Functional MDSCs Are Maintained During ART and Preclude HIV-1 Reservoir Reactivation

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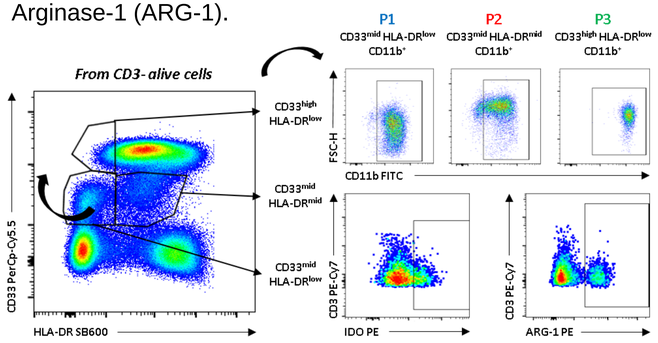
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BACKGROUND

In the past years, new therapeutic strategies aimed to deplete the HIV-latent infection by inducing viral reactivation have not been successful *in vivo*. The inability to reactivate and/or eliminate all HIV-infected cells could be explained by the presence of immune-regulatory mechanisms that inhibit viral reactivation and anti-HIV immune effector cells. We hypothesize that HIV-1 reactivation might be hindered by myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells with high immunosuppressive effects.

METHODS

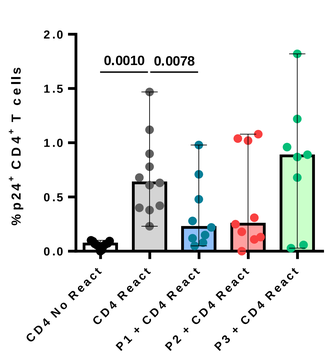
Phenotypic study: Samples from n=11 viremic (VIR) and n=14 ART-suppressed (ART) patients; and n=8 healthy donors (HD) were included. Frequency of three populations of MDSCs: P1 – CD33^{mid} HLA-DR^{low} (CD3^{-}, CD33^{mid}, HLA-DR^{low}, CD11b^{+}, CD14$^{+/-}$); P2 – CD33^{mid} HLA-DR^{mid} (CD3^{-}, CD33^{mid}, HLA-DR^{mid}, CD11b^{+}, CD14$^{+/-}$); and P3 – CD33^{high} HLA-DR^{low} (CD3^{-}, CD33^{high}, HLA-DR^{low}, CD11b^{+}, CD14$^{+/-}$); and immune activation (CD38^{+} and HLA-DR^{+}) in CD4^{+} and CD8^{+} T cells were assessed by flow cytometry. The functional status of the MDSCs was quantified by the expression of Indoleamine 2,3-dioxygenase (IDO) and Arginase-1 (ARG-1).



Functional study: Samples from n=14 ART patients and n=7 HD were used for functional studies in which reactivated CD4^{+} T cells and MDSCs subpopulations were co-cultured, and viral reactivation and cell activation were assessed by intracellular p24 and surface CD69 staining, respectively.

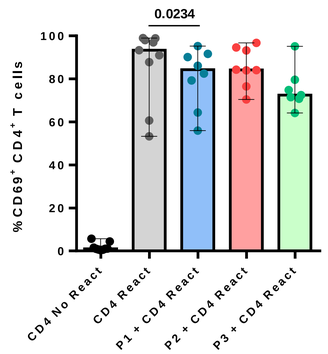
P1 – CD33^{mid} HLA-DR^{low} MDSCs significantly reduce HIV-1 reactivation and CD4^{+} T cells activation

HIV-1 Reactivation



P1 significantly reduces HIV-1 reactivation (2-fold reduction) from the latent reservoir *ex-vivo*

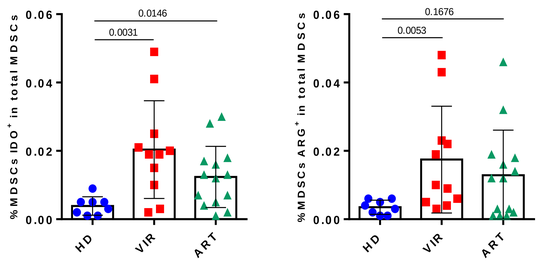
CD4^{+} T Cell Activation



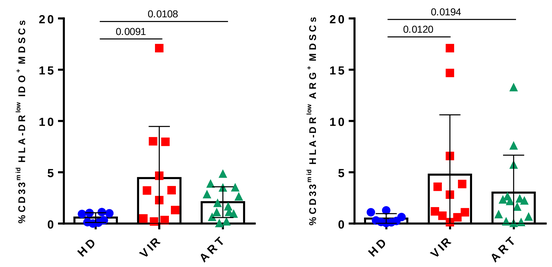
P1 significantly decreases CD4^{+} T cell activation levels (10% reduction)

RESULTS

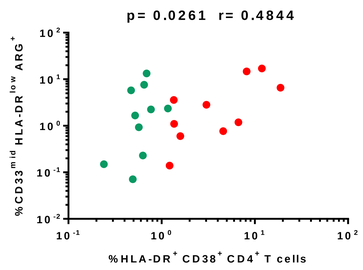
MDSCs IDO^{+} and ARG-1^{+} are expanded in VIR and ART patients

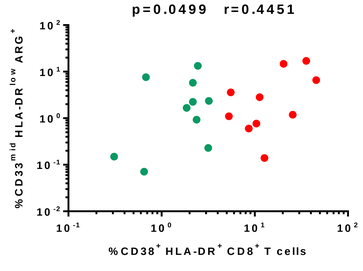


P1 – CD33^{mid} HLA-DR^{low} MDSCs IDO^{+} and ARG-1^{+} significantly increase in VIR and ART patients



Immune activation of T cells correlates with P1 – CD33^{mid} HLA-DR^{low} MDSCs ARG-1^{+}



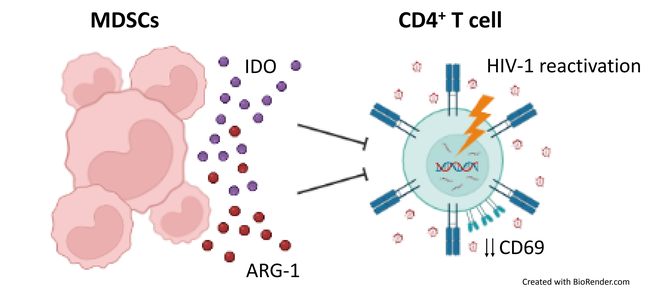


CONCLUSIONS

- HIV-infected patients show higher frequency of MDSCs expressing enzymes related to their immunosuppressive activity.
- HIV infection significantly expands the population of P1 – CD33^{mid} HLA-DR^{low} MDSCs expressing IDO and ARG-1, which is not normalized after ART initiation.
- P1 – CD33^{mid} HLA-DR^{low} MDSCs ARG-1^{+} frequency correlates with immune activation in CD4^{+} and CD8^{+} T cells.
- P1 – CD33^{mid} HLA-DR^{low} MDSCs seem to inhibit HIV-1 reactivation from the latent reservoir and decrease CD4^{+} T cell activation.

Finding new therapeutic strategies to modulate the immunosuppressive actions of MDSCs could significantly impact the HIV reservoir.

PROPOSED MODEL



P1 – CD33^{mid} HLA-DR^{low} MDSCs could be inhibiting HIV-1 reactivation and CD4^{+} T cell activation through the immunosuppressive effect of IDO and ARG-1 enzymes.

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