Consecutive analytical treatment interruption improves CD8 T cell activity during viral control

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BACKGROUND

In the PULSE clinical trial, 68 people living with HIV underwent three consecutive analytical treatment interruptions (ATIs). Of note, 10% of the participants transiently controlled HIV rebound during the 3rd ATI. We investigated whether this virological control is associated with improved antiviral CD8 T-cell function and response to mutationally-constrained and highly-conserved HIV epitopes.

METHODS

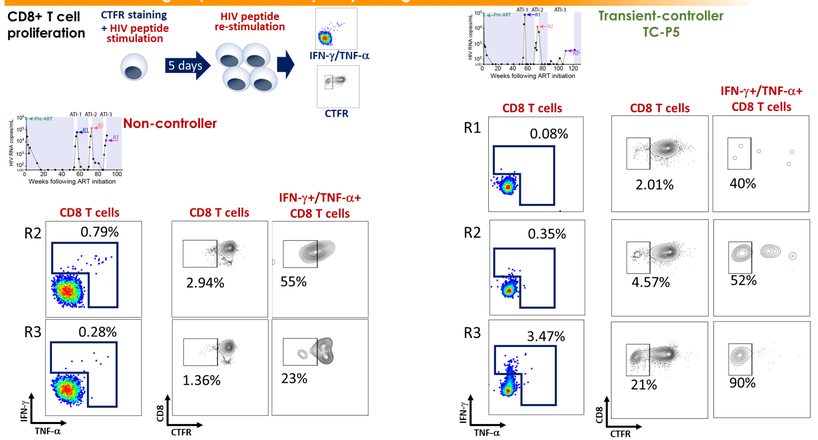
We obtained blood-derived mononuclear cells from four participants enrolled in PULSE: two non-controllers (NCs) with rapid viral rebound during all ATIs and two transient controllers (TCs) with virological control during the 3rd ATI.

- To evaluate CD8 T-cell functionality during the ATIs, CD8 T-cells were stimulated with HIV peptides to assess cytokine production (IFN-γ/TNF-α) and stained with CellTrace Far-Red to quantify proliferation by flow cytometry.
- To compare CD8 T-cell cytotoxicity across the ATIs, autologous CD4 T-cells were infected with HIV-NL4-3, co-cultured with CD8 T-cells from each ATI timepoint, and p24 levels were measured by ELISA.
- Using our novel Immunoinformatics Analysis Pipeline (IMAP), we identified 33 mutationally-constrained and unique Gag-derived HIV epitopes (Gag-IMAP-peptides). The response to these peptides was determined in NC- and TC-derived CD8 T-cells by measuring IFN-γ/TNF-α expression.

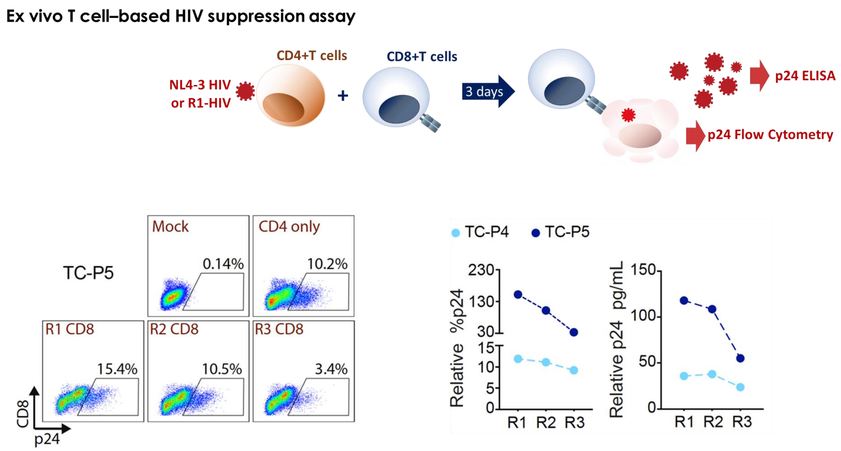
These findings indicate that **enhanced CD8 T-cell responses are pivotal** for **achieving viral control** after **consecutive analytical treatment interruptions**.

RESULTS

CD8 T cells exhibit higher proliferation capacity during transient viral control

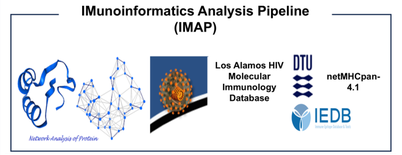


CD8 T cells exhibit higher cytotoxic capacity during transient viral control

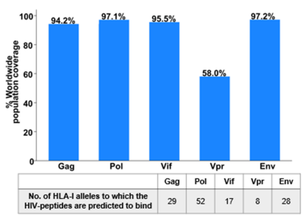


RESULTS

Identifying peptides from structurally important and mutation-intolerant regions of HIV-1 proteins



Gag	Integrase	Protease	RT	Vif	Vpr	Env gp160	Nef	Total
33	29	0	54	22	21	23	0	182



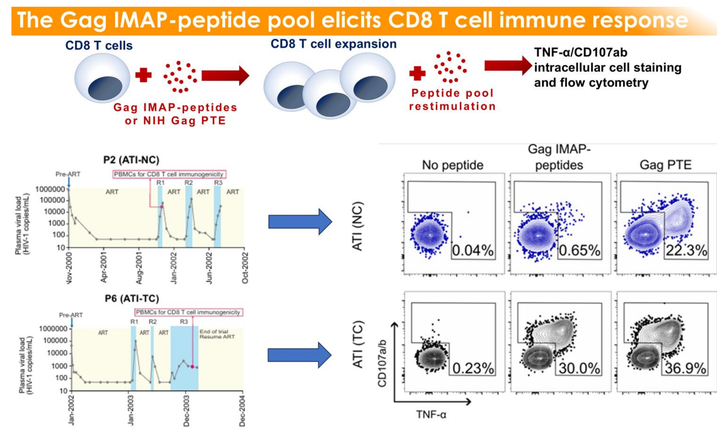
	Gag	Pol	Vif	Vpr	Env
No. of HLA-I alleles to which the HIV-peptides are predicted to bind	29	52	17	8	28

Select 182 peptides from structurally-important mutation-intolerant regions of 5 HIV-1 proteins:
1) avoid experimentally verified immune escape mutations; 2) were found within ≥85% of global HIV variants; 3) were predicted to bind to multiple HLA-I alleles; and 4) are immunogenic.

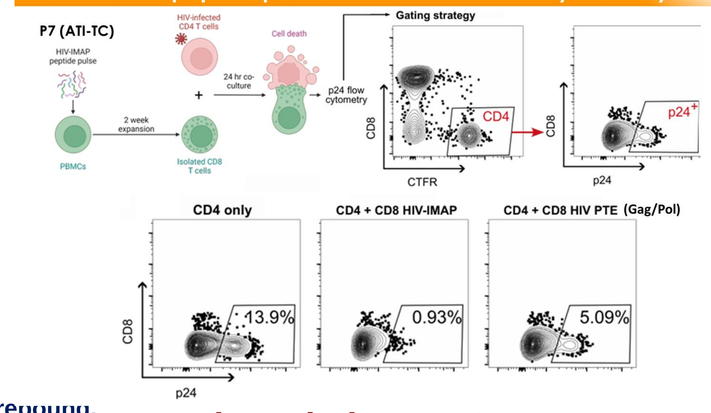
Gag 33

Investigate whether CD8 T cells from NCs and TCs respond to Gag IMAP-peptides and potentially target these HIV-1 protein regions.

The Gag IMAP-peptide pool elicits CD8 T cell immune response



The HIV IMAP-peptide pool enhances CD8 T cell cytotoxicity



CONCLUSIONS

1. **Consecutive ATIs results in a potential "vaccinal effect" improving CD8 T cell proliferation, cytokine production and cytotoxicity during the delayed HIV-1 rebound.**
2. **The higher potential of CD8 T cells from transient controllers to recognise mutational-constrained HIV epitopes, may also contribute to their virological control.**
3. **Redirecting CD8 T cell response to structurally important and genetically conserved HIV protein regions has the potential to clear HIV-infected cells during the ATI timepoints when immediate viral rebound is observed.**

4. **We acknowledge with gratitude the participants of these studies**

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