Interference of HIV-1 proviral integration through changes in CPSF6 and SC35 expression due to dasatinib and ponatinib in monocyte derived macrophages

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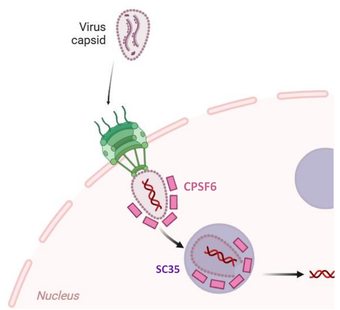
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BACKGROUND

Our objective was to determine if dasatinib or ponatinib may interfere with HIV-1 infection in macrophages via CPSF6 and/or SC35.

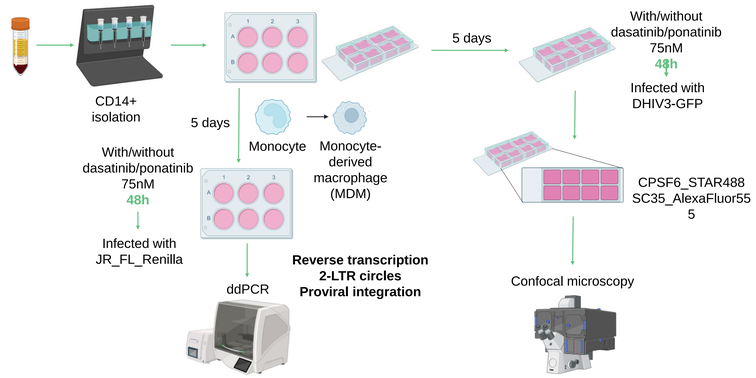
- HIV-1 infection is controlled by antiretroviral treatment but viral persistence in long-lived reservoirs formed by CD4+ T cells and macrophages impedes viral eradication.
- Pre-integration complex enters the nucleus assisted by mRNA processing proteins like CPSF6 and SRSF2/SC35.
- Dasatinib and ponatinib are tyrosine kinase inhibitors that interfere with HIV-1 integration by preserving antiviral factor SAMHD1.



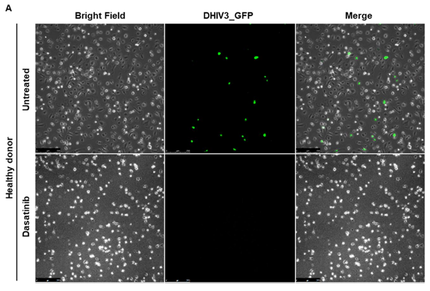
TKIs modify subcellular location and expression of CPSF6 and SC35 in MDMs

METHODS

15 PWH along with 16 healthy donors. All participants were recruited from hospitals and healthcare centers in Madrid, Spain.



RESULTS



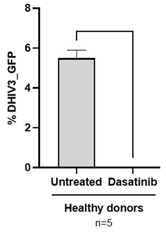


Figure 1. DHIV-GFP infected cells were detected 22h after infection in the untreated participant, while the dasatinib-treated participant remained nearly undetectable for 50h post-infection.

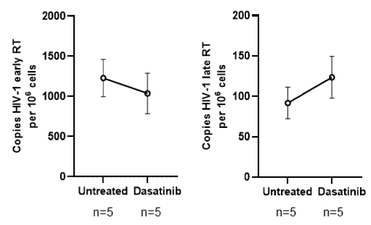


Figure 2. No differences were found when comparing dasatinib-treated and untreated MDMs in the formation of early and late RT after infection with pJR-FL_Renilla.

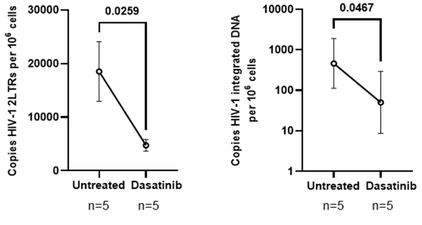
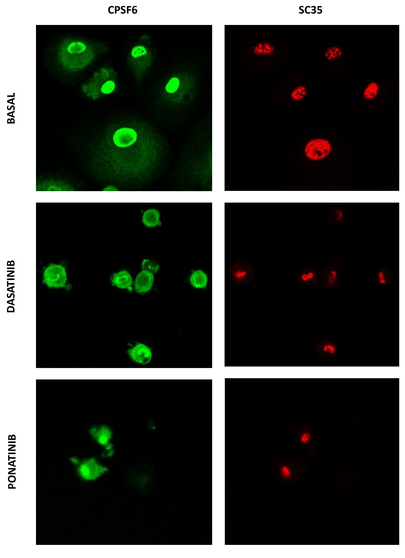


Figure 3. Formation of 2-LTR circles and proviral integration were 3.9 (p=0.0259) and 1.6-fold (p=0.0467) lower in dasatinib-treated MDMs 48h post-infection.

Figure 4. Confocal microscopy images of MDMs.



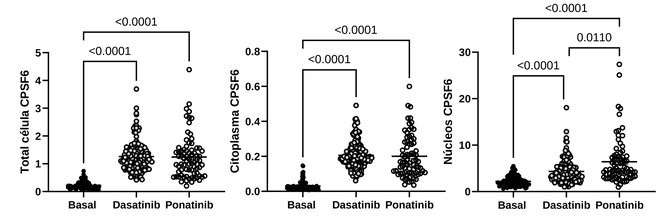


Figure 4A. Dasatinib-treated MDMs showed higher nuclear (p<0.0001) and cytoplasmic (p<0.0001) CPSF6 expression than untreated MDMs. Ponatinib-treated MDMs also showed higher CPSF6 expression in both regions (p<0.0001) than untreated MDMs, and a higher nuclear expression than dasatinib-treated MDMs (p=0.0110).

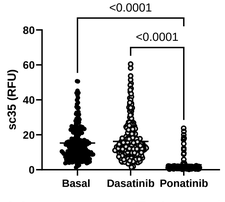


Figure 4B. Ponatinib-treated MDMs showed 5.4- and 5.8-fold lower SC35 expression than untreated and dasatinib-treated MDMs, respectively (p<0.0001).

CONCLUSIONS

- Dasatinib and ponatinib modify subcellular location and expression of CPSF6 and SC35, essential proteins in the integration and transcription of HIV-1 in MDMs. This may be a new mechanism of action for TKIs to interfere with HIV-1 infection.
- More studies are necessary to determine the validity of using dasatinib in combination with ART to impede the reservoir formation and maintenance in both CD4+ T cells and macrophages.

ACKNOWLEDGEMENTS

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