The effect of interferon-alpha subtypes on HIV-1 associated CD8$^+$ T cell hyperactivation and dysfunction

Saurav Saswat Rout[1], Yunyun Di[1], Kathrin Sutter[2], Ulf Dittmer[2] and Kerry J. Lavender[1]

[1]Department of Biochemistry, Microbiology and Immunology, University of Saskatchewan, Saskatoon, SK, Canada, S7N5E5

[2]Institute of Virology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, 47057

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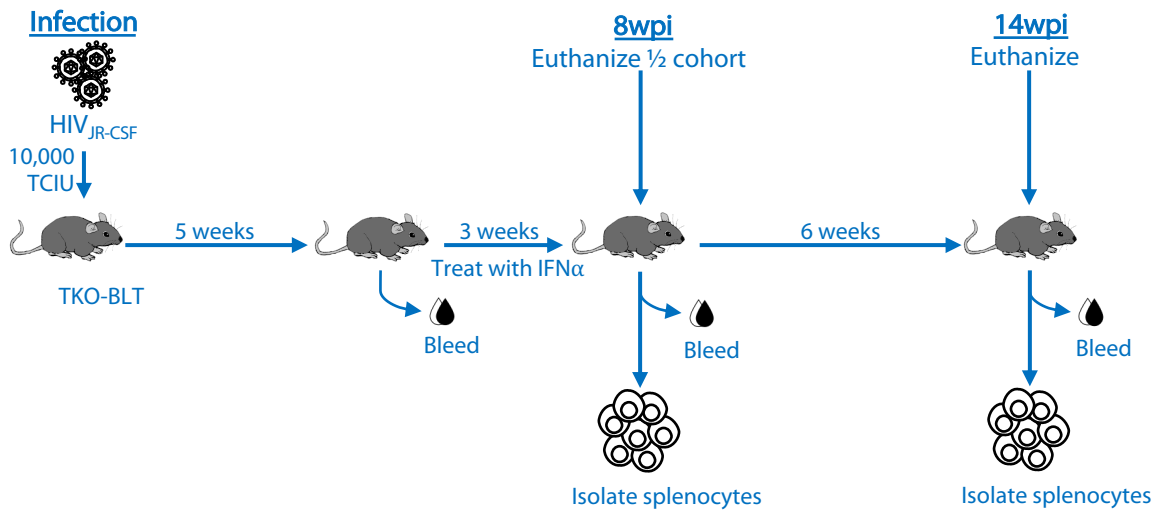
CONFERENCE CAHR 2021

1 INTRODUCTION

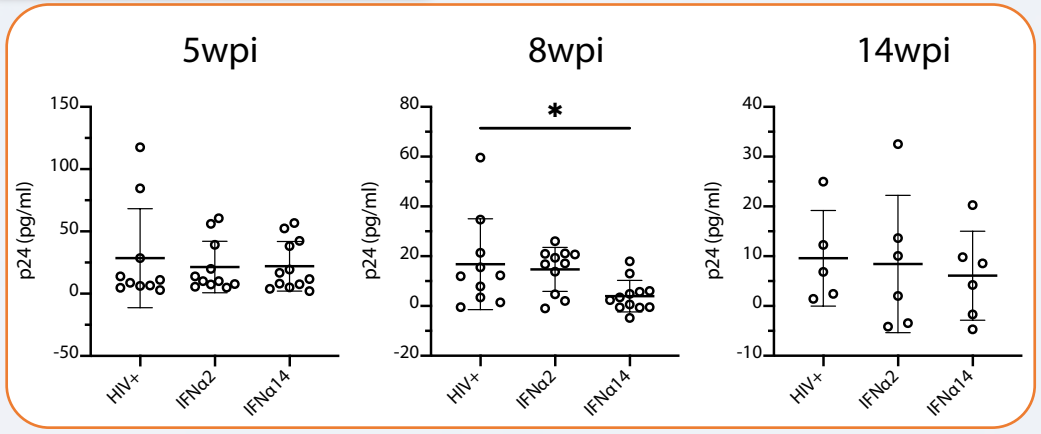
- HIV-1 infection is typically characterized by progressive loss of CD4⁺ cells and aberrant T-cell activation.
- Interferon-alpha (IFNα), mainly IFNα2, has been associated with exacerbation of HIV-1 disease progression, immune activation and related CD8⁺ T-cell dysfunction.
- Dysfunctional CD8⁺ T cells are characterized by hyperactivation, exhaustion, loss of effector function, including cytotoxic capacity, and production of pro-inflammatory mediators.
- During HIV-1 infection not all IFNα subtypes are produced in equal amounts.
- Also, some subtypes that have been shown to have beneficial effects that are produced at a later stage of HIV-1 infection and at a lower level than IFNα2[5,6] .
- Our previous study showed that IFNα14 was able to supress HIV-1 replication both *in vitro* and in humanized mice.
- The goal of this study is to determine if long-term IFNα14 therapy can alleviate CD8⁺ T-cell related activation and dysfunction.

2 EXPERIMENTAL APPROACH



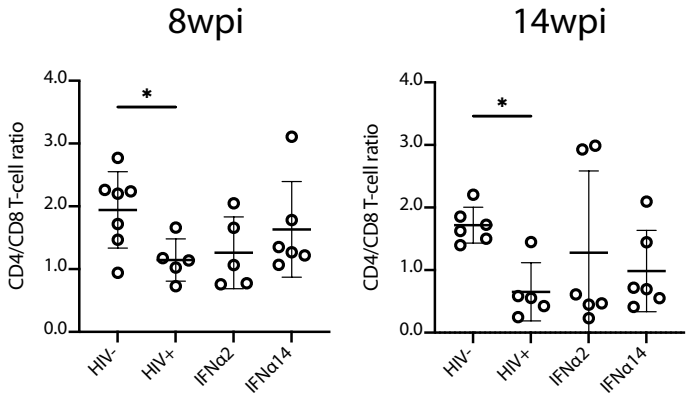
3 RESULTS

A Plasma viral load

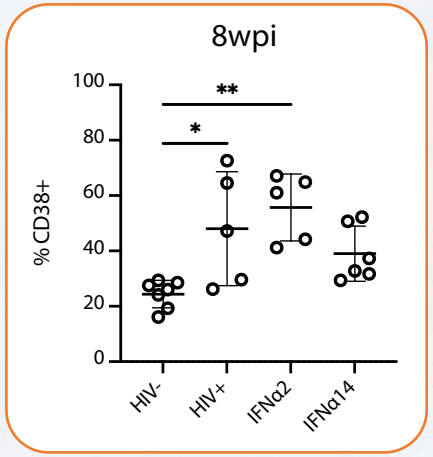


3 RESULTS

B T-cell ratio



C CD4⁺ T-cell activation



A. At 8wpi, viral load in the IFNα14 treated group was lower than untreated controls but the viral load normalized at 14wpi in all the groups.

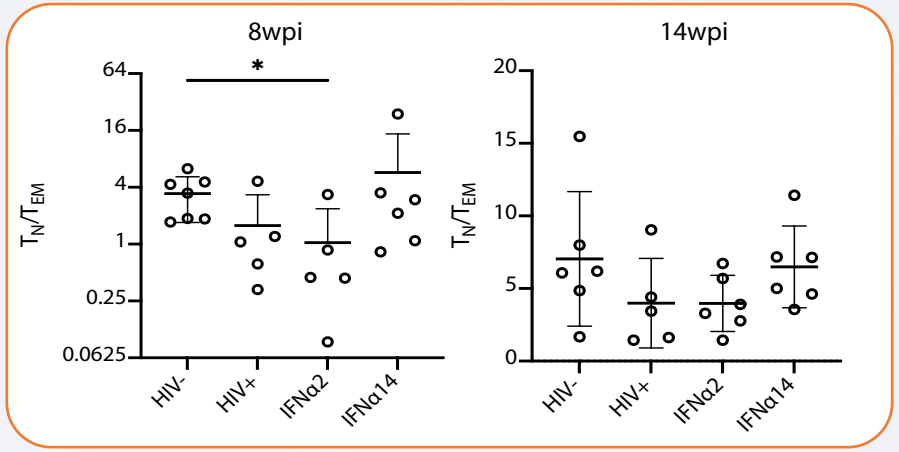
B. At both timepoints, the CD4/CD8 T-cell ratio was significantly lower in untreated mice. IFNα treated mice had lower CD4/CD8 T-cell ratios but there was no statistical significance.

C. IFNα14 reduced CD4⁺ T-cell activation at 8wpi compared to untreated and IFNα2 treated

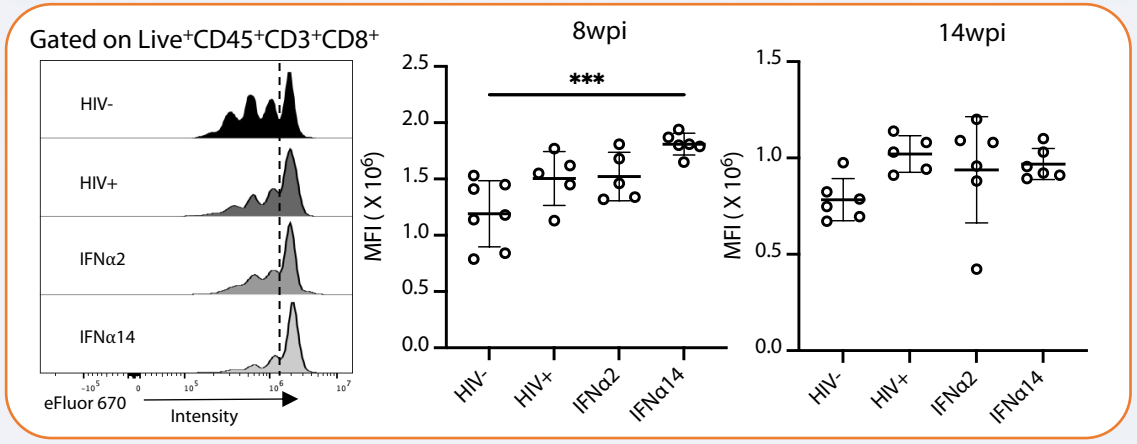
D. At 8wpi, IFNα2 treatment resulted in a lower T_N/T_{EM} ratio whereas IFNα14 treatment resulting in a T_N/T_{EM} ratio comparable to uninfected.

E. Proliferative capacity of CD8⁺ T cells was suppressed at 8wpi, but it reverted to normal after IFNα14 treatment was withdrawn.

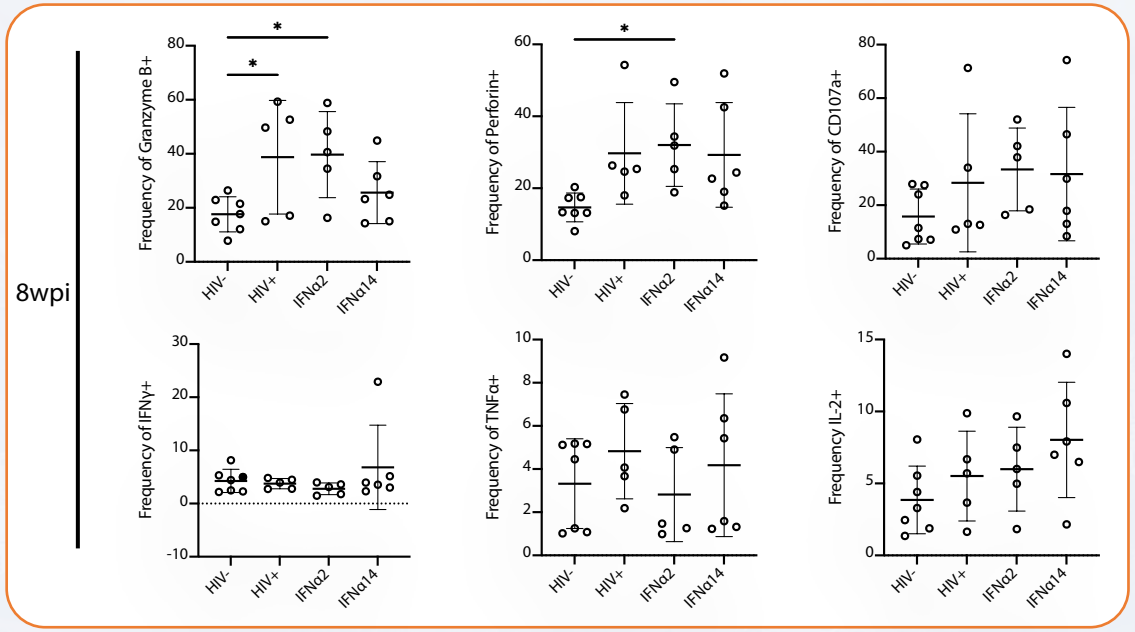
D CD8⁺ T-cell memory subsets



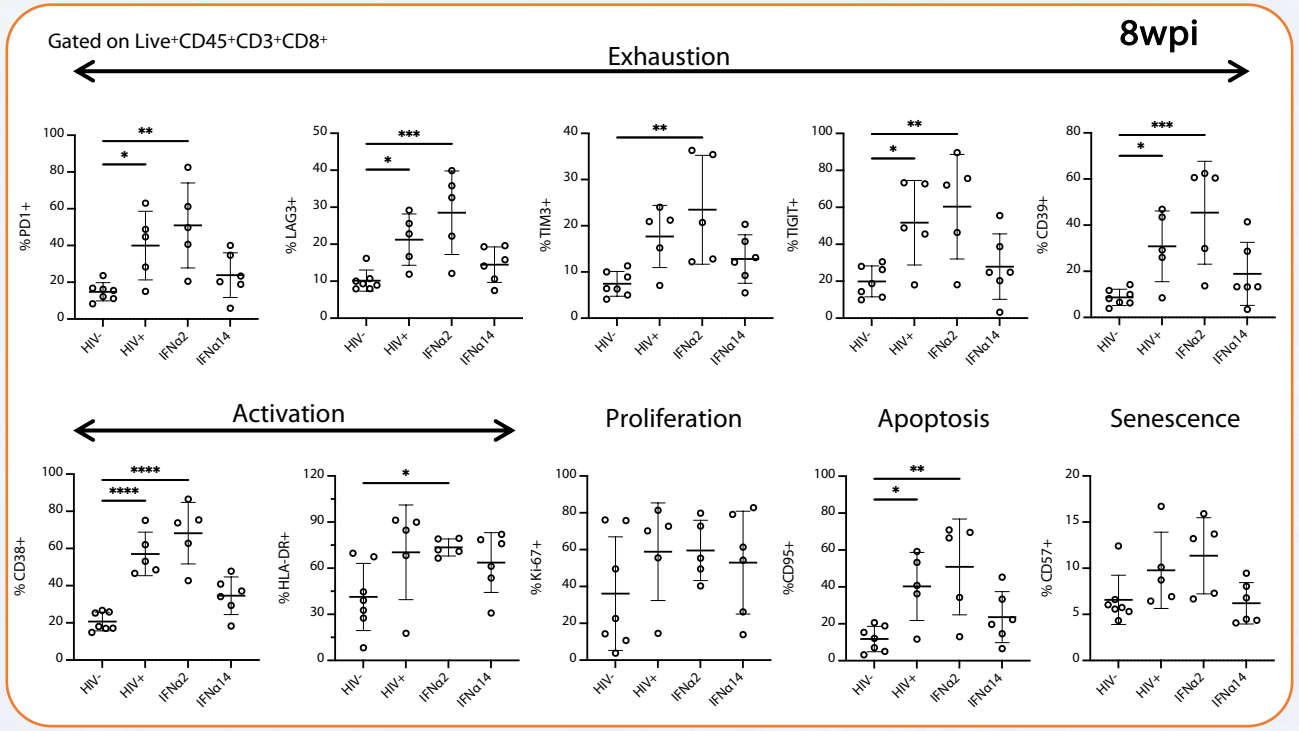
E CD8⁺ T-cell proliferation



G CD8⁺ T-cell functionality



H Phenotypic markers

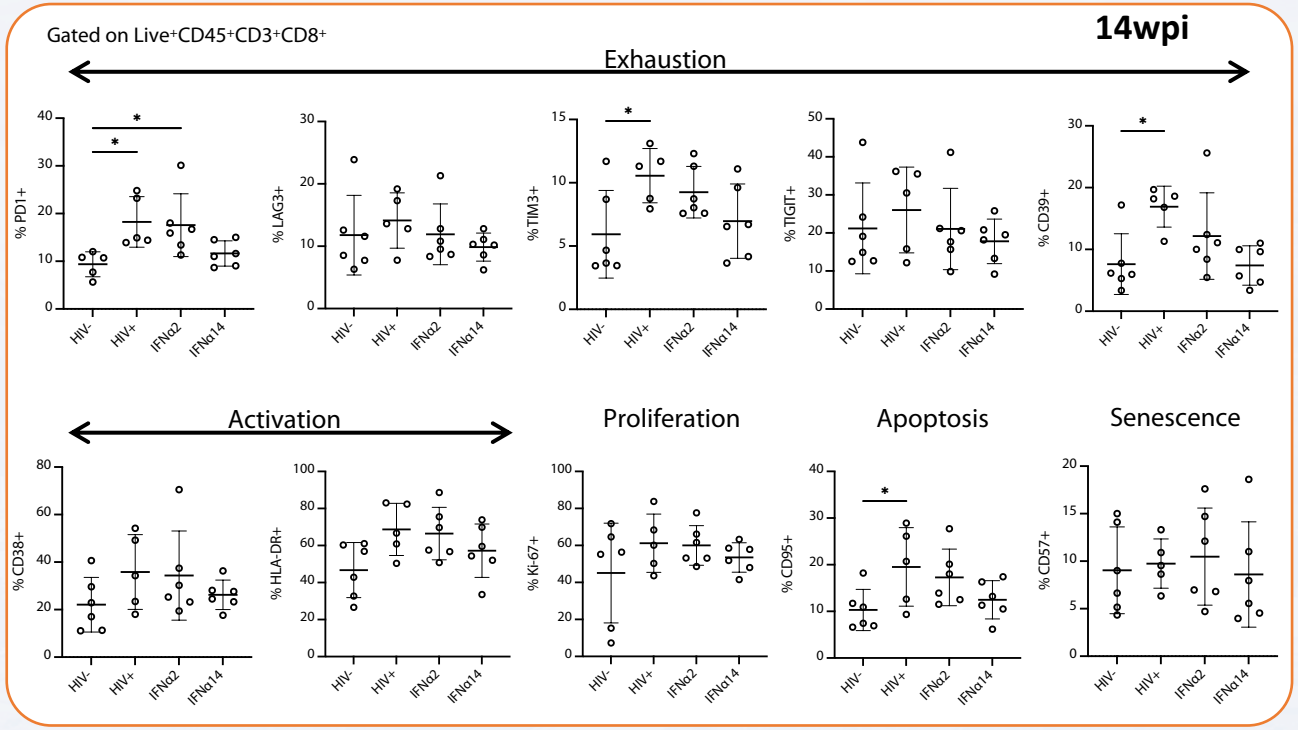


G. Immediately post-treatment (8wpi), untreated and IFNα2 treated mice had an increased frequency of cytolytic markers but at both 8 and 14wpi IFNα treatment did not affect CD8⁺ T-cell secretion of functional mediators.

H. IFNα14 treatment resulted in exhaustion, activation and apoptosis marker frequency comparable to uninfected controls at 8wpi. In contrast, untreated and IFNα2 treated mice had significantly increased frequencies of exhaustion, activation and apoptosis markers compared to uninfected controls. There was was no significant difference in senescence or proliferation markers but there was a trend toward increased frequency of CD57⁺ CD8⁺ T cells in both HIV-1⁺ and IFNα2 treated mice immediately post-treatment (8wpi).

I. Six weeks after treatment cessation (14wpi), frequencies of CD8⁺ T cells expressing some markers (TIM3, CD39, CD95) remained significantly higher in untreated controls but not in the IFNα14 treated group. Additionally, PD-1 remained significantly higher in untreated and IFNα2 treated groups at 14wpi despite similar viral loads between groups (Fig A).

1 Phenotypic markers



4 CONCLUSIONS

- IFNα14 treatment reduced the frequency of CD8⁺ T cells expressing markers of dysfunction to uninfected levels that persisted for six weeks post-treatment withdrawal
- Differentiation of the total CD8⁺ T cell compartment to the T_{EM} phenotype was reduced by IFNα14 suggesting it may assist in preventing bystander T-cell activation.
- Although IFNα14 did suppress CD8⁺ T-cell proliferation initially, it did not impact the production of functional mediators.

5 SIGNIFICANCE

IFNα14 treatment did not exacerbate disease progression and may have therapeutic potential to alleviate CD8⁺ T-cell hyperactivation and exhaustion during HIV-1 infection.

6 REFERENCES

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7 ACKNOWLEDGEMENTS

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