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PD-1 Expression is Associated With Preserved CD4+ T cell Homeostasis in Viremic Non-Progressors

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BACKGROUND

- Viremic non-progressors (VNPs) are a rare group of ART-naïve, 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

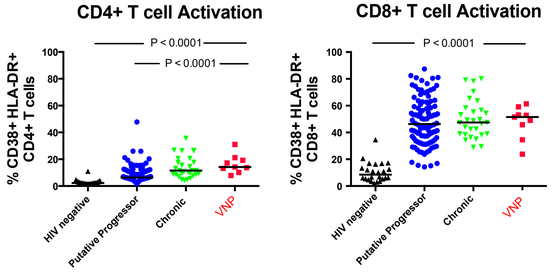
- Participants were selected from the UCSF SCOPE and OPTIONS cohorts based on the following criteria:
  - VNPs: Infected > 10 years, ART naïve, no history of opportunistic infections, CD4+ T cell count consistently > 500 cells/mm^3 (> 15%), HIV VL consistently > 10^4 copies/ml
  - Putative Progressors: Infected < 1 year based on detuned ELISA, ART naïve
  - Chronic Progressors: Infected > 1 year, ART naïve, CD4+ T cell count > 200 cells/mm^3
- Flow cytometry was performed on cryopreserved PBMCs for:
  - T cell phenotypes: % activated (CD38+HLA-DR+), naïve (CCR7+CD45RA+), central memory (T_{CM}) (CCR7+CD45RA-), effector memory (T_{EM}) (CCR7-CD45RA-) and terminal effector memory (T_{EMRA}) (CCR7-CD45RA+) CD4+ and CD8+ T cells
  - PD-1 expression: %PD-1 CD4+ and CD8+ T cells
  - HIV (Gag)-specific and CMV (pp65/IE)-specific CD4+ and CD8+ cytokine producing T cells: IFNγ, TNFα, IL-2, IL-21, CD107

RESULTS

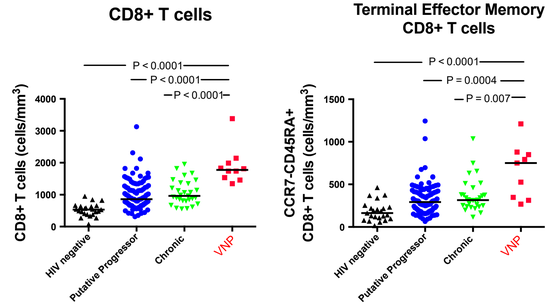
Characteristics of the Participants

Characteristic	HIV negative (n = 23)	Putative Progressor (n = 108)	Chronic (n = 9)	VNP (n = 10)
		Median (IQR)		
Age, years	44 (35-47)	36 (31-41)	42 (38-46)	55 (46-57)
Male	96%	97%	89%	90%
Proximal CD4+ T Cell Count, cells/mm^3	863 (745-1198)	560 (487-687)	395 (295-501)	723 (642-910)
Nadir CD4+ T Cell Count, cells/mm^3	____	356 (281-525)	350 (260-435)	540 (400-700)
HIV VIRAL LOAD (log_{10}VL)	____	4.6 (3.7-5.1)	4.6 (4.4-5.1)	4.6 (4.4-4.9)
TIME HIV+, years	____	0.2 (0.2)	5 (2.3-12)	18 (16-19)

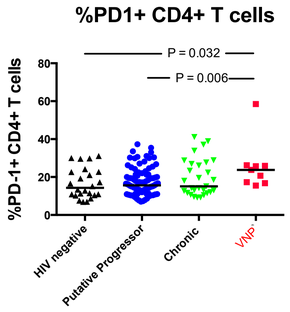
VNPs Have *High* Levels of T Cell Activation



VNPs Have *Very High* CD8+ T Cell Counts, Driven By Expansion of T_{EMRA} cells

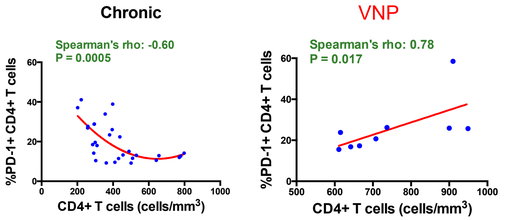


VNPs Have *Increased* PD-1 Expression on CD4+ T Cells

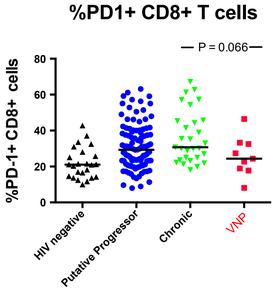


- VNPs have higher %PD-1 expression on T_{CM} (P = 0.006) and T_{EM} (P = 0.01) CD4+ T cells than putative progressors.

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

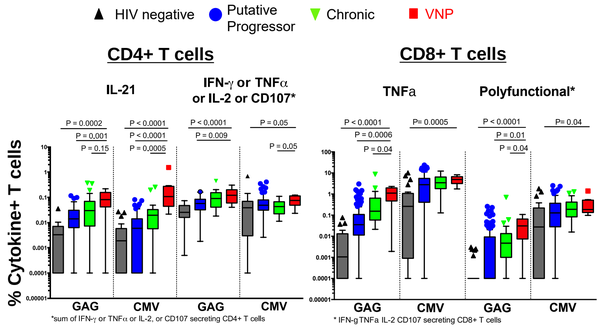


VNPs Tend to Have *Decreased* PD-1 Expression on CD8+ T Cells



- VNPs have lower % PD-1 expression on T_{EMRA} CD8+ T cells than putative progressors (P = 0.01) and chronically infected progressors (P = 0.059).

VNPs Have HIV- and CMV-specific T Cell Expansion



CONCLUSIONS/ IMPLICATIONS

- **VNPs share some features with natural hosts.**
  - *Decreased T_{CM} infection, increased IL-21 responses.*
- **VNPs are distinct from natural hosts in other respects:**
- **VNPs have ⇧ CD4+ and CD8+ T cell activation.**
  - *T cell activation is unlikely to be the only mediator of T cell decline in untreated HIV disease.*
  - *Protection of T_{CM} cells from HIV infection is insufficient to prevent systemic T cell activation in HIV infection.*
- **VNPs have preserved CD4+ T_{CM} homeostasis and a dramatic expansion of CD8+ T cells.**
  - *CD4+ T cell proliferation appears to result in T cell expansion in VNPs instead of depletion (as in typical HIV infection).*
- **Despite low T_{CM} 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 typical HIV infection).*
- **The mechanisms responsible for preserved IL-21 responses and *successful* 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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