ENHANCED CD8 T-CELL RESPONSES FOLLOWING CONSECUTIVE ANALYTICAL TREATMENT INTERRUPTIONS ARE ASSOCIATED WITH DELAYED HIV REBOUND

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Background
During the PULSE clinical trial, 68 men living with HIV in Australia underwent three analytical treatment interruptions (ATIs), and seven participants transiently controlled viral rebound during the third ATI. While T-cell proliferation is associated with HIV control, whether repeated ATIs enhance CD8 T-cell expansion and antiviral function remains unclear. We addressed this by combining clinical and *ex vivo* data from the PULSE study.

Methods
Participants initiated antiretroviral therapy (ART) during acute/early infection and remained on ART for one year prior to three consecutive ATIs. Seventeen non-controllers (NCs) experienced rapid viral rebound during all ATIs, whereas seven transient controllers (TCs) controlled viremia for up to six months during ATI-3. CD4/CD8 T-cell counts were analysed longitudinally.
Functional assays were performed using blood-derived mononuclear cells from four NCs and three TCs. Cells were stimulated with HIV peptides, and proliferation was assessed by CellTrace Far-Red dilution. Cytotoxicity was evaluated by coculturing autologous CD8 T-cells with HIV-NL4-3-infected CD4 T cells and measuring HIV-p24 levels.

Results
Before ART initiation, TCs had lower viral loads and higher CD4 T-cell counts than NCs ($p<0.0001$; $p=0.02$), with no difference in CD8 T-cell counts. During ATI-3, CD8 T-cell counts increased in TCs ($p=0.02$) but not in NCs, and correlated with delayed viral rebound ($r=0.2/p=0.03$). In TCs, CD8 T-cell proliferation increased 3-34-fold during viral control timepoints and correlated with delayed rebound ($r=0.5/p=0.02$), whereas no changes were observed in NCs. CD8 T-cells from TCs at ATI-3 reduced p24 levels 2-5-fold compared to earlier timepoints. No enhancement of CD8 T-cell cytotoxicity was observed across the ATIs in NCs.

Conclusions
Our data suggest repeated antigen exposure during consecutive ATIs contributes to a “vaccinal effect” that enhances CD8 T-cell functionality and delays viral rebound for a subset of participants. These findings provide insight into mechanisms of viral control and inform T-cell-based HIV cure strategies.

Disclosure of Interest Statement:
We have an active collaboration with ViiV Healthcare; however, we received no funding for this specific project.