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Low-level HIV viremia increases immunosuppressive markers elevating cancer and CVD risk in INSTI era

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01. Background

We previously reported that low-level HIV viremia (LLV) (50-200 copies/mL) is associated with higher cellular activation and senescence in a cohort composed primarily of males (78%) with a mean age of 53 years and treated mostly with integrase strand transfer inhibitors (INSTI)-based regimens. These phenomena are closely related to the development of cancer and cardiovascular diseases (CVD). However, data on the clinical consequences of LLV remain limited, especially in the INSTI era.

Our aim was to explore how LLV impacts on soluble and cellular markers related to these pathologies.

02. Methods

Participants

Cross-sectional observational study in 81 matched PWH

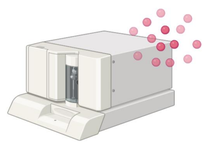
N=27 — ***Low-level viremia*** (LLV)
At least 2 consecutive viral loads (50-200 copies/mL) for the last two years before sample collection

N=27 — ***Suppressed viremia*** (SV)
Undetectable viral loads (<50 copies/mL) during the last two years before sample collection

N=27 — ***Non-HIV controls*** (NHC)

Biomarkers

Soluble



Plasma
Immunoassays (Luminex and ELISA)

28 **immune checkpoints** (ICs)
18 **cardiometabolic** markers

Cellular



PBMCs
Spectral flow cytometry

Tregs subpopulations
(CD3, CD4, CD25, CD127, FoxP3, Helios)

Statistics

Differences between groups were analyzed with a GAMLSS, adjusted by age, sex at birth and antiretroviral therapy (ART).
P-values were corrected by the False Discovery Rate (FDR) (q-value).

03. Results

A generalized increase in sICs levels was observed in **PWH** compared to NHC (26/28 biomarkers in LLV vs NHC; 27/28 biomarkers in SV vs NHC), highlighting with increases over 50% in several members of the B7, CD28, TNF/RSF, MHC-I, MACPF and Ig superfamilies (**Fig.1**). PWH groups also revealed an increase in the cardiometabolic markers NGAL, P-selectin, vWF and ST2.

LLV group showed a 2-fold increase of sIDO over SV group, as well as an increase in the cardiometabolic sICAM-1 and an upward trend of sCD14 (**Fig.1**).

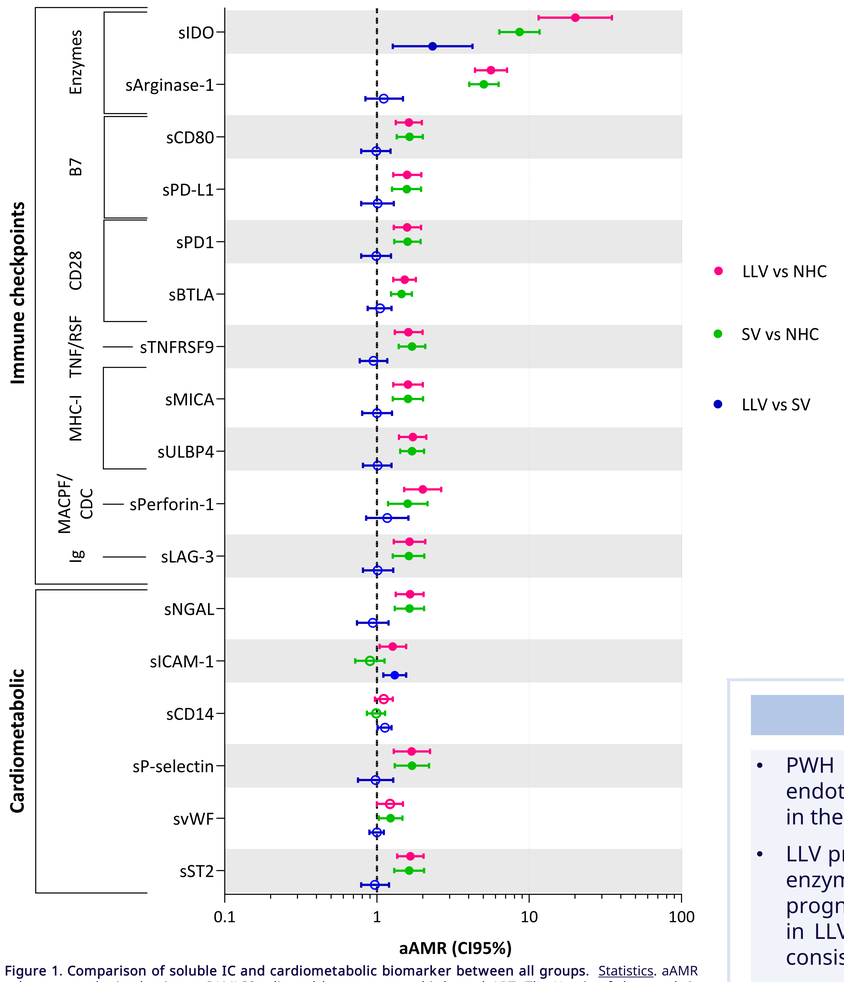
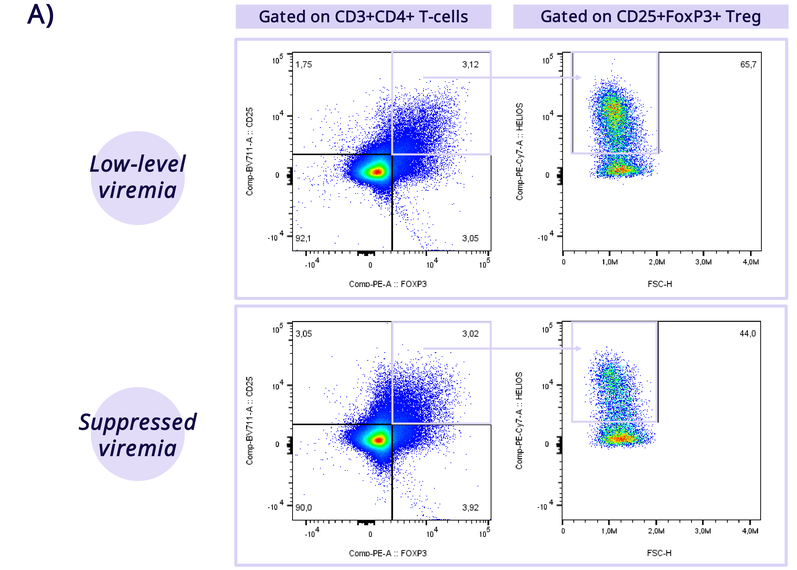


Figure 1. Comparison of soluble IC and cardiometabolic biomarker between all groups. Statistics. aAMR values were obtained using a GAMLSS adjusted by age, sex at birth, and ART. The X axis of the graph is represented in logarithmic scale. **Only soluble ICs with aAMR>1.5 are shown.** Statistically significant variables are represented with filled balls (p<0.05 and q<0.15). Abbreviations: LLV, PWH with LLV (50-200 copies/mL); SV, PWH with SV (<50 copies/mL); NHC, non-infected HIV controls; aAMR, adjusted arithmetic mean ratio.

A)



B)

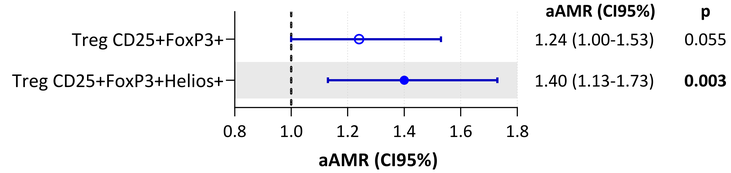


Figure 2. A) Representative example of Treg cell frequency. B) Comparison of Treg cells between LLV and SV groups. Statistics. aAMR values were obtained using a GAMLSS adjusted by age, sex at birth, and ART. Abbreviations: LLV, PWH with LLV (50-200 copies/mL); SV, PWH with SV (<50 copies/mL); aAMR, adjusted arithmetic mean ratio.

04. Conclusions

- PWH aged 50 years undergoing long-term ART showed higher soluble ICs levels, endothelial inflammation and hypercoagulable state, increasing the risk of cancer and CVD in the INSTI era.
- LLV promoted a stronger immunosuppressive environment, evidenced by elevated IDO, an enzyme that inhibits T-cell functions and induces cell death. IDO is considered a cancer prognostic marker, which aligns with the increase in suppressive Treg FoxP3+Helios+ cells in LLV group, also immuno-oncology targets. Besides, this enzyme is implicated in CVD, consistent with higher levels of subclinical atherosclerosis markers sICAM-1 and sCD14.
- Our findings suggest that IDO could be a promising marker for early detection of future complications related to cancer and cardiovascular disease especially important in LLV population allowing rapid intervention.

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