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Hope, Victories and Perseverance beyond 2020

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Espoir, Victoires et Persévérance au-delà de 2020

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Track: Basic Sciences

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

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**NOTHING TO DISCLOSE**

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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.

**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??**

## 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.

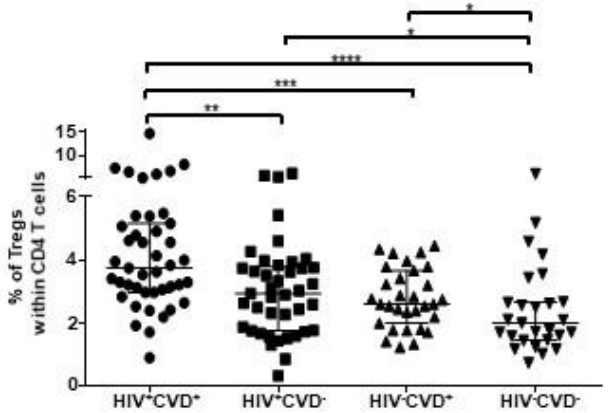
III. Decrease levels of atheroprotective CD39/CD73. (Huttinger , ***et al.*** (2012). Am J Pathol; Koszalka, ***et al.*** 2004. Circ Res)

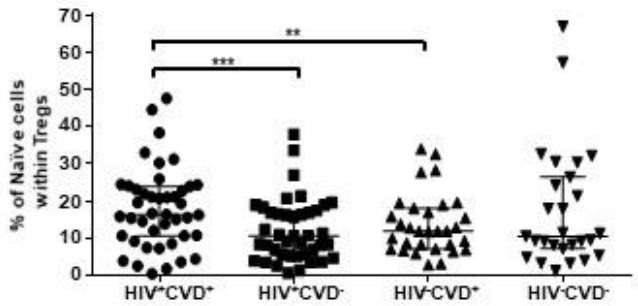
IV. Increase levels of pro-atherogenic Th17 cells. (Bixler, ***et al.*** 2013. Clin Dev Immunol)

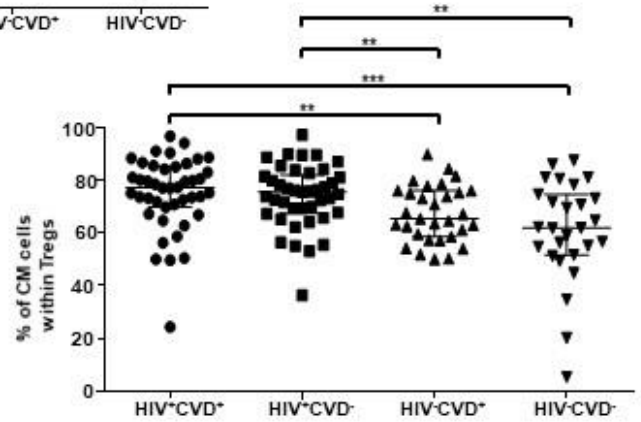
## METHODS:

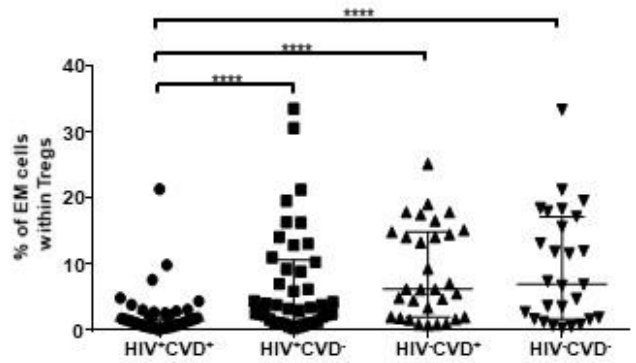
- n= 142, including ART-treated $HIV^+$ adults with (n=43) or without atherosclerosis (n=41) and $HIV^-$ individuals with (n=30) or without atherosclerosis (n=28).
- Atherosclerosis was determined by the presence of atherosclerotic features by computed tomography angiography of the coronary arteries.
- *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.

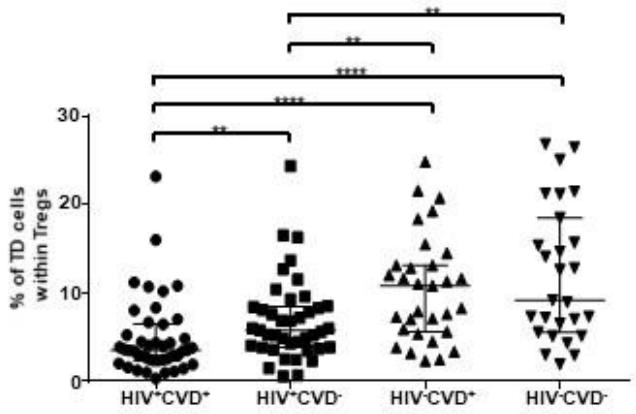
# HIV-infected individuals with atherosclerosis have higher levels of circulating total Tregs, while Tegs in HIV+CVD+ group are less differentiated



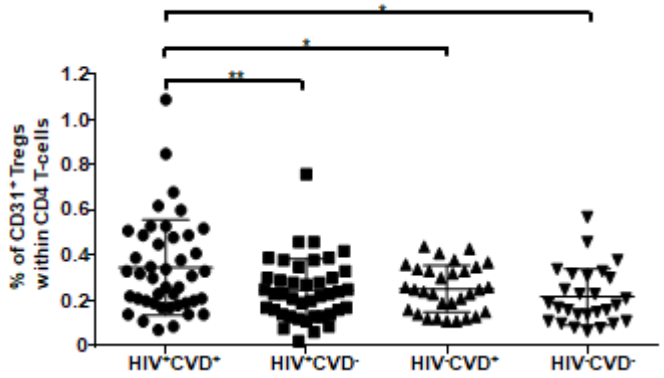



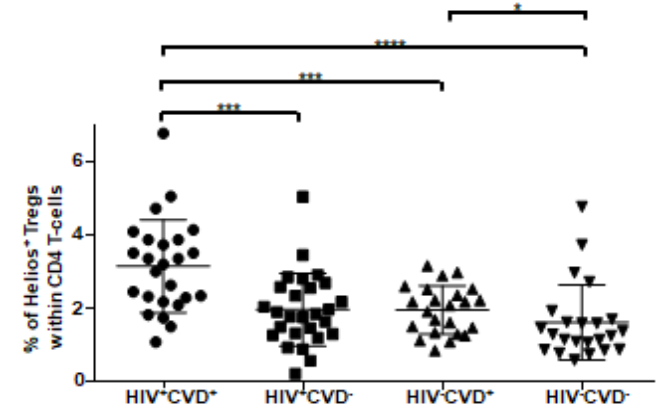



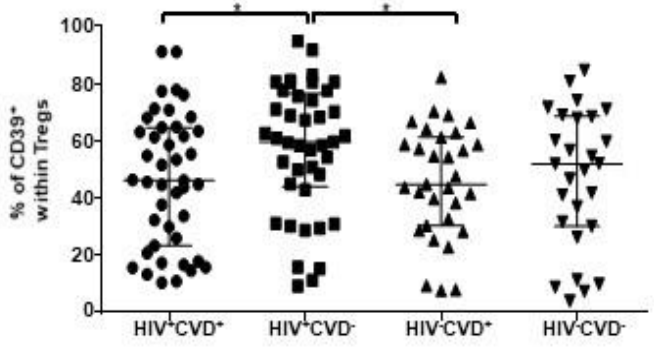

# Increased generation of thymic Tregs in HIV+CVD+ individuals

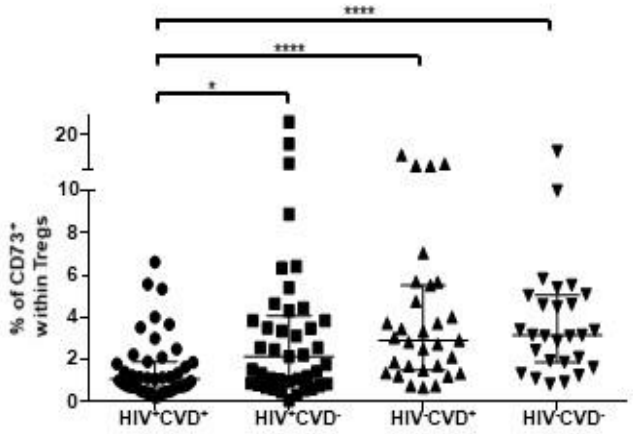


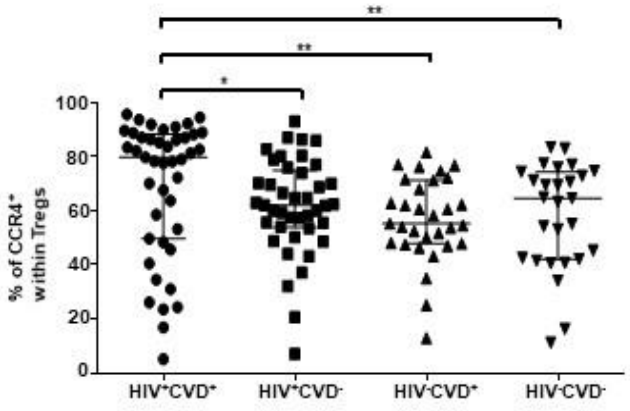

- **CD31**: marker of recently Treg migrated from the thymus
- **Helios**: marker of thymic Treg

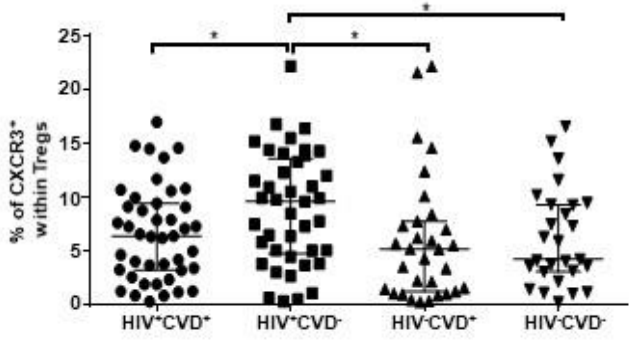
## HIV+CVD+ individuals have lower frequencies of circulating atheroprotective CD39/CD73-expressing Tregs

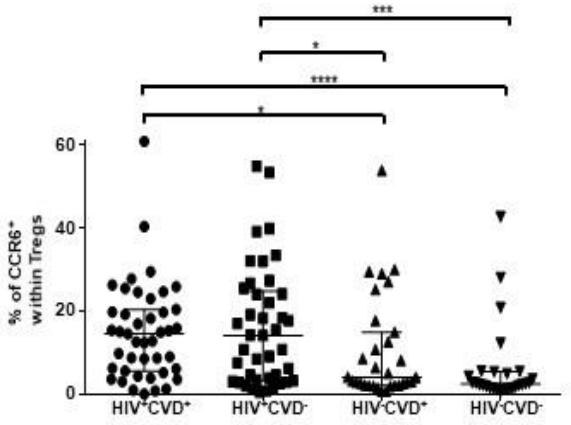



## Tregs in HIV+CVD+ individuals are characterized by low levels of CXCR3 and CCR4 expression suggesting an impairment in Treg maintenance and migration to the atheroma plaque

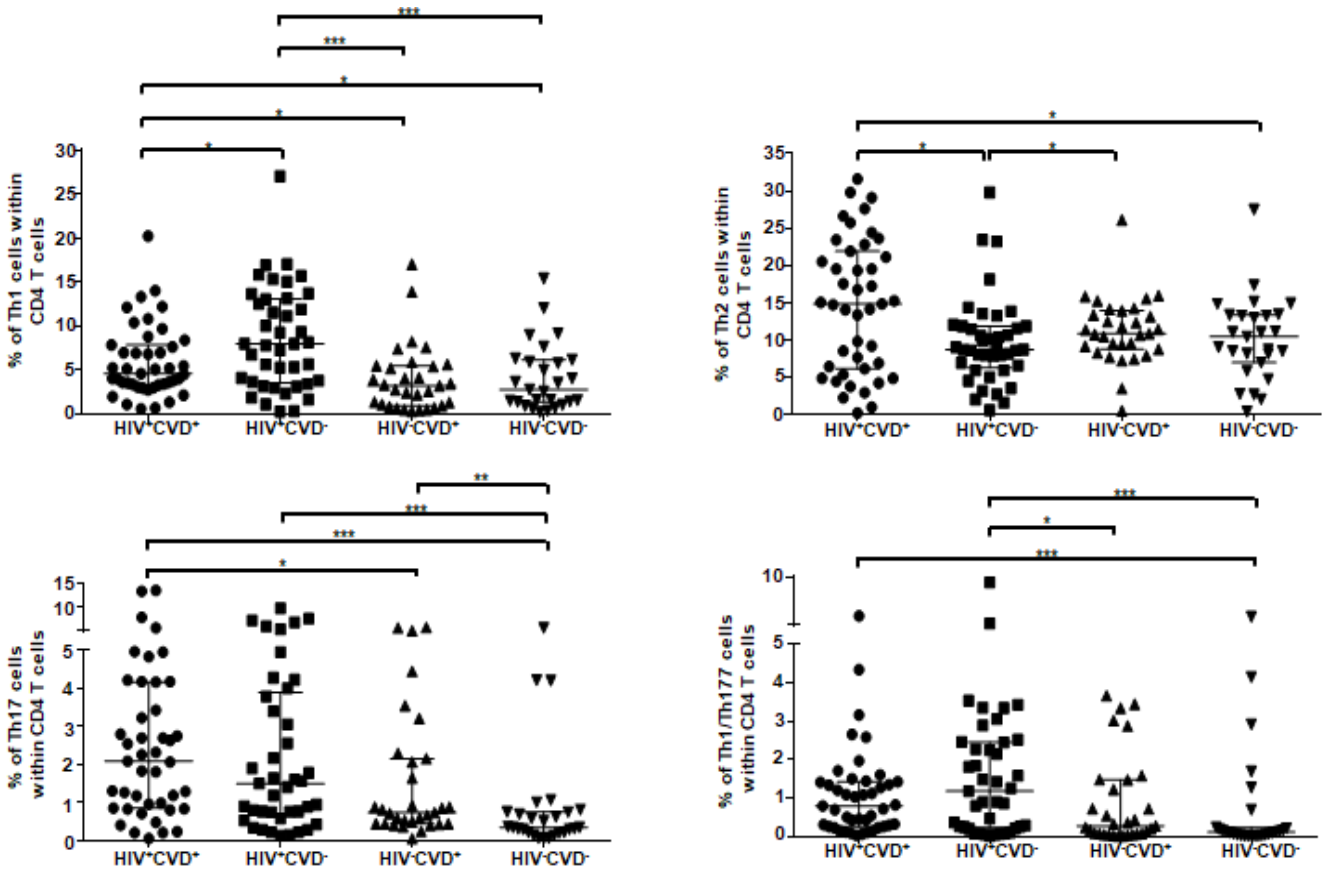



- CXCR3+ Tregs are protective in acute inflammation. (Fernandes, J. ***et al.*** (2004). Cytok)
- CXCR3 guide T-cells migration to atheroma plaque. (Clement, M. ***et al.*** (2015). J Autoimmun)
- CCR4-CCL17 axis can interfere with signaling pathways mediating Treg maintenance. (Weber, C. ***et al.*** (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). Arteriosc 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)