Pharmacologic intervention to reduce chronic inflammation in people with HIV

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BACKGROUND

- Chronic inflammation and persistent immune activation are critical for HIV-1 disease pathogenesis and progression.
- HIV-infected monocyte-derived macrophages (MDMs) contribute to long-lived reservoirs and chronic inflammation in people with HIV (PWH) due to persistent release of proinflammatory mediators.
- Tyrosine kinase inhibitor dasatinib, which is used to treat chronic myeloid leukemia (CML), inhibits HIV-1 infection in CD4+ T cells by preserving SAMHD1 antiviral activity.
- SAMHD1 also downregulates interferon (IFN) and other inflammatory responses to viral infections.

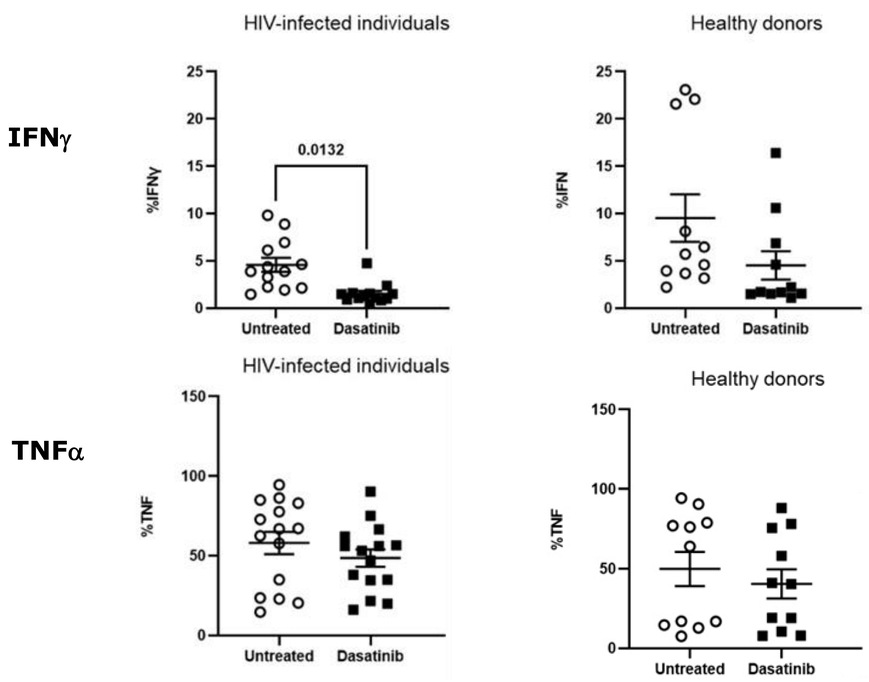
OBJECTIVE: to evaluate if dasatinib may control both infection and proinflammatory effects of HIV-1 on MDMs from PWH, as well as reduce the levels of proinflammatory cytokines in plasma of PWH on ART and dasatinib.

METHODS

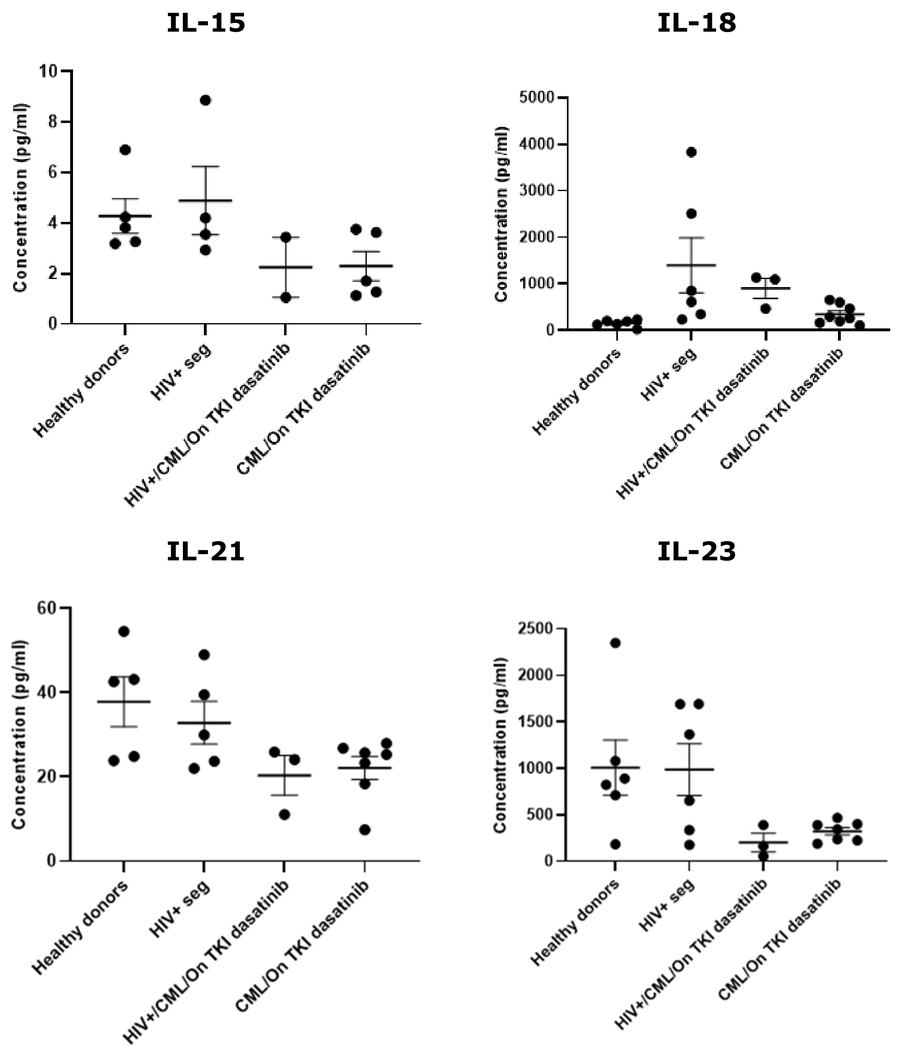
- 15 ART-treated PWH, 3 PWH with CML on ART and dasatinib, and 11 healthy donors were recruited.
- CD14+ cells from PBMCs were differentiated to MDMs and then infected with JR_FL_Renilla strain for 48h with or without dasatinib.
- HIV-1 infection was analyzed by flow cytometry.
- SAMHD1 phosphorylation and synthesis of IFNγ and TNFα were analyzed by flow cytometry after stimulation with lipopolysaccharide (LPS).
- Plasma cytokines were quantified by Luminex.

RESULTS

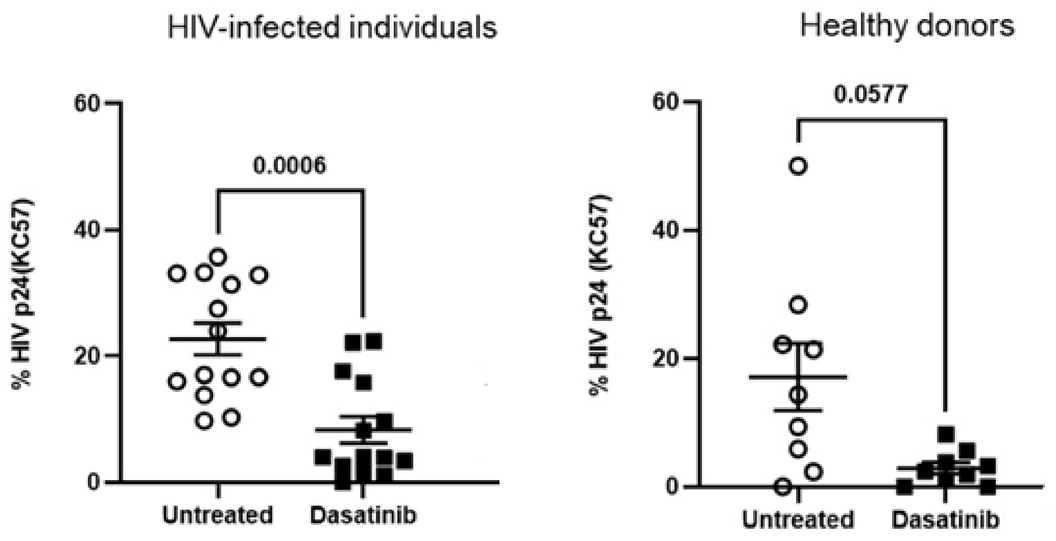
1 Dasatinib reduced 3.0-(p=0.0132) and 2.1-fold the LPS-induced synthesis of IFNγ from MDMs of PWH and healthy donors, respectively. TNFα synthesis remained unchanged.



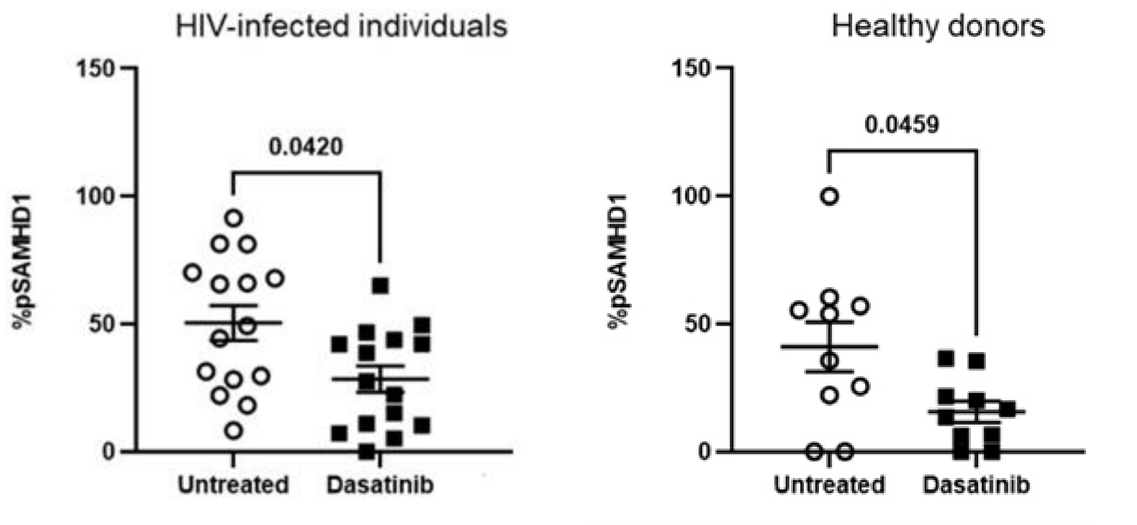
2 Plasma levels of proinflammatory cytokines IL-15, IL-18, IL-21, and IL-23 were reduced 2.17-, 1.55-, 1.61-, and 4.86-fold in PWH on ART+dasatinib, in comparison with ART-treated PWH. IFNγ was undetectable in plasma of PWH on ART+dasatinib.



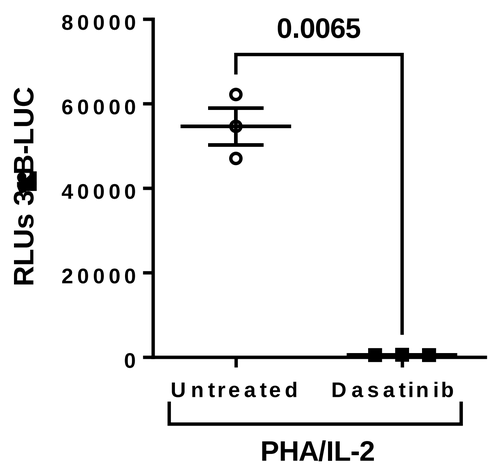
3 HIV-1 infection was reduced 2.4-(p=0.0006) and 5.9-fold (p=0.0577) in MDMs from PWH and healthy donors, respectively, after treatment with dasatinib.



4 Dasatinib reduced 1.8-(p=0.0420) and 2.6-(p=0.0459) fold SAMHD1 phosphorylation in MDMs from PWH and healthy donors, respectively.



5 Dasatinib interfered with proinflammatory NF-KB-dependent transcriptional activity (p=0.0065) in PBMCs.



CONCLUSIONS

- New therapeutic interventions are needed to reverse the chronic inflammation caused by HIV-1 persistence.
- Dasatinib reduced the levels of proinflammatory cytokines in plasma of ART-treated PWH and reverted SAMHD1 constitutive phosphorylation of MDMs, protecting them from HIV-1 infection and reducing their inflammatory potential.
- The use of dasatinib as adjuvant of ART would decrease the inflammatory environment characteristic of chronic infection, thereby improving health of PWH.

Presented at AIDS 2022 – The 24th International AIDS Conference

ACKNOWLEDGEMENTS

Red Española de Investigación en Sida
National Institutes of Health
The University of Utah School of Medicine
Centro de Salud Pedro Lain Entralgo
Gobierno de España – Ministerio de Ciencia, Innovación y Universidades
Hospital Universitario Severo Ochoa
AIDS 2022 29 July – 2 August