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Persistent PD-1 Expression is Correlated with Poor Immune Recovery in HIV Infected Patients on HAART

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Background: PD- 1 expression on T cells correlates with T cell exhaustion and disease progression in HIV infected patients. HAART induced control of viral replication is paralleled by a reduction of PD-1 expression and increase of CD4 T cells in most patients. However, a portion of patients shows discordant CD4 response in spite of viral suppression below detection limit. In this study we have assessed PD-1 expression on T lymphocytes in patients with poor immune recovery.

Methods: PD-1 expression was analyzed by flow cytometry of T cells isolated from HIV-1 infected patients showing a defect in immune reconstitution (IR) as defined by less than 250 CD4 cells /µl or an increase of less than 200 CD4 T cells /µl in spite of viral suppression of at least 1 year. For comparison PD-1 expression was analysed on T cells of patients with normal immune recovery and viremic patients. In addition, further T cell markers associated with activation were analysed. For this purpose blood samples were stained with labeled antibodies, lysed and analysed by multiparameter FACS gating on CD4 and CD8 T cells. Statistical significance was determined by Mann-Whitney-U-Test.

Results: Low levels of PD-1 expression were found on CD4 and CD8 T cells in patients with virological suppression below detection limit and immune recovery, i.e., with > 500 CD4 T cells/µl (n=11). In contrast, patients with poor immune reconstitution showed significantly higher expression of PD-1 on both T cell subsets (Fig. 2, n=11, p<0.01). PD-1 expression was comparable to PD-1 expression in viremic patients. Among CD4 T cells, PD-1 expression was seen on both effector and central memory T cells as well as on naive T cells (data not shown).
A slightly higher expression of the activation markers CD38 and HLA-DR as well as the PD-1 ligand PD-L1 could be seen on CD4 and CD8 T cells of patients with poor immune reconstitution as compared to those patients with good reconstitution (Fig. 2). However, this difference was not statistically significant. Other T cell activation associated markers (CD69, CCR5, CD25) were not expressed in either group (Fig.1).
In addition, PD-1 expression on T cells negatively correlated with absolute CD4 T cell counts (Fig. 3, r=0.53) and with quantitative T cell receptor excision circles (TREC) measurement in PBMCs (Fig. 4).

	current CD4 cell count	current CD4/CD8 ratio	current %CD4 cells	current CD8 cell count	CD4 nadir	CD4 increase	CDC-stage
IR	690±312	0.73±0.28	29.3±8	1010±620	129±97	539±253	A: 36.4% B: 36.4% C: 28.2%
no IR	203±60	0.48±0.31	18.5±8.2	652±449	66±58	137±76	A: 54.5% B: 9.1% C: 36.4%

Tab 1.: Basic characteristics of patients

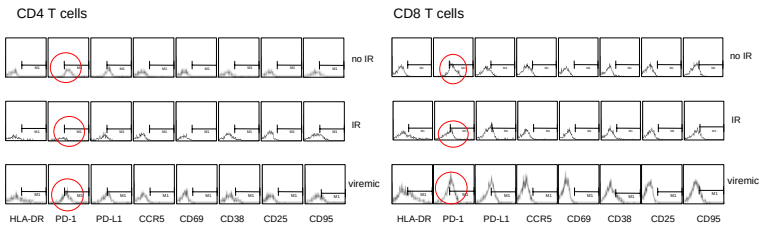


Fig 1.: Expression of indicated markers was analysed on CD4 and CD8 T cells for patients with (middle panel), without (upper panel) immune reconstitution and a viremic patient (lower panel). A representative experiment out of 10 is shown.

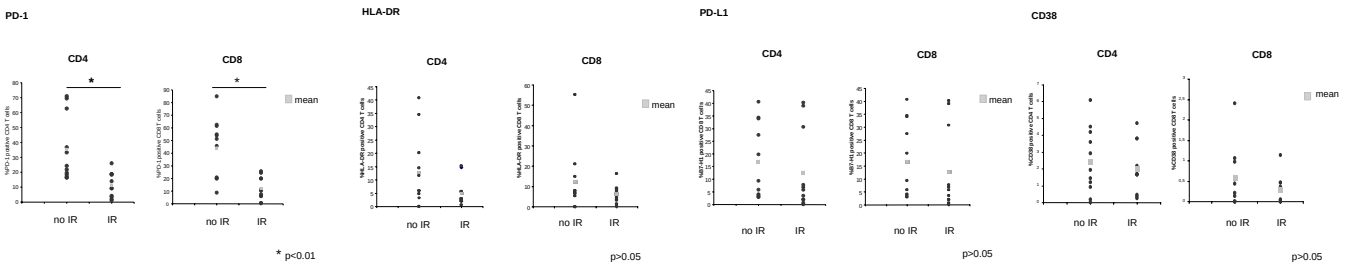


Fig 2.: A statistically significant higher (p<0.01) percentage of CD4 and CD8 T cells of patients with poor immune reconstitution expresses PD-1 than of patients with good immune recovery. Only slight differences in T cell activation associated molecules like HLA-DR and CD38 or PD-L1 were observed.

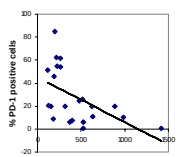
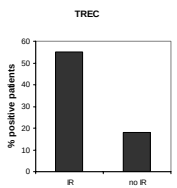


Fig 3.: PD-1 expression negatively correlates with the absolut CD4 cell number in patients under antiretroviral treatment (r=0.53).

Fig 4.: TREC as a measurement of recent thymic emigrants can be detected in a higher proportion of patients with good than with poor immune reconstitution.



Conclusion: Persistent increase in PD-1 expression on T cells in spite of suppression of viral replication below the detection limit defines patients with poor immune reconstitution. Signs of T cell activation and exhaustion persist in patients with incomplete numeric immune recovery. In addition, those patients exhibit lower thymic activity.

Acknowledgement: KP was supported by the CROI young investigator award.