



ART-treated adults with diagnosed atherosclerosis are characterized by a particular expression of Regulatory T-cells (Tregs)

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Chronic HIV infection: accelerated aging and increased Treg frequencies

I. Generalized **immune-activation** and persistent **inflammation**, which promote:

a) Release of **pro-inflammatory cytokines** and **endothelial adhesion molecules**. (Zicari, *et al.* 2019. Viruses)

b) Recruitment of leukocytes

c) Oxidative stress (Aukrust, *et al.* 2005. Blood)

result in accelerated aging and cardiovascular diseases:

- Immuno-senescence and exhaustion
- Organ damage and dysfunction

II. **Increased in Tregs frequencies** (Jenabian *et al.* 2011. PLoS Pathogens)

a) Inhibition of specific anti-HIV response

b) Promote tissue fibrosis (Sanchez *et al.* 2015. JID)

c) Contribute to viral persistence (Yan-Mei *et al.* 2015. Int J Inf Diseases)

III. **Increased CD39/Adenosine purinergic pathway** (Jenabian et al., 2013, PLoS Path)

IV. **Decrease in Th17 cells counts**. (Ancuta *et al.* 2010. Curr Opin HIV AIDS)

Contribute to microbial translocation in the gut and further generalized immuno-activation.

Atherosclerosis:

I. Inflammatory disease

II. Decrease levels of atheroprotective Tregs (Winkels, H. *et al.* 2017. Eur Heart J)

a) Tregs also promote atheroma plaque stability.

III. Decrease levels of atheroprotective CD39/CD73. (Huttinger, *et al.* (2012). Am J Pathol; Koszalka, *et al.* 2004. Circ Res)

IV. Increase levels of pro-atherogenic Th17 cells. (Bixler, *et al.* 2013. Clin Dev Immunol)

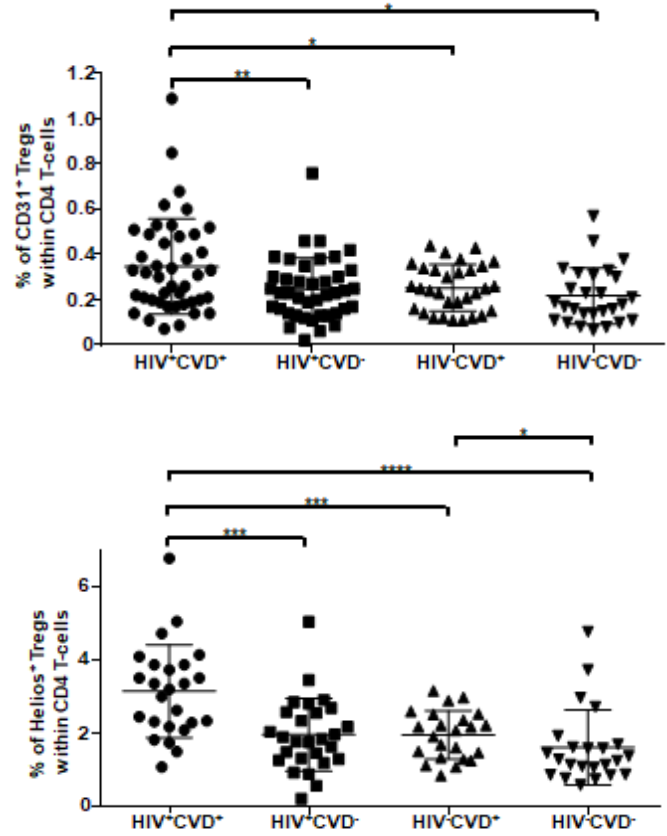
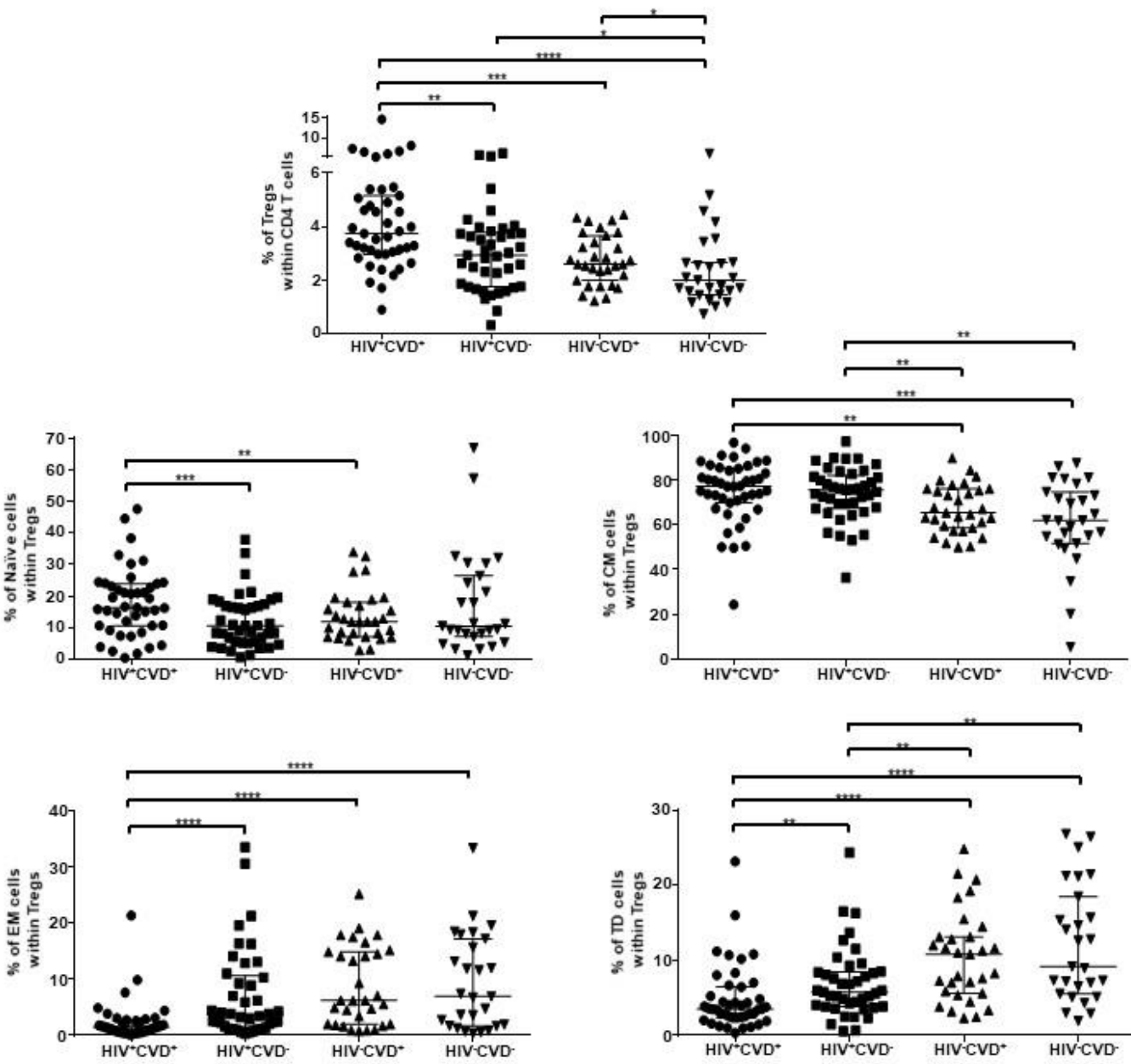
METHODS:

- n= 142, including ART-treated HIV⁺ adults with (n=43) or without atherosclerosis (n=41) and HIV⁻ individuals with (n=30) or without atherosclerosis (n=28).
- Atherosclerosis was determined by the presence of atherosclerotic features by computed tomography angiography of the coronary arteries.
- *Ex vivo* analysis of the frequency of Treg subsets and T-helper (Th) cells, as well as T-cell immune activation were assessed by flow cytometry.

Despite increased proportion of Tregs, increased expression of CD39 and decreased number of Th17 in HIV infection, the incidence of atherosclerosis is increased in HIV-infected patients??

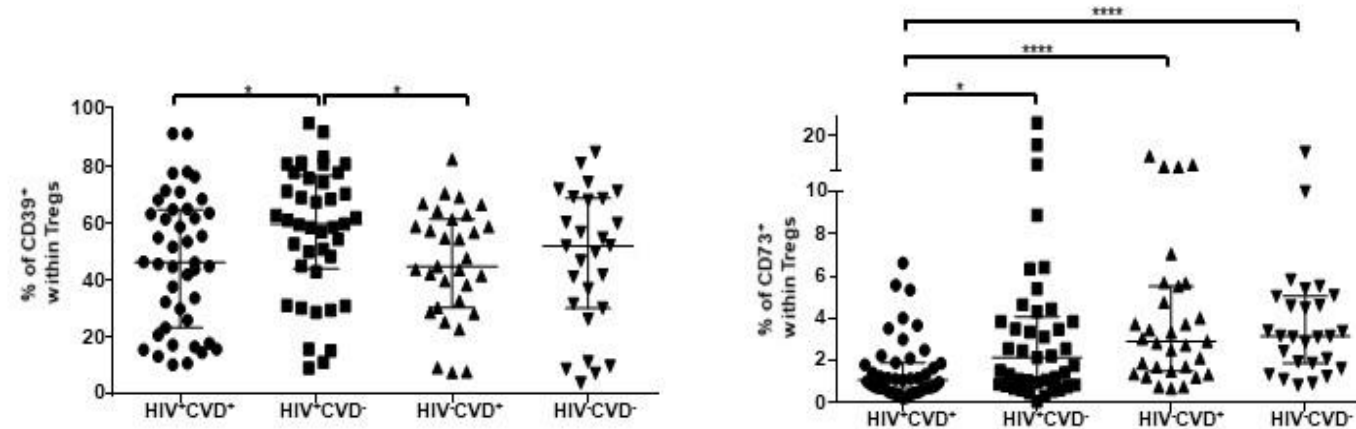
HIV-infected individuals with atherosclerosis have higher levels of circulating total Tregs, while Tregs in HIV+CVD+ group are less differentiated

Increased generation of thymic Tregs in HIV+CVD+ individuals

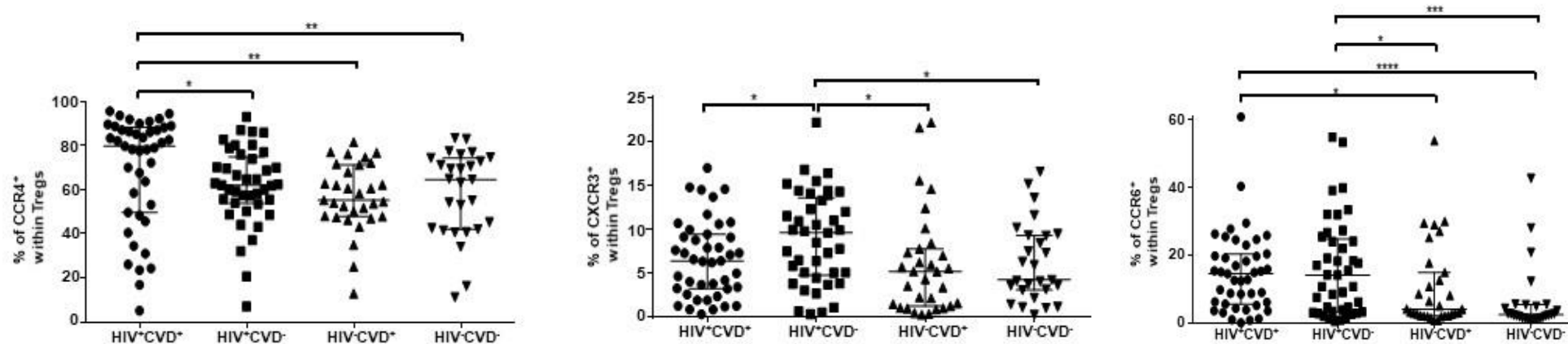


- **CD31:** marker of recently Treg migrated from the thymus
- **Helios:** marker of thymic Treg

HIV+CVD+ individuals have lower frequencies of circulating atheroprotective CD39/CD73-expressing Tregs

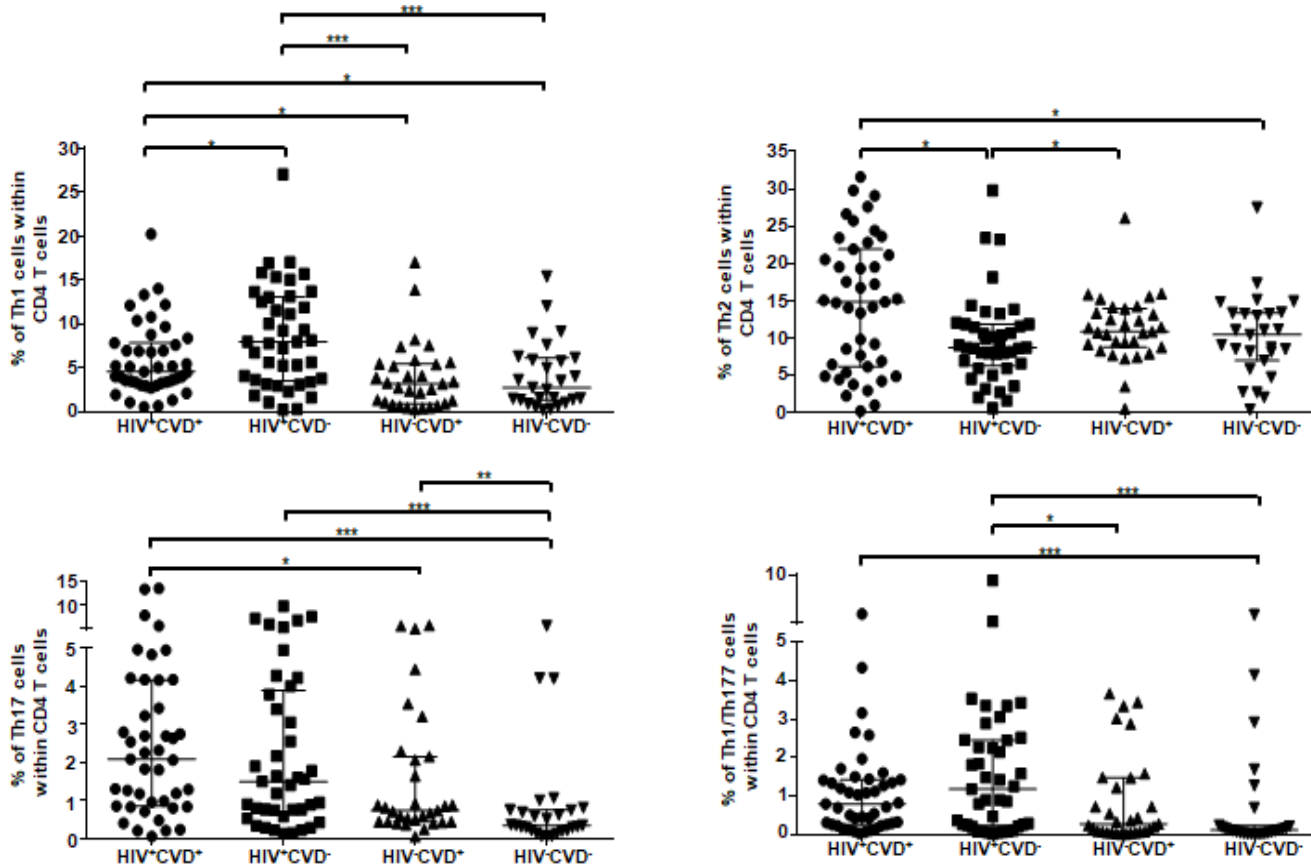


Tregs in HIV+CVD+ individuals are characterized by low levels of CXCR3 and CCR4 expression suggesting an impairment in Treg maintenance and migration to the atheroma plaque



- CXCR3⁺ Tregs are protective in acute inflammation. (Fernandes, J. *et al.* (2004). Cytok)
- CXCR3 guide T-cells migration to atheroma plaque. (Clement, M. *et al.* (2015). J Autoimmun)
- CCR4-CCL17 axis can interfere with signaling pathways mediating Treg maintenance. (Weber, C. *et al.* (2011). J Clin Invest)
- CCR6 is a marker for migration to inflammatory sites. CCR6 and CCL20 are expressed at higher levels in human atherosclerotic plaques. (Calvayrac, O. *et al.* (2011). Arterioscler Thromb Vasc Biol)

HIV+CVD+ individuals have particular signature of CD4 effector T-cells. Individuals in HIV+CVD+ group present highest levels of pro-atherogenic Th17 cells and Th2 cells.



Conclusions

These results reveal profound alterations in the frequency of regulatory and effector CD4+ T-cell subsets associated with atherosclerosis in ART-treated PLWH. The paucity and poor tissue-infiltration potential of anti-inflammatory CD39/CD73 Treg subsets may represent one mechanism contributing to atherosclerotic plaque formation during ART-treated HIV infection.

Acknowledgments



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Canadian HIV & Aging Cohort

Canadian HIV and Aging cohort (CTN 272)