Premature Cardiovascular Disease Development In HIV-1 Infected Individuals From The Canadian HIV And Aging Cohort Study Is Associated With Discrepancies In BAFF and APRIL Levels

Matheus Aranguren[1,2], Carl Chartrand-Lefebvre[1,2], Jean-Pierre Routy[1,3], Cecile Tremblay[1,2], Madeleine Durand[1,2], Johanne Poudrier[1,2*], Michel Roger[1,2,4*]

1. Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM); 2. Université de Montréal, Montréal. 3. McGill University, Montréal; 4. Laboratoire de Santé Publique du Québec, Montréal.

* Co-seniors

Introduction

- HIV infection causes a **chronic infection** that persists well beyond antiretroviral therapy (ART) beginning. This chronic inflammation is related to the premature development of manifestations normally associated with aging, such as **cardiovascular diseases (CVD)** like **atherosclerosis**.
- We have shown that **B-cell Activation Factor (BAFF)** levels are augmented in the blood of HIV-infected individuals from acute infection and up to one year post-ART and correlates with B-cell deregulations.
- BAFF is an important B-cell cytokine, implied in shaping the **Marginal Zone B-cell** (MZ) pool, shown to be atheroprotector in mice.
- We have also shown that HIV-infection correlates with MZ and their precursors (**MZp**) deregulations, who we have recently shown to possess a **Breg function**.
- MZp Breg function is related to the expression of immunomodulating molecules such as the **NR4A** family of transcription factors, IL-10 and CD83.
- BAFF possess an analog, **A Proliferation-inducing Ligand (APRIL)**, with whom it shares a strong homology and function. However, while excess BAFF is assumed to have a pathological role in HIV infection, **APRIL seems to posses a protective role**: higher levels of APRIL were correlated to a slower progression of HIV.

Objectives

- We will measure BAFF and APRIL levels by ELISA and Flow Cytometry in the blood of selected individuals from the **Canadian HIV and Aging Cohort Study (CHACS)**, a cohort of long-term HIV-infected and treated individuals (15 years+), some of whom developed CVD like atherosclerosis.
- We will correlate BAFF and APRIL levels with the Total Atherosclerosis Plaque Volume (TPV) of HIV- and HIV+ individuals.
- We will measure NR4A3 and IL-10 expression levels by flow cytometry of APRIL and APRIL+BAFF treated B-cells *in vitro.*

Results

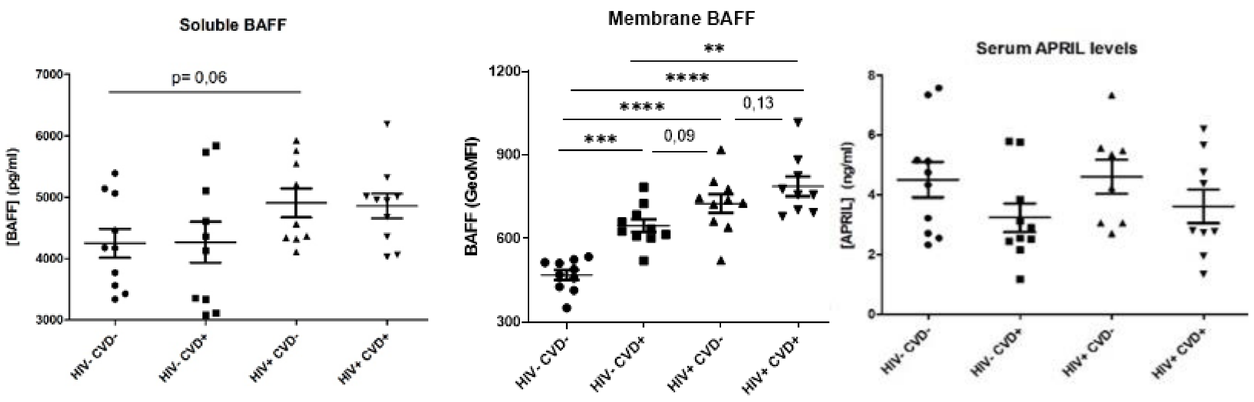

Fig.1: Soluble and membrane BAFF are augmented in HIV-infected individuals, even after several years of ART therapy. APRIL levels, however, remain unchanged between HIV- and HIV+ individuals, and tend to be lower in CVD+ individuals. (GeoMFI = Geometric Mean Fluorescence Intensity)

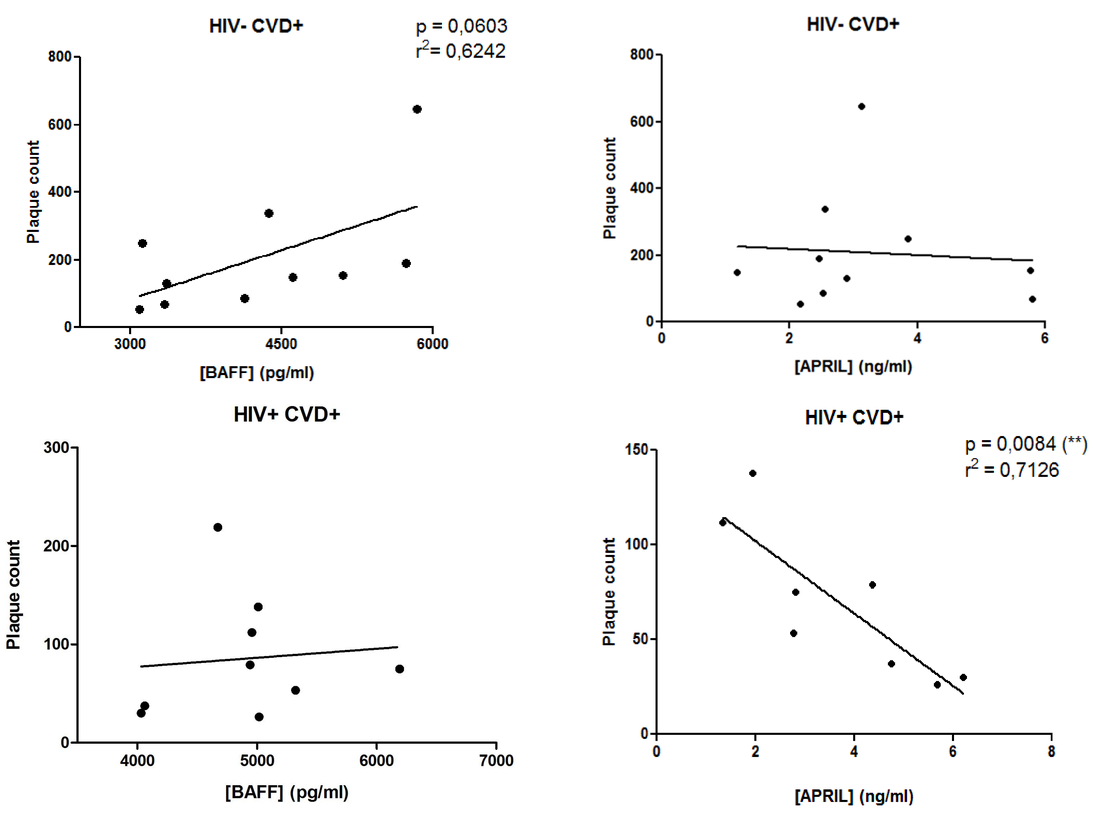

Fig. 2: BAFF (but not APRIL) correlates positively with TPV in HIV- individuals. In HIV+ individuals, however, APRIL correlates negatively with TPV.

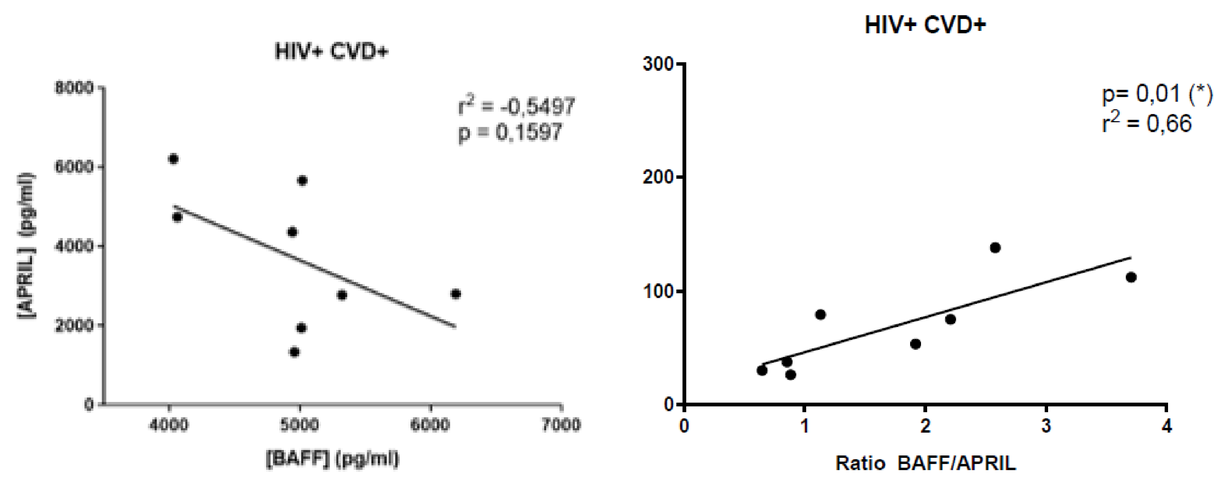

Fig. 3: APRIL levels tend to correlate negatively with BAFF levels in HIV+ individuals. Accordingly, a higher BAFF/APRIL ratio correlates positively with TPV in HIV+ individuals.

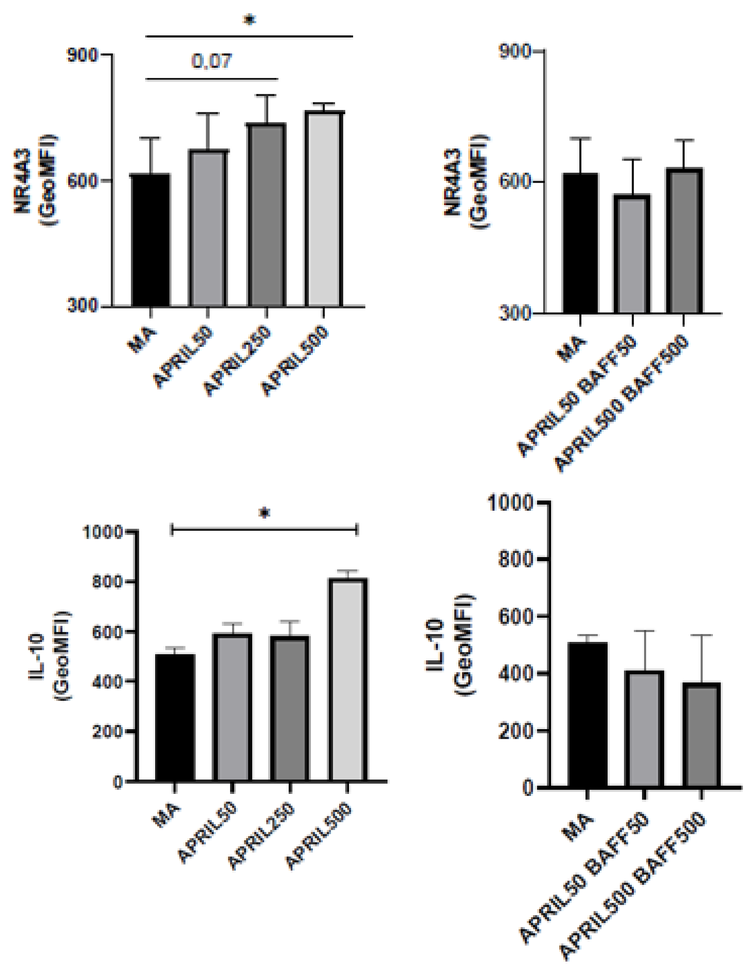

Fig. 4: High levels of APRIL increase MZp NR4A3 and IL-10 expression. This increase is dampened in the presence of high levels of soluble BAFF.

Conclusion

- Excess BAFF persists in long-term treated HIV-infected individuals.
- BAFF seems to correlate positively with atherosclerosis progression, while APRIL seems to correlate negatively, **suggesting an atheroprective role**.
- An imbalance in the BAFF/APRIL ratio seems to be involved in CVD development of HIV-infected individuals.
- APRIL seems to favour MZp Breg potential, and the presence of BAFF dampens this role.
- **APRIL could be atheroprotective by shaping Breg profile and keeping inflammation at bay.**
- **Modulation of APRIL could be envisaged in future treatments to prevent CVD development in HIV+ inidivudals.**

Aknowledgements

Kim Doyon-Laliberté
Laurence Blondin-Ladrie
Alessandro Modica
Lyvia Fourcade
Michelle Byrns
Marie-Claude Faucher
Johanne Poudrier
Michel Roger

Dr. Tremblay's Lab.
Mohammed Sylla
Mohammed El-Far

Cytometry Platform
Dominique Gauchat
Philippe St-Onge

Dr. Bilodeau's Lab
Francis Dilauro

Mario Legault
Daniel Tremblay-Sher