# Polyfunctional VNPs

**BACKGROUND**

- Viremic non-progressors (VNPs) are a rare group of ART-naive, HIV-infected individuals that remain asymptomatic with normal CD4+ T cell counts for >10 years despite high-level viremia.
- Like natural hosts of SIV infection (i.e., sooty mangabeys & African green monkeys), VNPs maintain low levels of central memory CD4+ T cell infection.
- The immunologic characteristics of VNPs are unknown.
- Studying HIV-infected human “natural hosts” is critical to understanding the progression to AIDS in normal HIV-infected hosts.

**METHODS**

- Participants were selected from the UCSF SCOPE and OPTIONS cohorts based on the following criteria:
  - VNP: Infected >10 years, ART naïve, no history of opportunistic infections, CD4+ T cell count considerably >500 cells/mm³ (>15%), HIV VL consistently >10⁵ copies/ml
  - Putative Progressors: Infected <1 year based on detuned ELISA, ART naïve
  - Chronic Progressors: Infected >1 year, ART naïve, CD4+ T cell count >200 cells/mm³
- Flow cytometry was performed on cryopreserved PBMCs for:
  - T cell phenotypes: % activated (CD38+HLA-DR+), naïve (CCR7+CD45RA-), central memory (Tcm) (CCR7+CD45RA-), effector memory (TEMRA) (CCR7-CD45RA-), and terminal effector memory (TEMRA) (CCR7-CD45RA-)
  - CD4+ and CD8+ T cells
  - PD-1 expression: %PD-1+ CD4+ and CD8+ T cells
  - HIV (Gag)-specific and CMV (pp65)–specific CD4+ and CD8+ cytokine producing T cells: IFN-γ, TNF-α, IL-2, IL-10, CD107

**RESULTS**

**Characteristics of the Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV naïve (n=9)</th>
<th>Putative Progressors (n=10)</th>
<th>Chronic (n=15)</th>
<th>VNP (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39.6 (26-57)</td>
<td>28.4 (19-41)</td>
<td>43.5 (23-61)</td>
<td>200</td>
</tr>
<tr>
<td>Male</td>
<td>78%</td>
<td>60%</td>
<td>88%</td>
<td>100%</td>
</tr>
<tr>
<td>% PD1+ CD4+ T cells</td>
<td>40-50 (35-55)</td>
<td>40-50 (35-55)</td>
<td>38-45 (35-55)</td>
<td>100%</td>
</tr>
<tr>
<td>% PD1+ CD8+ T cells</td>
<td>35-40 (30-45)</td>
<td>35-40 (30-45)</td>
<td>35-40 (30-45)</td>
<td>100%</td>
</tr>
<tr>
<td>% TNFα+ cells</td>
<td>8-10 (7-9)</td>
<td>8-10 (7-9)</td>
<td>8-10 (7-9)</td>
<td>100%</td>
</tr>
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**VNPs Have Increased PD-1 Expression on CD4+ T Cells**

<table>
<thead>
<tr>
<th>%PD1+ CD4+ T cells</th>
<th>P = 0.033</th>
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**VNPs Have Very High CD8+ T Cell Counts, Driven By Expansion of TEMRA Cells**

**PD-1 Expression on CD4+ T Cells Positively Correlates With Absolute CD4+ T Cell Count**

**VNPs Tend to Have Decreased PD-1 Expression on CD8+ T Cells**

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<thead>
<tr>
<th>%PD1+ CD8+ T cells</th>
<th>P = 0.017</th>
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**VNPs Have High IL-2, CMV- and HIV-specific T Cell Expansion**

**CONCLUSIONS/ IMPLICATIONS**

- VNPs share some features with natural hosts.
  - Decreased TNFα infection, increased IL-21 responses.
- VNPs are distinct from natural hosts in other respects:
  - VNPs have higher %PD-1 expression on TEMRA (P = 0.006) and TEMRA (P = 0.01) CD8+ T cells than putative progressors.
  - VNPs have lower % PD-1 expression on TEMRA CD8+ T cells than putative progressors (P = 0.01) and chronically infected progressors (P = 0.059).
- VNPs have higher %PD-1 expression on TEMRA (P = 0.006) and TEMRA (P = 0.01) CD8+ T cells than putative progressors.
- Protection of T cell activation appears in VNP with absolute CD4+ T cell count.
- CD4+ T cell proliferation appears to result in T cell expansion in VNPs instead of depletion (as in typical HIV infection).
- Despite low TNFα infection, VNPs have high %PD1+CD4+ T cells.
- PD-1 may reflect successful CD4+ T cell proliferation in VNPs (as opposed to unsuccessful/proliferation in VNPs remain unclear).
- The mechanisms responsible for preserved IL-21 responses and successful CD4+ T cell proliferation in VNPs remain unclear, but may provide important clues to the pathogenesis of proliferative T cell defects in HIV disease, which may persist despite ART and may contribute to morbidity/mortality.

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