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DASATINIB PREVENTS HIV INFECTION OF MACROPHAGES AND REDUCES THE INFLAMMATORY POTENTIAL

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BACKGROUND

- Monocyte-derived macrophages (MDMs) contribute to the long-lived HIV-1 reservoirs.
- MDMs also release soluble factors that contribute to chronic inflammation in PWH.
- Our group previously demonstrated that tyrosine kinase inhibitor (TKI) dasatinib, but not imatinib, prevents HIV-1 infection of CD4+ T lymphocytes, the main HIV-1 reservoir.
- In this proof-of-concept study, we analyzed whether dasatinib or imatinib also protected MDMs from HIV-1 infection and/or reduced their inflammatory potential.

METHODS

- CD14+ cells isolated from PBMCs of ART-treated individuals with chronic HIV-1 infection (n=15) and healthy donors (n=11) were differentiated to MDMs for 5 days and then infected with JR_FL_Renilla strain for 48h in the presence or not of dasatinib 50nM or imatinib 10µM.
- HIV-1 infection was analyzed by chemiluminiscence and flow cytometry.
- SAMHD1 phosphorylation and synthesis of IFNγ and TNFα after stimulation with lipopolysaccharide (LPS) were analyzed by flow cytometry.
- Cell viability was determined by microscopy and flow cytometry.

Dasatinib reverted **SAMHD1** constitutive phosphorylation of MDMs from ART-treated PWH, **protecting them from HIV infection.**
Dasatinib also reduced the levels of proinflammatory cytokines such as **IFNγ** in plasma of ART-treated PWH, **reducing their inflammatory potential.**

CONCLUSIONS

- Dasatinib reverted SAMHD1 phosphorylation of MDMs to induce protection from HIV-1 infection, being imatinib less effective.
- Dasatinib, but not imatinib, reduced IFNγ production, which has been involved in HIV-1 chronic inflammation.
- Dasatinib was more effective to inhibit HIV-infection in MDMs from healthy donors but the interference with IFNγ synthesis was more effective in MDMs from HIV-infected individuals.

ACKNOWLEDGEMENTS

RESULTS

Table 1. Demographical characteristics of the participants

HIV-infected individuals (n = 15)		
Gender	female	20%
	male	80%
Age (median)		67
CD4+ T cells (mean)		761.53
CD8+ T cells (mean)		910.8
CD4/CD8 ratio (mean)		0.98
Nadir CD4 (mean)		397.93

Figure 1. Dasatinib reduced 2.4- (p=0.0006) and 5.9-fold (p=0.0577) HIV-1 infection in MDMs from HIV-infected individuals and healthy donors, respectively, whereas imatinib reduced the infection 1.2- and 1.7-fold, respectively.

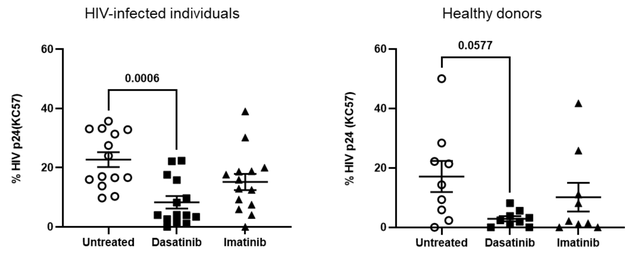

Figure 2. Dasatinib reduced 1.8- (p=0.0420) and 2.6–fold (p=0.0459) SAMHD1 phosphorylation in MDMs from HIV+ individuals and healthy donors, respectively, whereas imatinib did not induce changes.

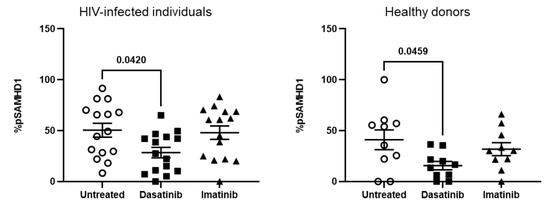

Figure 3. IFNγ production decreased 3.0- (p=0.0132) and 2.1-fold from MDMs of HIV+ individuals and healthy donors treated with dasatinib, respectively, while imatinib showed no significant effect.

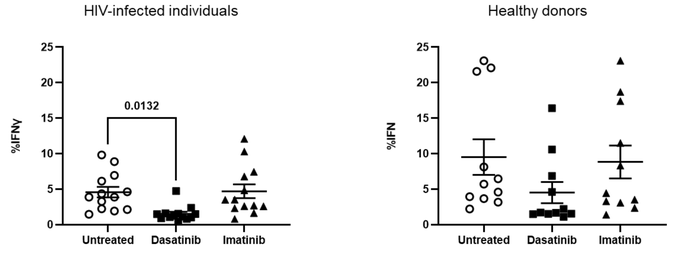

Figure 4. The synthesis of TNFα was not significantly modified by any TKI.

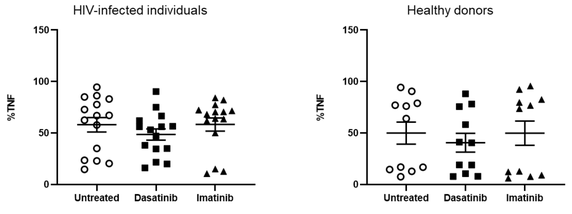

Figure 5. MDMs acquired a rounded morphology with dasatinib, but the synthesis of mitochondrial ATP and adhesion capacity did not change.

