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Myeloid GDF15 influences risk of non-AIDS comorbidities and HIV reservoir size independently of inflammation in ART-treated PLWH

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No conflict of interest

Background

GDF-15 = Growth Differentiation Factor 15
Atypical member of the TGF-β family

Circulating levels of GDF-15 are elevated in people with:

- → **Aging**
- → Cardiovascular diseases
- → Sepsis
- → Cancer
- → Asthma
- → Severe COVID-19
- → Mitochondrial diseases

Objectives

- Comparing GDF-15 plasma levels between groups of PLWH.
- Assessing the potential of GDF-15 as a biomarker of increased risk of non-AIDS comorbidities and HIV persistence.
- Deciphering the mechanisms of GDF-15 regulation in PLWH.

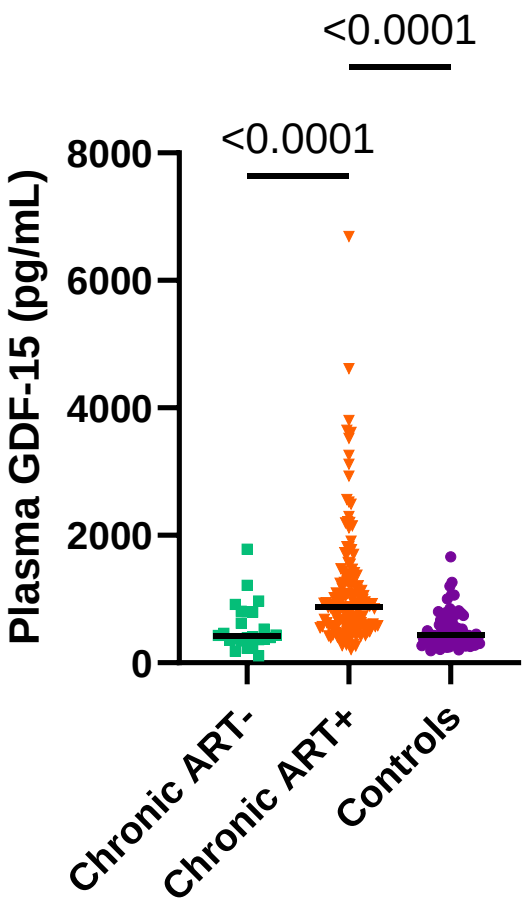
Study population

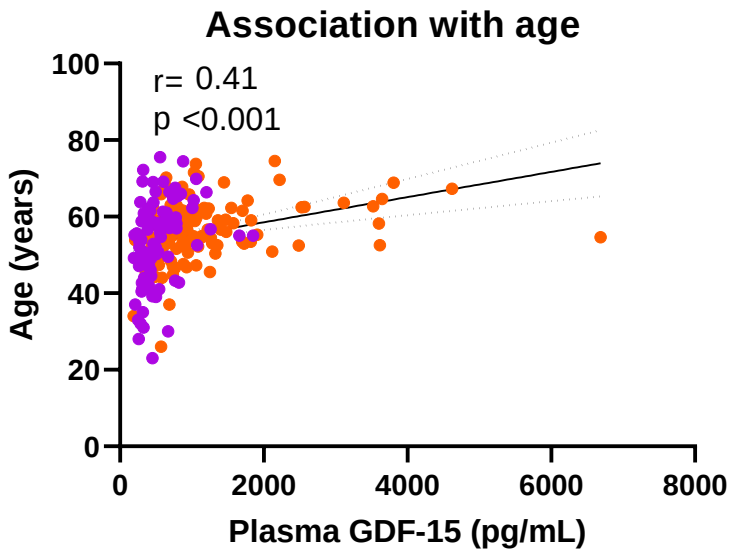
Study groups	HIV TAR- (n = 42)	HIV TAR+ (n =140)	Controls without HIV (n = 83)
Age, Median (IQR)	38 (33-50)	55 (49,1-62,2)	52 (44-59)
Sexe : Female (%) Male(%)	22,7 77,3	9,9 90,1	26,2 73,8
Ethnicity (%) Caucasians Afro-americans Latino	 64% 18% 18%	 70% 19% 11%	 74% 14% 12%
CD4 count, Median (IQR)	220 (35-345)	588 (408-700)	854 (558-1011)
CD8 count, Median (IQR)	770 (406-1147)	685 (565-804)	425 (281-689)
CD4/CD8 ratio, Median (IQR)	0,19 (0,06-0,43)	0,74 (0,47-0,77)	1,58 (1,22-2,73)
Viral load, log_{10} copies/mL, Median (IQR)	5,12 (4,42-5,47)	<1,7	NA

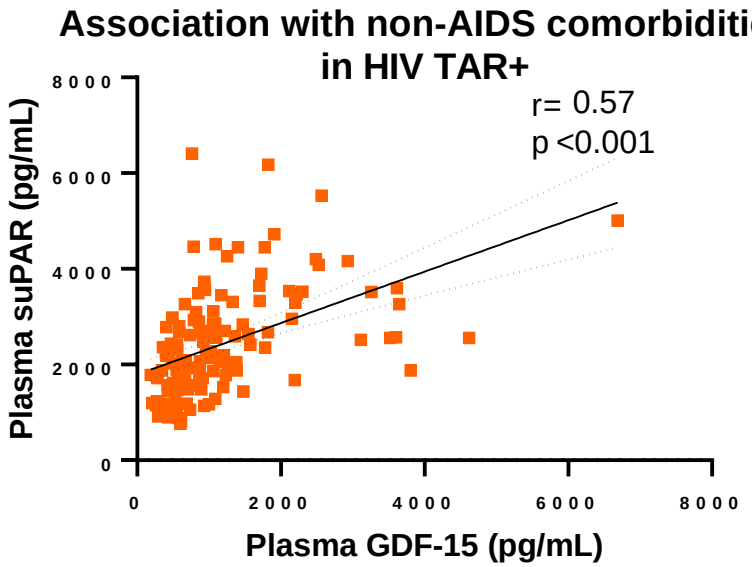
Methodes

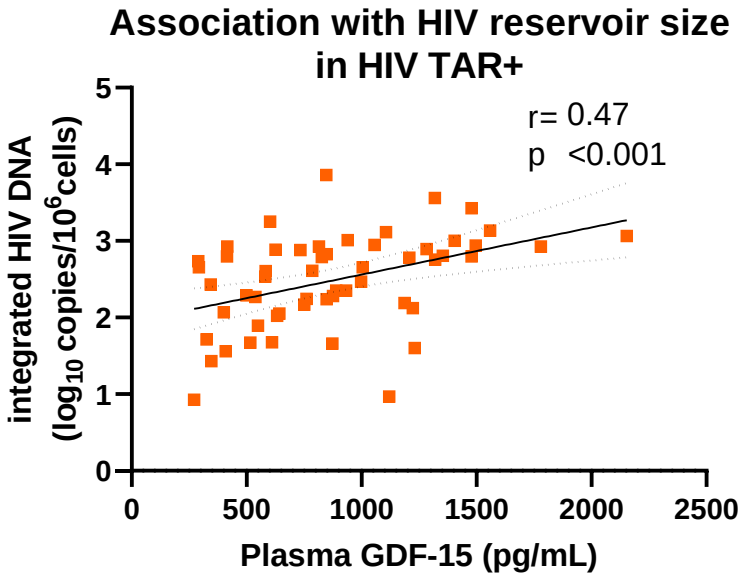
- ELISA/multiplexes in plasma or supernatant: GDF-15, suPAR, inflammation markers
- Flow cytometry: labelling of GDF-15 in PBMCs
- HIV reservoirs: nested qPCR in sorted CD4 T-cells
- In vitro stimulations and ELISA or RT-ddPCR

Plasma levels of GDF-15 in PLWH are linked with age, risk of non-AIDS comorbidities and HIV reservoir size in ART-treated PLWH







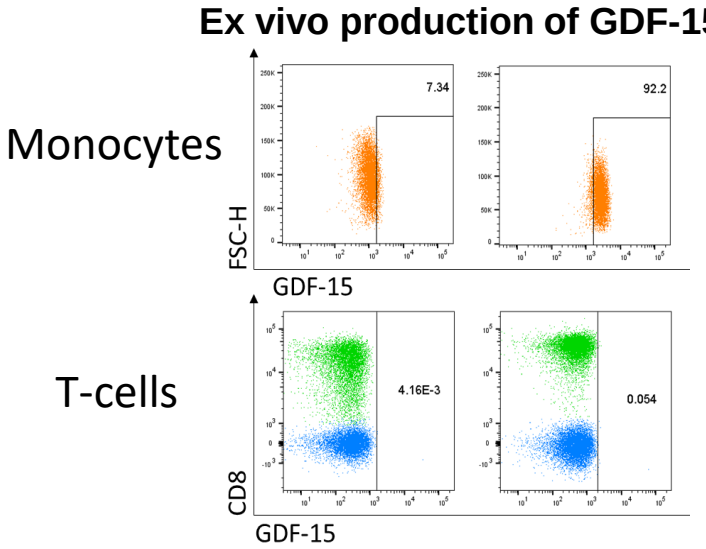


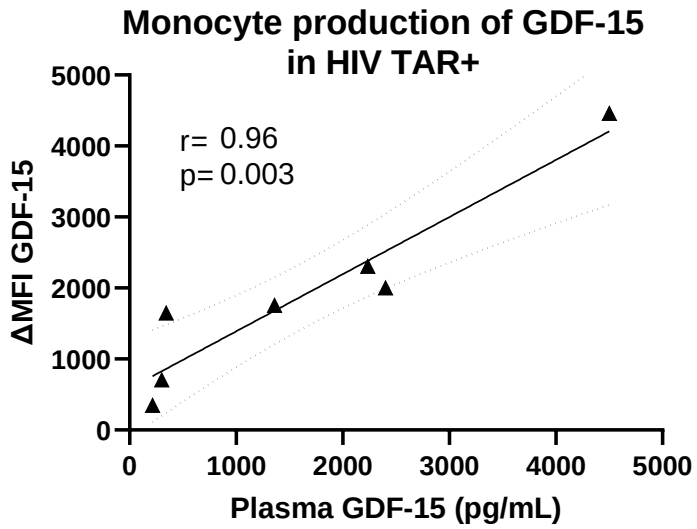
Plasma GDF-15 levels

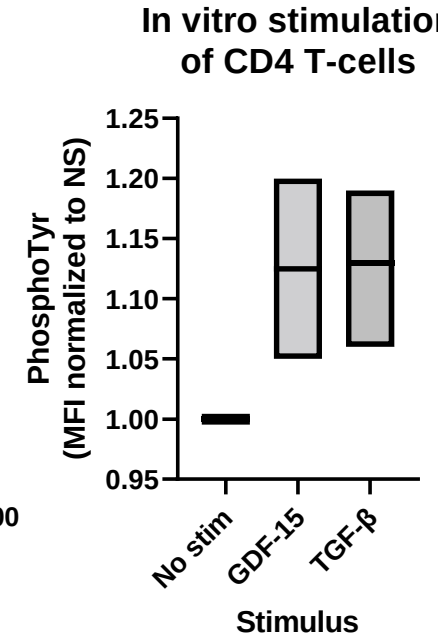
- **Higher in ART-treated PLWH** compared to uninfected controls or untreated PLWH. Sex and type or class of ART had no influence on GDF-15 levels.
- Associated with **age**.
- Associated with the marker of non-AIDS comorbidities **suPAR** and **HIV reservoir size.**

→ **Elevated GDF-15 as a sign of accelerated or accentuated aging.**

GDF-15 is produced in monocytes independently of inflammation and has a direct effect on CD4 T-cells.



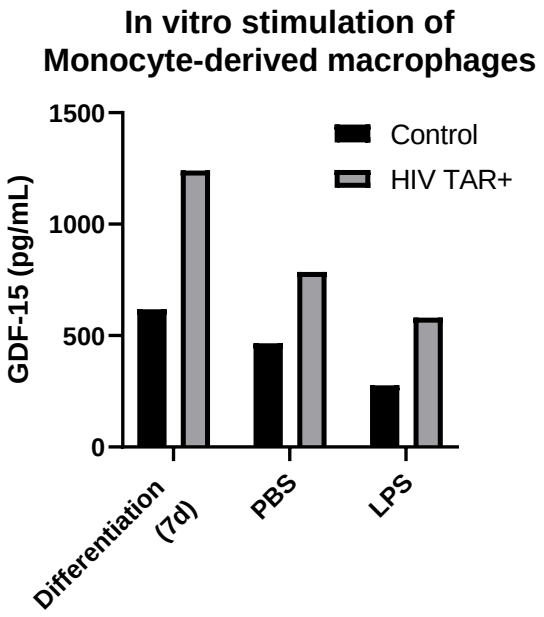




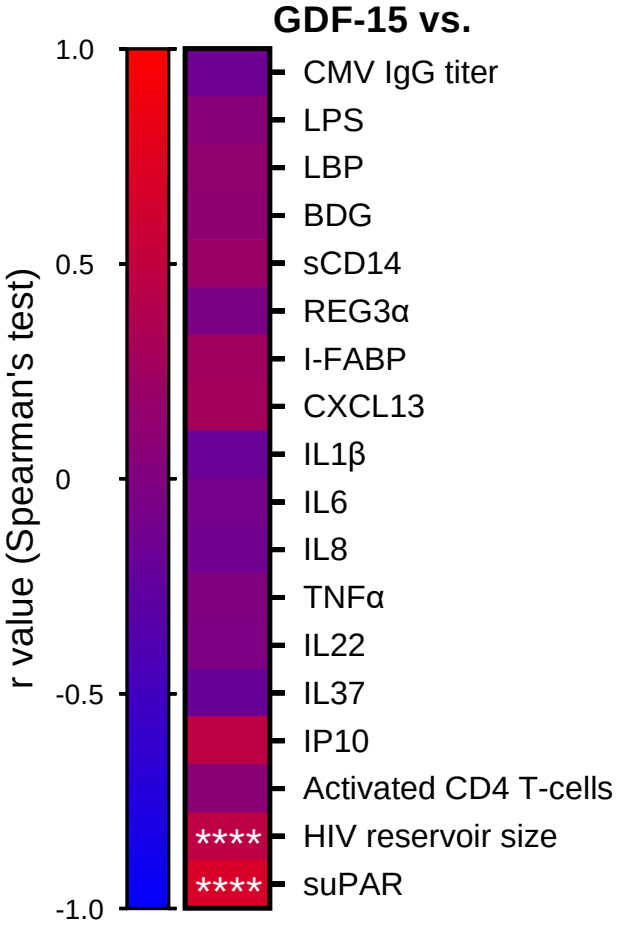
GDF-15:

- In PBMC, only found in **monocytes**. Plasma GDF-15 correlated with GDF-15 levels in monocytes.
- GDF-15 and TGF-β stimulation induced phosphorylation of tyrosine in **CD4 T-cells → possible direct effect**.
- Ex vivo et in vitro, **no effect of inflammatory signals** on GDF-15 levels. GDF-15 was produced upon differentiation of macrophages from monocytes.

→ GDF-15 is produced in monocytes/macrophages, independently of inflammatory pathways.



In ART-treated PLWH:



**** = p<0.001

Conclusion: Circulating GDF-15 levels

- Associated with **HIV reservoir size** and **non-AIDS comorbidity** marker suPAR.
- Produced by monocytes/macrophages, independently of age, sex, and inflammation pathways.
- In vitro stimulations: GDF-15 might have a direct effect on CD4 T-cells (ongoing RNAseq experiments).

→ **GDF-15 elevation** as a sign of **accelerated/accentuated aging**, **and HIV persistence.**

Future directions: Molecular mechanism and confirmation of the role of GDF-15 on increased risk of non-AIDS comorbidities and HIV persistence.

GDF-15 as a potential biomarker of non-AIDS comorbidities? Possible target to alleviate HIV persistence.

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Montreal Primary HIV-infection cohort
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