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# P09-18. Cw*0303/0304 HIV specific CTL response toward GagYL9 select for HIV escape variants with low fitness that is compensated by intra-codon variation

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## Background

The potential importance of HLA-C CD8+ specific responses in control of HIV replication is still unknown and controversial. Many known CTLs are restricted by HLA-A or HLA-B but only a small number are restricted by HLA-C. This study examines the impact on HIV-1 immune escape and viral fitness of a CTL response restricted by HLA-Cw*0303/0304 (YL9) in a very conserved region of HIV Gag p24.

## Methods

HIV CD8+ specific responses to a panel of overlapping peptides (OLP) were measured by INF-γ ELISPOT and HIV Gag sequences were obtained from HLA-Cw*0303/0304 subjects with chronic HIV infection (n = 80). The avidity of RI9 responses was measured by IFN-γ Elispot assay to serial diluted peptides for each variant (T303V, T303I, T303A). Plasmids containing YL9 mutations were constructed by site-directed mutagenesis. Viral replication kinetics were measured by GFP expression. DNA from a patient with T303V was amplified by PCR and cloned into pGEM. Gag proviral clones were analyzed and phylogenetic analysis carried out.

## Results

60% of Cw*0303/0304 HIV individuals have a pattern of Gag recognition focus on OLPs containing the YL9 epitope. There is a strong association between the expression of Cw*0303/0304 and changes at the C-terminal of the epitope YVDRFFKTL 296–304 (YL9) from Thr-303 to Val, Ile and Ala with ($p = 1.62 \times 10\text{-}10$). In addition, changes T303I and T303A in YL9 decrease epitope avidity by 5-fold and show a significant reduction of replicative capacity. However, the selection of T303V restores viral fitness and in vitro recognition. Clonal analysis suggests the mutational pathway of T303V selection through WT and T303A intermediates.

## Conclusion

These studies demonstrate that HLA-Cw*0303/0304 YL9 CTL responses targeting p24 can drive viral immune escape and changes in viral replication to similar extent to other HLA-B described responses. This data highlight the importance to define relevant HLA-C responses that drive HIV evolution and impact in viral fitness.