HIV Adaptation and T Cell Receptor Diversity Following Vertical Transmission

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BACKGROUND

Human immunodeficiency virus (HIV) can adapt to an individual's T cell immune response via mutations that affect antigen recognition and impact disease outcome. Adaptation can occur via different mechanisms (Figure 1): classical (loss of antigen recognition) and non-classical adaptation (continued antigen recognition; gain of antigen recognition via neo-epitopes). In vaccine design, it is vital to understand this complex host-viral interaction, including the mechanisms that underpin viral adaptations that subvert/alter the immune response and the T cell receptor (TCR) repertoire that respond to the non-adapted (NAE) and/or adapted (AE) form of T cell epitopes.

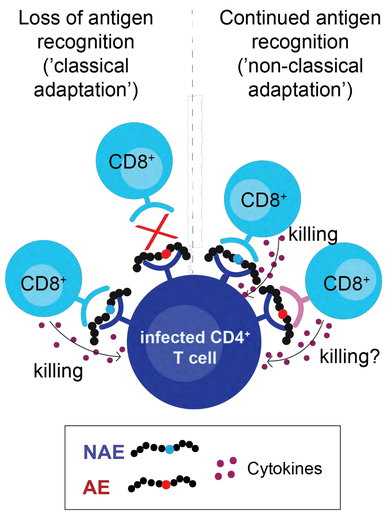


Figure 1. Proposed viral adaptation strategies against anti-HIV immune responses. Schematic depicts classical and non-classical adaptation based on recognition of the HLA-peptide complex by the TCR.

Objectives: (i) To examine HIV quasispecies from mother-child transmission pairs to demonstrate the dynamics of transmitted adaptations (maintenance and reversion) in different immune selection environments in the new host (child). **(ii)** To identify TCR combinations that recognise the NAE and AE form of an epitope (non-classical adaptation) at the single cell level and determine any overlap between mother and child.

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Viral adaptations are transmitted from mother-to-child and there is an overlap in _TCR repertoire._

RESULTS

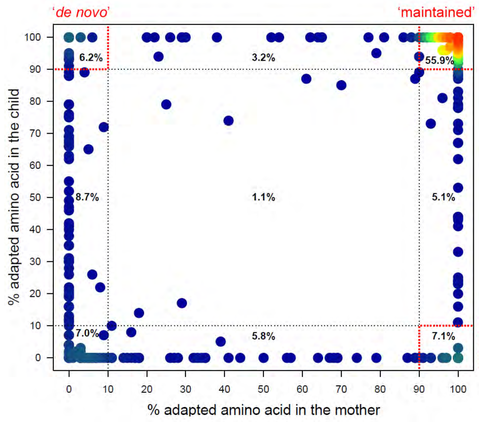


Figure 2. Adaptation dynamics following transmission affected by bottleneck event, selection pressure and fitness cost. Corresponding percentage of adapted amino acids present in HIV quasispecies in the mother/child pairs (n=633). Over half of the adaptations present in the mother at ≥90% were transmitted and maintained in the child at ≥90%. Those adaptations of particular interest regarding cure strategies are those that revert in the child (reflecting fitness cost), and those that appear as *de novo* adaptations in the child representing new immune targets in a heavily adapted virus.

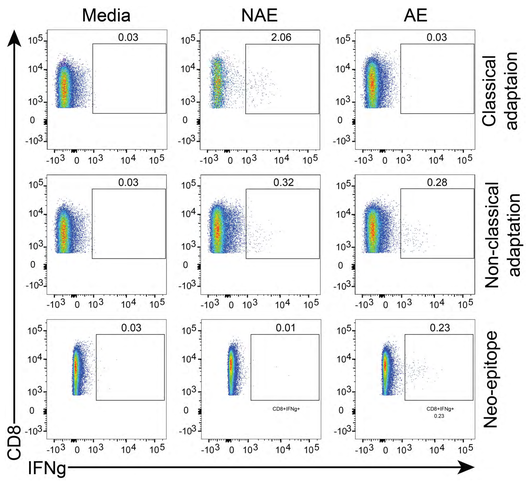


Figure 3. _De novo_ adaptations followed three described modes of adaptation. Peptides for *de novo* adaptations identified using next-generation sequencing were created based on NetMHC scores. Using intracellular cytokine staining, CD8⁺ T cells were stimulated with either the NAE or the AE form of the epitope with IFNɣ output used as a marker for T cell response. For those epitopes with a response, they were found to either only have a response to the NAE form (classical adaptation), have a response to the NAE and AE form (non-classical adaptation), or create a new target (response to the AE form; neo-epitope).

METHODS

- 26 mother-child HIV⁺ pairs from Haiti for adaptation analysis (next-generation sequencing and intracellular cytokine staining), 1 of these pairs for TCR analysis (single cell TCR sequencing).
- Clinical information and demographics: age at sampling (yrs; median, IQR): mother 32.8 (27.7-26.1), child 3.2 (2.4-4.1); viral load (log; median, IQR): mother 4.46 (3.65-5.09), child 4.41 (4.02-5.06); CD4+ T cell % (median, IQR): mother 22.45 (15.94-29.58), child 29.94 (21.85-39.65); no. on antiretroviral treatment: 2 mothers, 9 children.

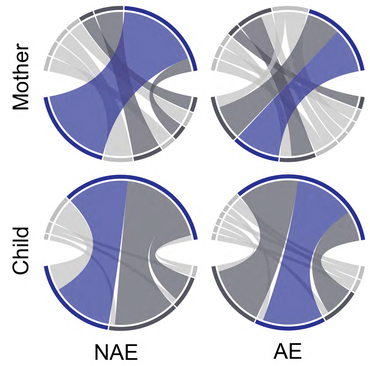


Figure 4. There was a common alpha/beta TCR combination (blue) observed at the family level in a mother/child pair after stimulation with the NAE and AE form of the Nef epitope TL10. Furthermore, there were other TCR combinations observed after NAE and AE stimulation within a subject, but not between (dark grey).

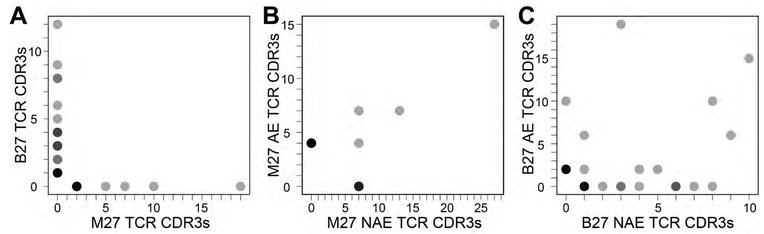


Figure 5. TCR overlap was only observed at the family level, not at the CDR3 level. (A) Comparison of TCR CDR3 combinations between mother and child showed no overlap. However, comparison of TCR CDR3s recognising either the NAE or AE form in the mother (B) and child (C) separately revealed overlap within an individual.

CONCLUSIONS

Adaptations were present in the mother and child with *de novo* adaptations representing the main three modesof adaptation present in children. TCR repertoire was largely overlapping within an individual, and to some extent between mother and child. Understanding adaptation and subsequent TCR repertoire is crucial to vaccine design.