Low-level HIV viremia affects T cell activation and senescence in INSTI-era

348

Violeta Lara-Aguilar[1], Manuel Llamas-Adán[1], Oscar Brochado-Kith[1,2], Celia Crespo-Bermejo[1], Sergio Grande-García[1], Sonia Arca-Lafuente[1], Ignacio De los Santos[2,3], María Carmen Prado[1], Mario Alía[1], Coral Sainz-Pinós[1], Amanda Fernández-Rodríguez[1,2], Luz Martín-Carbonero[2,4], Ricardo Madrid[5], Verónica Briz[1,2].

[1]Institute of Health Carlos III (ISCIII), Spain, [2]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), ISCIII, Spain, [3]La Princesa University Hospital, Spain, [4]La Paz University Hospital, Spain, [5]Complutense University, Spain.

BACKGROUND

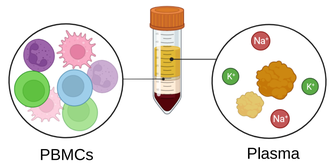
Around 10% of people with HIV (PWH) show a low-level viremia (LLV) under antiretroviral therapy (ART), but its clinical relevance is still unclear especially in the era of integrase strand transfer inhibitors (INSTIs). We evaluated the influence of this poor virological response on the immune system in comparison to individuals with suppressed viremia (SV).

METHODS

Transversal observational study was performed following a case-control strategy in 54 matched PWH.

LLV group (n=27): at least two consecutive viral loads (50-200 copies/mL) maintained for two years.

SV control group (n=27): undetectable viral loads (<50 copies/mL) maintained for two years.



Immunophenotypic T-cell profile

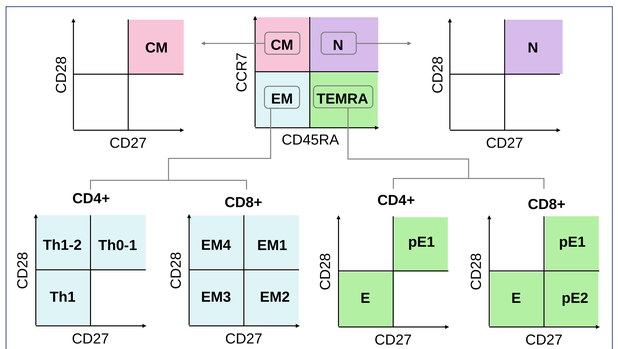


Figure 1. Gating strategy for memory T-cells. CD3+CD4+ and CD3+CD8+ T-cells from participants were separated into four subsets N, CM, EM, and TEMRA based on CD45RA and CCR7 expression. Within each of these subsets, distinct subpopulations were characterized by analyzing differential expression of CD27 and CD28. Abbreviations: N, naïve; CM, central memory; EM, effector memory; TEMRA, terminally differentiated effector; Th0-1 (subset composed of Th0 and Th1 EM cells); Th1-2 (subset composed of Th1 and Th2 EM cells); pE1, pre-terminally differentiated effector memory RA+ 1; pE1, pre-terminally differentiated effector memory RA+ 2; E, Effector.

Inflammatory profile

45 soluble biomarkers of inflammation were evaluated in plasma by multiplex immunoassays (EPXR450-12171-901, ThermoFisher): Th1/Th2 and Th9/Th17/Th22/Treg response, chemokines, growth factor, and inflammatory cytokines.

Statistics

- **GAMLSS** (ZOIB) and **GLM** (log-link) adjusted by age, sex at birth, and ART were used for the statistical analysis of cell frequencies and plasma biomarkers, respectively.
- P-values were adjusted by the false discovery rate (FDR) using Benjamin-Hochberg correction setting a cut-off point of 0.15 (**q-value**).
- Statistical significance: **p<0.05** and **q<0.15**

CONCLUSION

- The persistence of LLV between 50-200 copies/mL leads to a reduction of CD8+ EM1 subpopulation and higher activation mainly in EM and TEMRA subpopulations that could be functionally exhausted.
- These findings suggest a reduced cytotoxic activity and T-cell dysfunction affecting the cytokine production, which partially explain the absence of significant differences in the inflammatory profile between LLV and SV.
- All this indicates T-cell dysfunction in LLV individuals unable to control and eliminate infected cells.

REFERENCES

[1] Paris RM. PLoS One. 2015; [2] Jones RB. J Exp Med. 2008; [3] Day CL. Nature. 2006; [4] Trautmann L. Nat Med. 2006; [5] De Jong LC. PLoS Pathog. 2021; [6] Douek DC. Nature 2002; [7] Papagno L. PloS Biol. 2004; [8] Guerville F. AIDS. 2023

CORRESPONDING EMAIL: violeta.lara.aguilar@hotmail.com

RESULTS

The median age was 53 years and 77.8% were men. 74% of LLV were on INSTIs compared to 48% in SV (p<0.001).

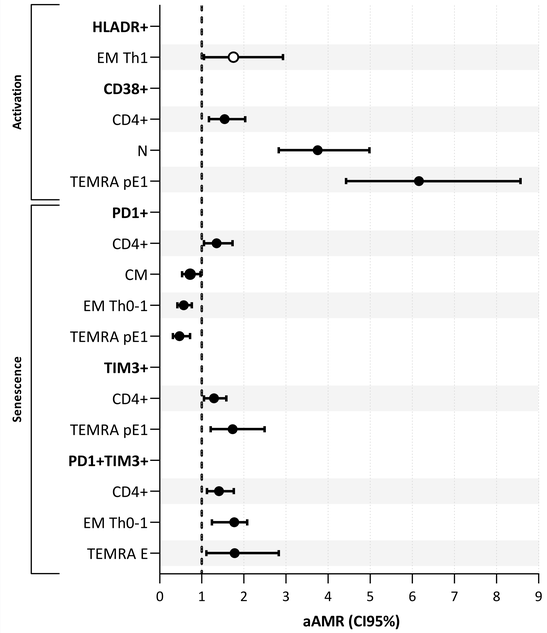


Figure 2. Comparison of CD4+ T-cell profile between PWH with LLV and SV. Statistics: The adjusted Arithmetic Mean Ratio (aAMR) values were obtained using a GAMLSS with ZOIB distribution adjusted by age, sex, and ART. Only statistically significant populations (filled balls, p<0.05; q<0.15) or close to significance (unfilled balls p<0.05; q>0.15) are shown.

CD4+

T-cell activation could lead to a strong effector function. However, a generalized **increase** in the expression of **senescence** markers was also observed.

PD1+ early differentiated subpopulations represent highly functional populations more susceptible to HIV infection and selectively lost in chronic infection[1]. Their lost in LLV indicates a potential inability to execute an effective CD4+ T.

The **up-regulation of TIM3** and **PD1+TIM3+** expression has also been associated with T-cell dysfunction by inhibiting cell proliferation in response to antigen and net cytokine production[2,3,4], which may partly explain the absence of significant differences in the inflammatory profile compared to SV.

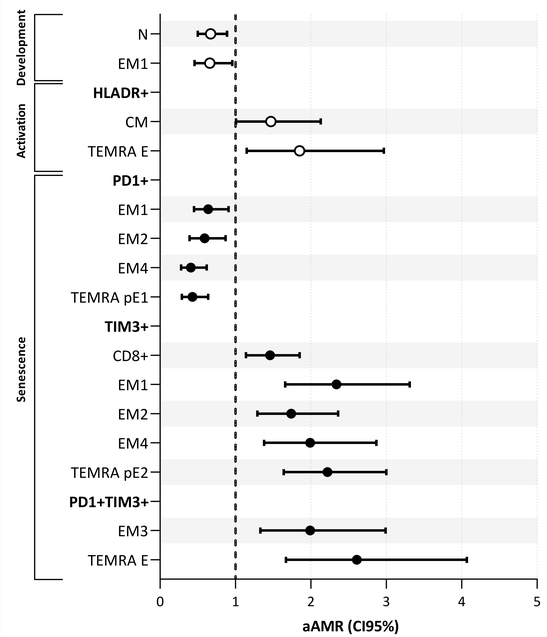


Figure 3. Comparison of CD8+ T-cell profile between PWH with LLV and SV. Statistics: The adjusted Arithmetic Mean Ratio (aAMR) values were obtained using a GAMLSS with ZOIB distribution adjusted by age, sex, and ART. Only statistically significant populations (filled balls, p<0.05; q<0.15) or close to significance (unfilled balls p<0.05; q>0.15) are shown.

CD8+

CD8+ EM1 express high levels of granzyme K, which targets viral proteins crucial for replication[5], as well as promoting cell apoptosis. This suggest that LLV could contribute to reduced cytotoxic activity, allowing further spread of the virus.

The expression of **HLA-DR** and **CD38** has previously been correlated with higher viremias (40-999 copies/mL). A strong immune activation and elevated levels of circulating viral antigens may contribute to the development of T-cell exhaustion[6,7].

The **up-regulation** of **TIM3** and **PD1+TIM3+** expression on CD8+ T-cells has been associated with reduced effector functions and clonal elimination of antigen-specific T cells[8].