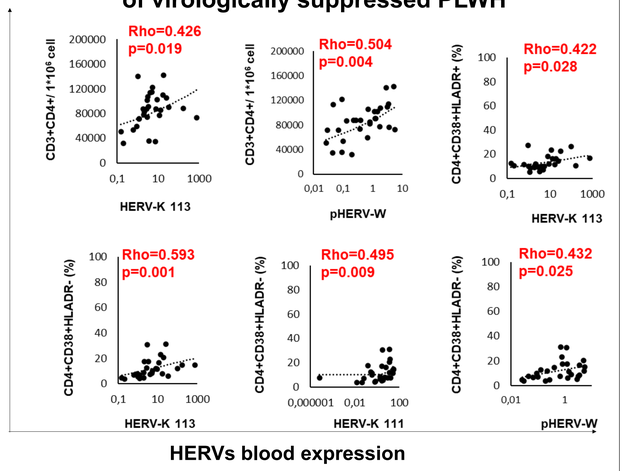
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PCA showed associations of HERVs expression, lymphocyte activation and HIV clinical features in PLWH

	Component 1	2	3	4	5
HERV-K 113	0.850	-0.030	-0.233	-0.106	0.273
HERV-K 111	0.802	0.221	-0.091	0.399	0.054
HERV-H	0.724	-0.145	-0.045	-0.093	-0.198
HIV-DNA in PBMCs (copies/10^6CD4)	0.705	0.102	-0.172	0.442	0.165
pHERV-W	0.610	0.304	-0.195	-0.366	0.100
CD8+CD38+ %	0.092	0.913	-0.114	0.097	-0.096
CD8+CD38+HLADR+ %	0.031	0.879	-0.122	0.098	0.105
CD19+CD38+ %	0.375	0.725	-0.120	-0.130	-0.144
Residual Viremia (cp/mL)	-0.144	0.599	0.032	0.232	-0.084
CD4+/CD8+ Ratio	-0.230	-0.284	0.802	-0.034	-0.140
Nadir CD4	-0.261	-0.203	0.780	-0.125	0.063
CD4+CD38-HLADR+ %	0.007	-0.288	-0.723	-0.186	0.371
CD4+ absolute count	-0.288	-0.201	0.683	-0.005	0.591
CD4+CD38+HLADR+ %	-0.294	-0.215	-0.493	0.330	0.488
SYN-1	0.258	0.044	0.083	0.769	0.148
CD8+CD38-HLADR+ %	0.075	-0.123	0.261	-0.724	0.022
CD4+CD38+ %	-0.148	0.300	0.183	0.425	-0.126
CD8+ absolute count	0.300	-0.031	-0.149	0.014	0.857

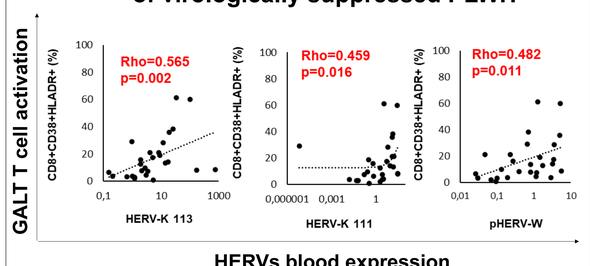
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HERVs expression correlates with CD38 and HLADR in CD4+ T cells in GALT of virologically suppressed PLWH



8

HERVs expression correlates with CD38 and HLADR in CD8+ T cells in GALT of virologically suppressed PLWH



CONCLUSION: Our analysis suggest that HERV expression may contribute to immune dysregulation and HIV persistence in people living with HIV. The observed immune activation in both blood and GALT underscores a systemic link between peripheral and mucosal immunity. Although this preliminary analysis did not reveal significant associations between HERV expression in blood and HIV-DNA levels in biopsies, further studies assessing HERVs expression could provide further insights into the mechanisms of chronic inflammation and HIV latency, potentially guiding the development of targeted therapeutic strategies

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