Ultra-Low Level Soluble p24 Is Associated With Inflammation in People With HIV on Suppressive ART

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BACKGROUND

Despite suppressive antiretroviral therapy (ART), **residual inflammation** persists in people with HIV (PWH), thus driving higher risk of **serious non-AIDS events** (SNAEs) and **mortality** compared to people without HIV (PWoH). Circulating **HIV proteins** have been detected in some virologically-suppressed PWH, as an expression of the persistence of intact and/or defective **translation-competent proviruses**.

We therefore seek to investigate whether **peripheral inflammation** and **mortality risk** as estimated by VACS Index 2.0 are associated with production of **p24** in PWH on suppressive ART.

METHODS

PWH on suppressive (HIV-RNA <20 copies/mL) **ART** (*n*=120) and **age/sex-matched PWoH** (*n*=20) were enrolled.

The following were cross-sectionally measured:

- ultra-low level **soluble p24** [serum → acid dissociation of immune complexes → *Simoa*];
- **soluble markers of inflammaging** (IP-10, TNF-α, IL-2, IL-4, IL-17A, IL-6, IL-8, sCD14, sCD163, TIMP-1, GDF-15, ROMO-1) [plasma → *Luminex/ELISA*];
- **activated** (CD38+) **CD8+ T-cells** [whole blood → *flow cytometry*].

Mortality risk was estimated by **VACS Index 2.0**.

Mann-Whitney test and linear regression were used for statistical analysis.

RESULTS I

Demographic, clinical and HIV-related characteristics of PWH

Characteristics	PWH (*n*=120)
Age, years [median (IQR)]	54 (47–59)
Male sex [*n* (%)]	100 (83.33)
Ethnicity [*n* (%)]	
Caucasian	106 (88.33)
Latin	5 (4.17)
African	6 (5)
Asian	3 (2.5)
Epidemiology [*n* (%)]	
MSM	59 (49.17)
MSW/ WSM	37 (30.83)
IDU	22 (18.33)
Unknown	2 (1.7)
Comorbidities [*n* (%)]	
None	66 (55)
Cardiovascular disease	32 (26.67)
Chronic kidney disease	15 (12.5)
Liver disease	17 (14.17)
COPD/asthma	11 (9.17)
Neurologic disease	13 (10.83)
Diabetes	19 (15.83)
Viro-immunologic parameters [median (IQR)]	
CD4 T cell *nadir*, cells/μL	226 (55–372)
CD4 T cell count, cells/μL	725 (504–908)
CD4/CD8 ratio	0.8 (0.6–1.06)
HIV-RNA, copies/mL	<20
Previous AIDS diagnosis [*n* (%)]	80 (66.67)
Time from HIV diagnosis, months [median (IQR)]	135 (88–303)
Current ART regimen [*n* (%)]	
INSTI-based triple	55 (45.84)
INSTI-based dual	27 (22.5)
PI-based	4 (3.33)
NNRTI-based triple	34 (28.33)
Duration of ART, months [median (IQR)]	123 (76–222)

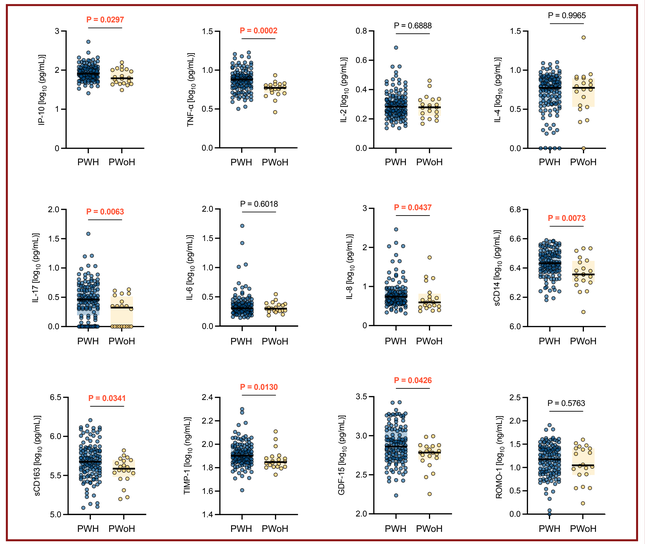
*Despite long-term suppressive ART, **ultra-low level soluble p24** is detectable in **~20% PWH** and associated with higher levels of **IP-10**, a **pro-inflammatory chemokine** which predicts the **mortality risk***

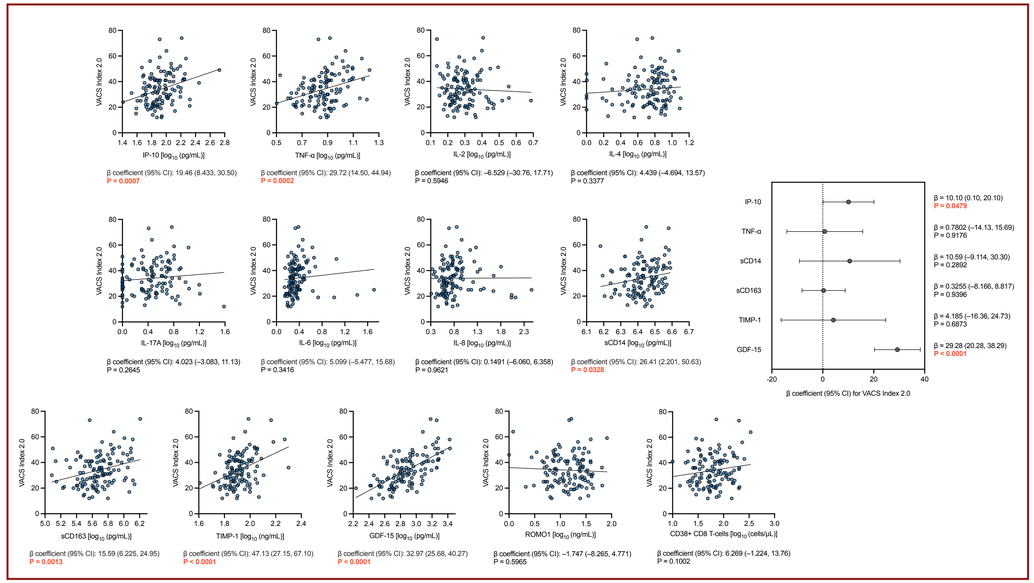
Compared to PWoH, **PWH** showed **higher levels** of circulating **IP-10**, **TNF-α**, **IL-17A**, **IL-8**, **sCD14**, **sCD163**, **TIMP-1**, **GDF-15**.

VACS Index 2.0 was positively associated with **IP-10**, **TNF-α**, **sCD14**, **sCD163**, **TIMP-1**, and **GDF-15** at univariable linear regression analysis.

Yet, by fitting a multivariable regression model including all these six markers, only **IP-10** and **GDF-15** confirmed **independently associated with VACS Index 2.0**.

RESULTS II

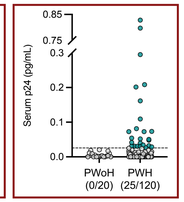


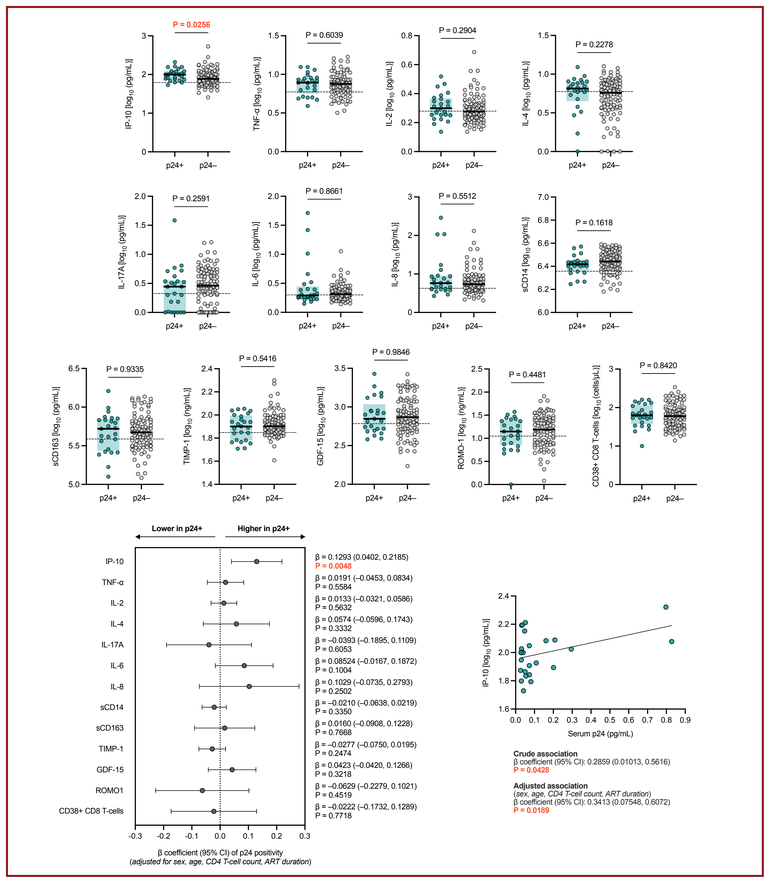


RESULTS III

By setting the p24 positivity cut-off at 0.025 pg/mL based on the mean+3SD of controls, **25 (20.8%) PWH had detectable p24**.

When assessing inflammaging markers in PWH according to p24 detectability, **p24+ PWH showed significantly higher IP-10 levels**. Accordingly, **soluble p24 was positively associated with IP-10** at both univariable and multivariable (adjusted for sex, age, CD4 T-cell count, ART duration) regression analysis.





CONCLUSIONS

Despite long-term suppressive ART, **ultra-low level soluble p24** is detectable in **~20% PWH** and associated with **higher circulating IP-10**, a pro-inflammatory chemokine involved in the recruitment of innate and adaptive immune cells into sites of inflammation. Given the positive **association between IP-10 and VACS Index 2.0**, a measure of physiologic frailty and risk of death, these data suggest that **p24-driven inflammation may affect the risk of SNAEs and mortality** in virologically-suppressed PWH.

ADDITIONAL KEY INFORMATION

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