Identification of HIV-2 infected extreme elite controllers offers insight into spontaneous functional cure

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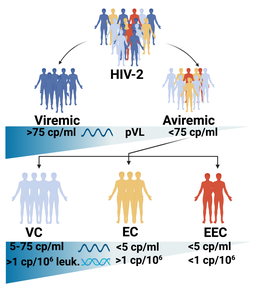
BACKGROUND

HIV-2, compared to HIV-1, is less pathogenic and infected individuals usually have undetectable or low plasma viral load (pVL). Although HIV-1 elite controllers (ECs) are rather well characterized HIV-2 ECs are still less so.

We set out to study pVL and cell-bound DNA load in aviremic HIV-2-infected individuals, especially focusing on HIV-2 ECs in relation to levels and pathogenic properties of CD4+ T-cells, as well as inflammation markers.

MATERIAL AND METHODS

- HIV-2-infected and seronegative study participants within an occupational cohort in Guinea-Bissau were recruited.
- HIV-2 RNA pVL was analysed by RT qPCR (detection level = 5 RNA cp/ml).
- Cell-bound HIV-2 DNA load was determined by qPCR (detection level = 1 cp/10^6 leukocytes).
- Percentage of CD4+ T-cells (%CD4), %CD4 at midpoint follow-up and CD4+ T cell phenotypes were determined by polychromatic flow cytometry.
- Levels of plasma inflammatory proteins were analyzed by multiplexing assay and proximity extension technology.

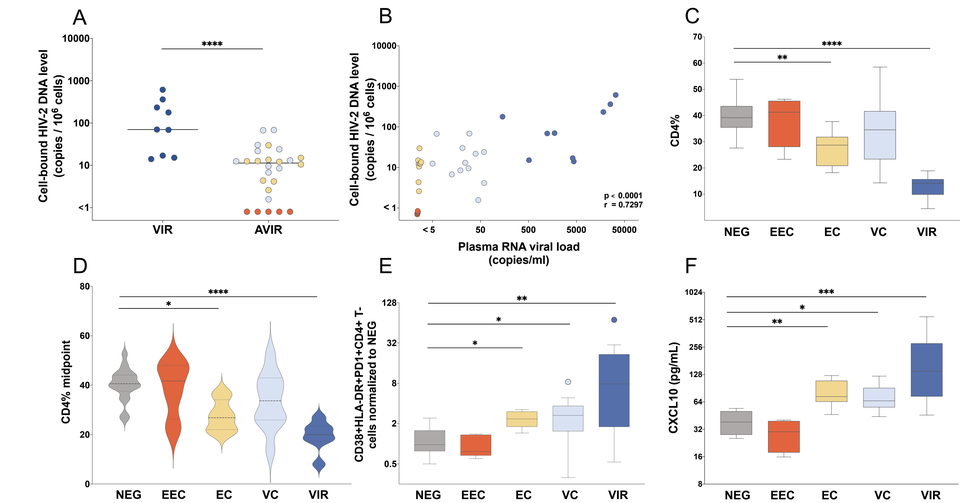


	HIV-Neg	HIV-2 Viremic	HIV-2 Aviremic	HIV-2 Aviremic		
				Viral controller (VC)	Elite Controller (EC)	Extreme Elite Controller (EEC)
Numbers (F/M)	18 (6/12)	9 (0/9)	26 (9/17)	12 (5/8)	9 (3/6)	5 (1/4)
Age in years	52 (39-67)	57 (49-65)	54 (39-82)	58 (39-82)	45 (45-59)	50 (44-54)
CD4+ T-cell count (cells/µl)	911 (545-1675)	232 (68-536)	606 (237-1322)	576 (278-1081)	513 (237-971)	851 (630-1322)
% CD4+ T cells	39.0 (27.6-53.8)	14.0 (4.5-18.9)	32.0 (14.3-58.5)	34.5 (14.3-58.5)	28.7 (18.2-37.7)	41.3 (23.3-46.2)
pVL (RNA cp/ml)	-	4184 (144-32943)	6 (0-59.6)	26 (5-60)	<5	<5
Cell-bound DNA load (cp/10^6 leuk.)	-	70 (16-296)	11 (3-15)	13 (8-27)	12 (7-14)	<1

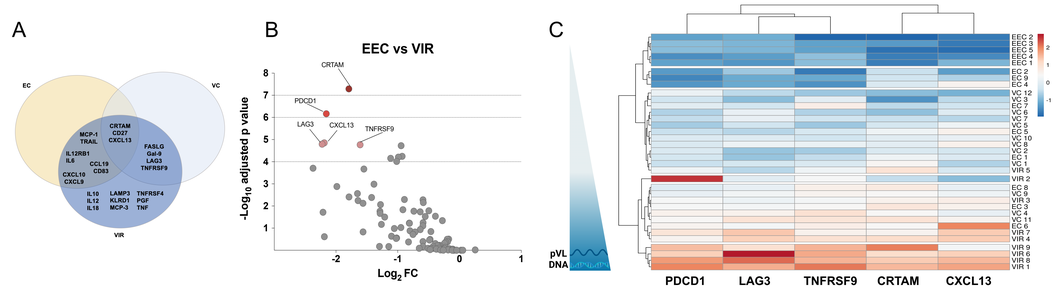
Characteristics of study participants

- HIV-2 **extreme elite controllers** (EECs), uniquely **lack** both detectable **plasma viral load and cell-bound DNA**.
- EECs are **indistinguishable from seronegatives** in regard to **CD4+ T-cell** level and phenotype, as we all as, **plasma inflammation markers**.
- Proteome profiling revealed that reduced plasma concentrations of soluble immune checkpoint markers **differentiate EECs from other HIV-2**-infected individuals.

RESULTS

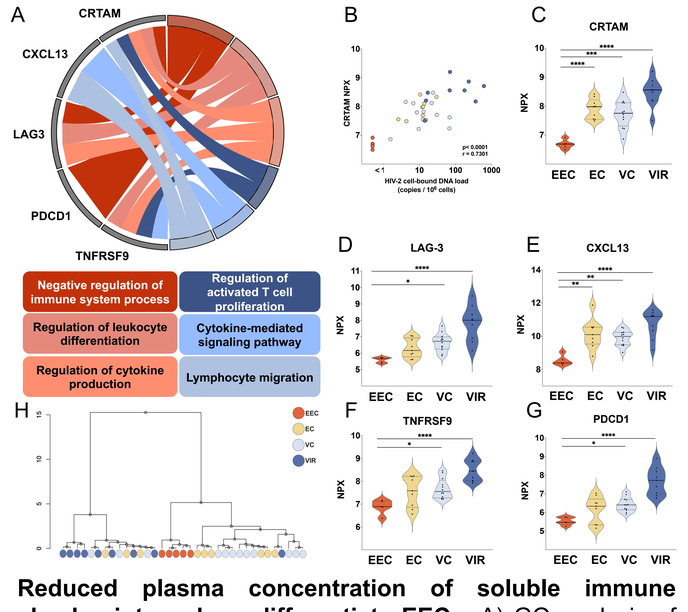


Identification of HIV-2 extreme elite controllers, lacking immunodeficiency and chronic inflammation. A) Cell-bound HIV-2 DNA load in aviremic (AVIR) and viremic (VIR) individuals. B) Correlation HIV-2 pVL and cell-bound DNA load. C) CD4%, E) midpoint CD4% during follow-up, F) fold difference CD4+ T cells being CD38+HLA-DR+PD-1+ and G) CXCL10 plasma concentration.



Profiling of regulatory plasma proteins in HIV-2-infected individuals with varying degree of viral control. A) Venn diagram illustrating differentially expressed proteins (DEPs) comparing HIV-2 EEC to other groups. B) Volcano plot of DEPs comparing EEC and VIR. C) Plasma concentrations of CRTAM, LAG3, PDCD1, CXCL13 and TNFRSF9 analyzed by hierarchical clustering.

RESULTS CONTINUED



Reduced plasma concentration of soluble immune checkpoint markers differentiate EECs. A) GO analysis of the five DEPs, displaying the top six biological processes. B) Correlation between HIV-2 cell-bound DNA load and CRTAM level. HIV-2-infected groups compared to EECs in regard C) CRTAM, D) LAG-3, E) CXCL-13 F) PDCD1 and G) TNFRSF9 plasma concentration. H) Unsupervised hierarchical clustering analysis, based on the plasma concentrations of CRTAM and TNFRSF9.

CONCLUSIONS

- HIV-2 aviremic/low viremic individuals with detectable cell-bound DNA load, i.e. elite controllers (EC) and viral controllers (VC), display signs of immunodeficiency and chronic immune activation.
- Instead, a small, unique group of HIV-2 individuals, extreme elite controllers (EEC), without detectable pVL and cell-bound DNA load do not differ from seronegative individuals, in regard to CD4+ T-cell levels, concentrations of plasma inflammation markers, or frequencies of chronically activated and exhausted CD4+ T cells.
- Lack of immune pathology, including chronic immune activation/ aging, among HIV-2 EECs suggests that this group of individuals could offer a model of spontaneous functional cure, which merits further studies.

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