Dasatinib + Quercetin Drugs Reduced Senescent-Associated Secretory Phenotype (SASP) in PLWH PBMCs

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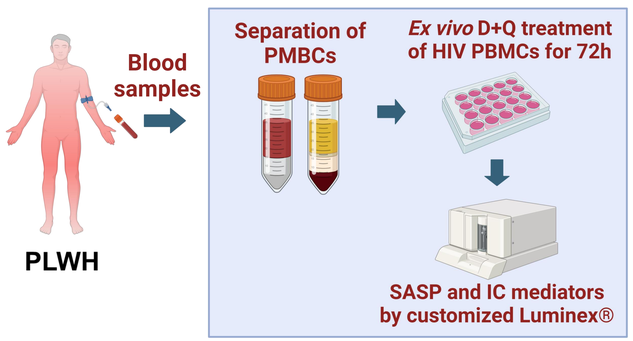
BACKGROUND

Despite virologic suppression on ART, PLWH present chronic inflammation and are more vulnerable to **age-related diseases**. Research in cellular aging has identified key biomarkers that define **senescent cells** (SC) and new senolytic drugs that can eliminate them. These biomarkers include SA-βGal, $p16^{INK4a}$ and cytokines such as MCP-1, IL-8, IL-6 that are principal components of the **Senescence-Associated Secretory Phenotype** (SASP). We have previously found that HIV-1 infection increase SC biomarkers such as SA-βGal, $p16^{INK4a}$, BCL-2, ϒ-H2AX and IL-6 in $CD4^+$ T cells. The role of HIV-1 in promoting cellular senescence and SASP is not fully understood and could be key to develop new treatments for HIV-associated aging comorbidities. We aim to determine whether **Dasatinib** plus **Quercetin** (D+Q) senolytic drugs or Dasatinib can influence these SC-biomarkers and SASP levels.

METHODS

PLWH from **acute, chronic** and **advanced** infection (<100 CD4 cells/µl at diagnosis, ADV) before and after a year on **ART** matched by sex and age were included (n=12). D+Q senolytic drugs were added to an *ex vivo* 3-day culture of PBMC with IL-2 from those cohorts. A set of 34-top **SASP** and 6 **IC mediators** were quantified by a customized Luminex in plasma and cell culture supernatants including **pro-inflammatory cytokines** and other **SASP** soluble mediators. Unpaired or paired non-parametric T-test were performed.



CONCLUSIONS: These findings suggest that *ex vivo* **D+Q senolytic treatment** decreased SC-biomarker levels and the majority of **SASP factors** analyzed. These drugs could be useful to reverse **cellular senescence**, **chronic inflammation** and **comorbidities** associated to HIV infection in PLWH.

RESULTS

Figure 1. SASP (IL-6, IL-8, IL-10, RANTES, GRO-α, TNF-RI/RII, CD30, CD30L, VEGF-A) and IC (PD-1, PD-L1, PD-L2, LAG-3, CTLA-4) mediator levels were higher in advanced and chronic patients than in NC. These mediators were only reduced to NC levels by a year of ART in the acute cohort.

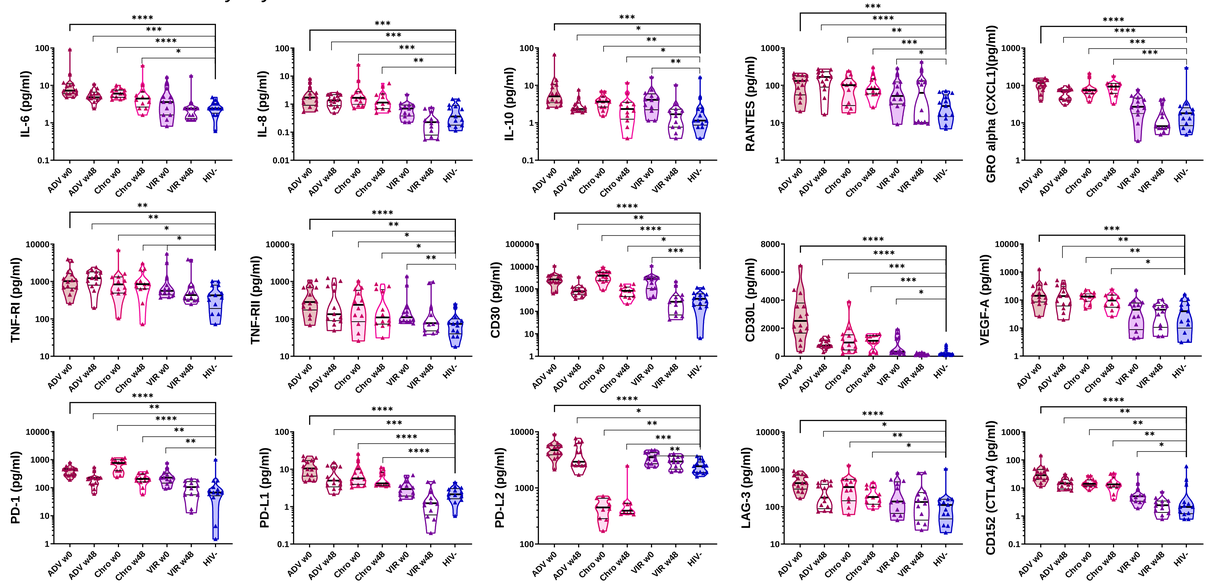


Figure 2. SA-βGal in CD4 T cells and IL-6 levels positively correlated with SASP mediators and IC such as IL1-beta, IL-8, MIP-1α, LAG-3, PD-L1 and CTLA-4 in advanced and chronic PLWH.

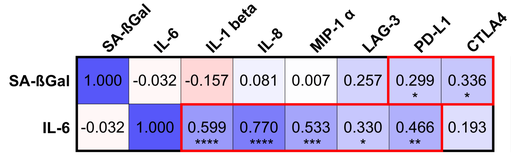


Figure 3A. SASP mediators such as coagulation related proteins (uPAR, and PAI-1), matrix-metalloproteinases (MMP-1 and MMP-12) and growth factors (PlGF-1 and HGF) were significantly reduced by D+Q treatment in PLWH.

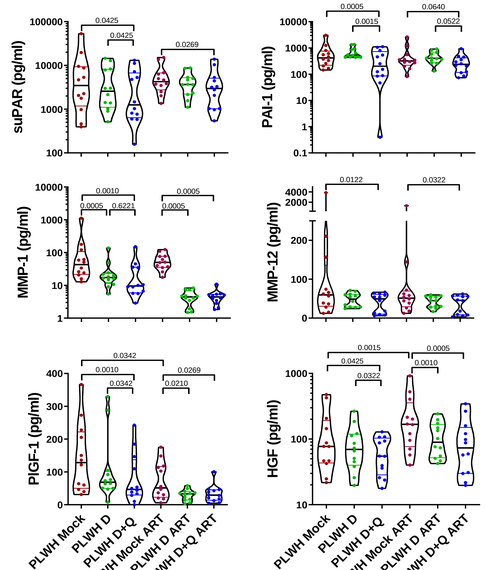
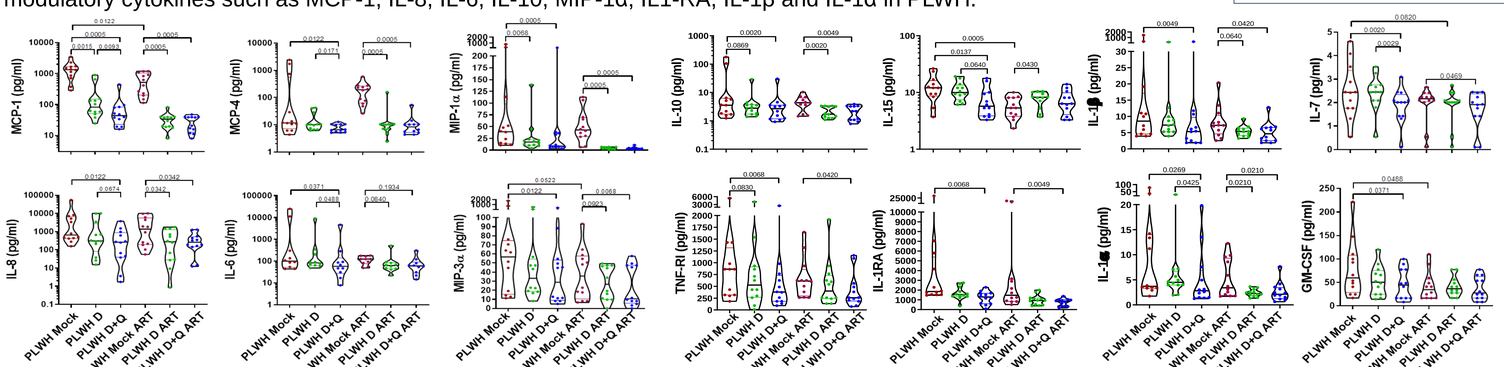


Figure 3B. D+Q treatment decreased many SASP proteins including pro-inflammatory cytokines and immune-modulatory cytokines such as MCP-1, IL-8, IL-6, IL-10, MIP-1α, IL1-RA, IL-1β and IL-1α in PLWH.



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