Determinants of PD-1 Expression on CD4⁺ and CD8⁺ T Cells in Treated and Untreated HIV Disease

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Background

- There is intense interest in the role of inhibitory molecules, especially programmed death 1 (PD-1), in causing persistent T cell dysfunction in HIV infection.
- Expression of programmed death 1 (PD-1) is upregulated on CD4⁺ and CD8⁺ T cells in untreated HIV infection, resulting in decreased proliferation and function.
- However, the impact of HIV infection and antiretroviral treatment (ART) on the expression of PD-1 on T cells and the determinants of PD-1 expression is still poorly defined.

Methods

- PD-1 was measured longitudinally in a cohort of recently HIV-infected individuals (Options, n=121) who started ART early (≤ 6 months after infection) vs. later (≥ 2 years after infection).
- Mixed effects modeling was performed to assess the impact of ART timing, clinical factors and immunologic factors on PD-1 expression.
- PD-1 was also measured cross-sectionally in a diverse cohort of chronically HIV-infected adults (SCOPE, n=206), including elite controllers and long-term immunologic non-responders (INRs; individuals who failed to achieve a CD4⁺ T cell count >350 cells/mm^3 on long-term ART).
- PD-1 MFI was measured by flow cytometry on total CD4⁺ and CD8⁺ T cells and T cell subsets.

Results

Baseline characteristics of SCOPE cohort, chronically infected

	HIV negative n=24	Controllers n=47	Untreated n=18	ART Suppressed n=117
Median Age	44 (34-46)	50 (46-54)	43 (39-47)	50 (46-54)
Male	23 (96%)	31 (66%)	17 (94%)	100 (85%)
Median CD4 count, cells/uL	863 (745-1198)	719 (572-1013)	388 (303 - 489)	532 (346-690)
Median VL, copies/mL	-	40 (40-73)	41,243 (30,901-125,279)	59 (40-75)

Data are medians (IQR) or numbers (%)

Baseline characteristics of Options cohort, recently infected

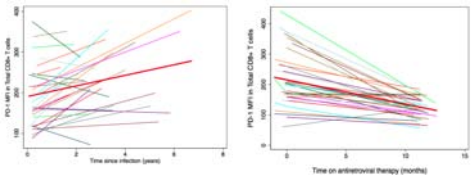
	Early ART n=34	Later ART n=32	Untreated n=36	HIV-neg n=19
Age	37 (33-42)	36 (34-42.5)	33 (26.5-36.5)	37 (30-42)
Male	33 (97%)	32 (100%)	35 (97%)	17 (89%)
HIV duration at diagnosis, mos	2.4 (1.0 - 2.4)	2.4 (2.4 - 3.7)	2.4 (2.4-3.5)	-
Baseline CD4 count, cells/uL	533 (434-742)	562 (499-704)	581 (512-680)	-
Baseline log VL, copies/mL	5.2 (4.5-5.7)	4.2 (3.5-4.7)	4.2 (3.3-5.0)	-
Baseline CD4+ PD-1, MFI	134 (116-179)	118 (104-137)	130 (96-150)	125 (98-153)
Baseline CD8+ PD-1, MFI	206 (160-278)	162 (129-245)	182 (135-223)	115 (94-135)
Baseline CD4+38+DR+, %	6.5 (5.2-10.8)	6.3 (5.2-8.6)	6.3 (5.3-10.5)	3.8 (2.8-7.4)
Baseline CD8+38+DR+, %	52.1 (35.5-70.5)	45.8 (33.0-57.3)	46.1 (36.5-57.7)	15.7 (9.1-24.2)
Immediate pre-ART CD4 count, cells/uL	526 (375-748)	298 (244-379)	-	-
Immediate pre-ART CD4+ PD-1, MFI	134 (116-179)	146 (119-183)	-	-
Immediate pre-ART CD8+ PD-1, MFI	206 (160-278)	229 (192 - 293)	-	-

Data are medians (IQR) or numbers (%)

PD-1 expression increases over time without therapy and decreases rapidly during the first year of ART

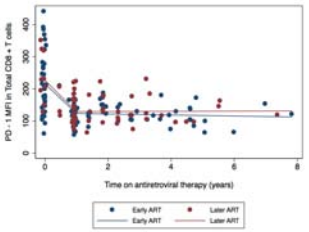
Prior to therapy: PD-1 on CD8⁺ T cells increases average of 7.9% each year

After ART initiation: PD-1 on CD8⁺ T cells decreases average of 41% over first year on ART

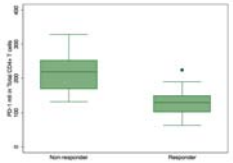


* Similar results seen in total CD4⁺ T cells, data not shown

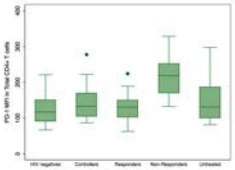
PD-1 levels are similar between Early and Later ART groups



PD-1 expression on CD4⁺ T cells is highest in immunologic non-responders (INRs)

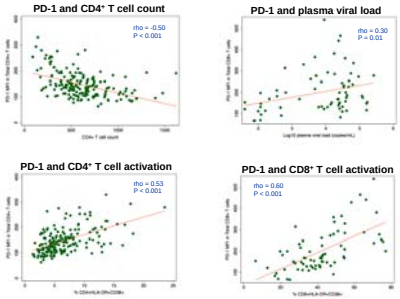


PD-1 expression remained high in INRs compared to IRs (median MFI of 218 vs. 130), p <0.001



PD-1 expression was highest in INRs compared to all other groups of subjects (p <0.01 for each pairwise comparison)

Determinants of PD-1 expression differ in CD4⁺ vs. CD8⁺ T cells



Conclusions / Implications

- PD-1 expression increases without treatment and decreases rapidly after ART initiation in both CD8⁺ and CD4⁺ T cells. However, INRs still have persistent elevation in PD-1 expression despite effective ART.
- PD-1 expression on CD8⁺ T cells is associated with viremia and CD8⁺ T cell activation .
- PD-1 expression on CD4⁺ T cells is strongly associated with peripheral CD4⁺ T cell count and frequency of activated CD4⁺ T cells
- PD-1 expression appears to be driven by both direct antigen and homeostatic pathways. Prospective studies of anti-PD-1 antibody therapy will be needed to define whether PD-1 expression on CD4⁺ T cells is a cause or consequence of CD4⁺ T cell lymphopenia.

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