# *The impact of protein specificity on function and crosstalk between the HIV-specific T cells*

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## BACKGROUND

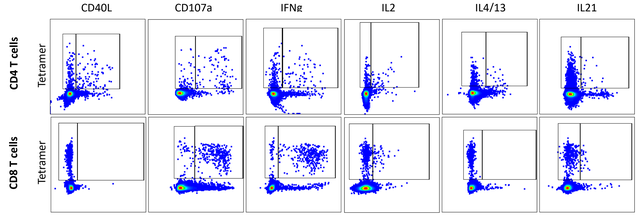
- Loss of CD4+ T cells and alteration of their functional programme during HIV infection disrupts the support required for CD8+ T cell activation, memory formation, and killing of virally infected cells.
- In addition, continuous exposure of CD8+ T cells to HIV antigens leads to impaired cytotoxicity, loss of polyfunctionality, and increased expression of PD-1.
- Despite these challenges, the cytotoxic function of CD8+ T cells, supported by CD4+ T cells, is essential for the control of viremia.
- The role of specific CD4+ and CD8+ T cell functions and their interplay in relation to protein specificity remain poorly understood.

## METHODS

- Peripheral blood samples were collected from 27 treatment-naïve chronically HIV-infected individuals.
- Based on the prevalence of HLA alleles among HIV-infected individuals and the frequency of T cell responses to particular epitopes we synthesised 15 HLA class II and 7 HLA class I tetramers covering compatible HLA-peptide combinations most frequently recognized by T cells of HIV-infected individuals.



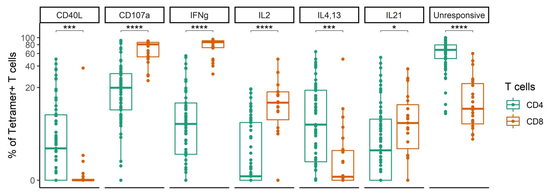

- Peripheral blood mononuclear cells were labelled with fluorescent HLA-peptide tetramers and stimulated with the corresponding peptides.
- The expression of surface proteins and cytokines in response to stimulation was monitored by flow cytometry.

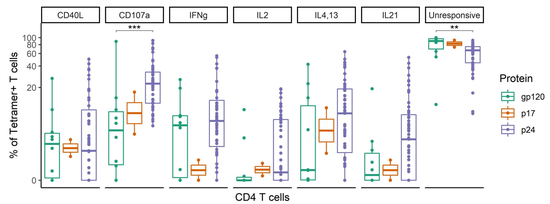



**The functional profiles of HIV-specific CD4+ and CD8+ T cells are distinct, with a stronger dependence of CD4+ T cells on protein specificity. Interplay between CD4+ and CD8+ T cells is present but not reliant on co-targeting of the same**

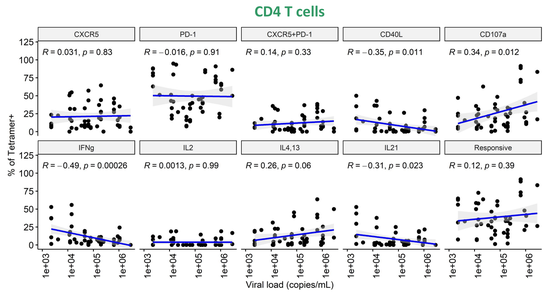
## RESULTS

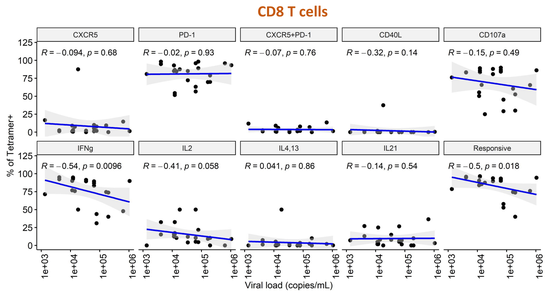
- HIV-specific CD4+ and CD8+ T cells had distinct functional profiles. The function of CD4+ but not CD8+ T cells was dependent on protein specificity.



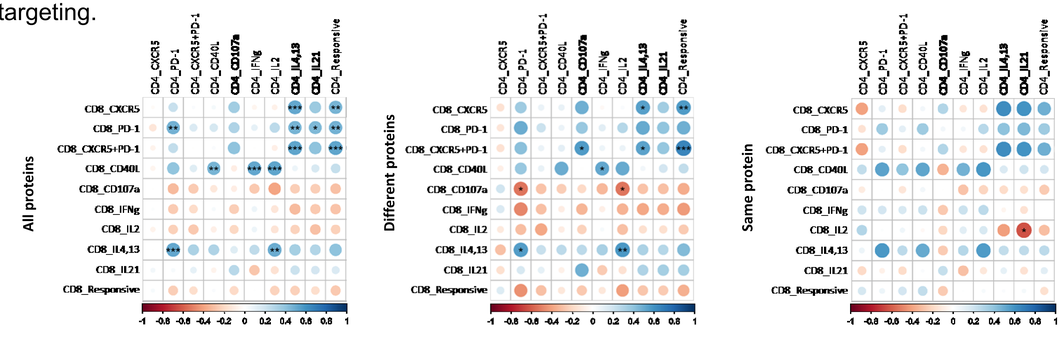




- Viral load correlated with distinct functions of CD4+ and CD8+ T cells.




- Several functions of HIV-specific CD4+ and CD8+ T cells were correlated independently of protein co-targeting.




## CONCLUSIONS

- Compared to CD4+ HIV-specific T cells **CD8+** T cells showed an increased **responsiveness** to stimulation, a higher frequency of **PD-1** expression, a lower proportion of **CXCR5**-expressing cells, and a more **cytotoxic** functional profile.
- **CD4+** T cell function is more dependent o the protein specificity, with **p24** being particularly immunogenic.
- Most T cell functions were negatively correlated with **viral load** in particular **IFN-γ** expression showed a strong negative correlation with viral replication in both subsets.
- **Crosstalk** between the HIV-specific CD4+ and CD8+ T cells was present but not dependent on the protein specificity.

## SIGNIFICANCE

- Our findings provide an insight into the phenotype and function of HIV-specific T cells and their interplay during chronic HIV infection which might benefit the development of vaccination and cure strategies.
- Using HLA tetramers in combination with peptide stimulation represents a major advance in the study of T cell responses, as it allows for the detection of unresponsive antigen-specific cells. This is particularly important in HIV infection, where these cells may be abundant due to T cell exhaustion.

## ACKNOWLEDGEMENTS

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