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ORIGINAL RESEARCH

Elevated Plasma GDF-15 Levels Are Associated with Aging, Multimorbidity, and Tobacco Exposure in People with HIV

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ABSTRACT

Introduction: Aging in people with HIV (PWH) is accompanied by an increased burden of multimorbidity and persistent inflammation. Identifying biomarkers that reflect comorbidity risk can help improve long-term care. This study evaluated the association of multimorbidity with GDF-15, sICAM-1, sVCAM-1, and sP-selectin in PWH.

Methods: A cross-sectional study was performed in two cohorts of adults receiving antiretroviral therapy: a discovery cohort ($n=74$) and a validation cohort (Spanish CoRIS network) ($n=150$). Median age was 53 years in both cohorts (IQR 44–60 and 45–58), and women represented 19 (25.7%) and 75 (50.0%), respectively. Multimorbidity was defined as ≥ 2 comorbidities, including but not limited to cardiovascular, metabolic, renal, and non-AIDS-defining cancers. Plasma GDF-15, sICAM-1, sVCAM-1, and sP-selectin were quantified by multiplex immunoassay. Associations with log-transformed GDF-15 were assessed using multivariable linear

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regression including age-multimorbidity ordinal categories, tobacco smoking, and CD4+ nadir.
***Results*:** Multimorbidity prevalence was 48.6% (36) in the hospital cohort and 54.7% (82) in CoRIS. In both cohorts, participants with multimorbidity had significantly higher GDF-15 levels (hospital: 771.5 vs. 390.0 pg/ml; CoRIS: 485.2 vs. 360.1 pg/ml; both $p<0.001$). In the hospital cohort, smoking and age-multimorbidity were independently associated with elevated GDF-15, with 26.1% and 16.0% increases per category, respectively ($p<0.05$). These associations were confirmed in CoRIS, with 5.44% and 19.0% increases ($p<0.01$). CD4+ nadir showed no significant association with GDF-15. No significant associations were observed between multimorbidity and sICAM-1, sVCAM-1, or sP-selectin (all $p>0.05$).
***Conclusions*:** Elevated GDF-15 was consistently associated with multimorbidity in PWH, primarily driven by aging and tobacco smoking. GDF-15 appears to reflect a broader state of multisystem physiological stress than traditional endothelial activation markers, supporting its utility as a biomarker to identify PWH at higher risk of age-related comorbidities and to monitor the impact of modifiable risk factors in clinical care.

Keywords: Aging; Biomarkers; GDF-15; HIV; Multimorbidity

Key Summary Points

Why carry out this study?

People with HIV (PWH) experience earlier multimorbidity and frailty than HIV-negative individuals, but the mechanisms of accelerated aging are unclear.

No biomarker reliably predicts non-AIDS-related multimorbidity in PWH, limiting early detection and prevention.

This study assessed circulating biomarkers, including GDF-15, for associations with multimorbidity in aging PWH.

What was learned from the study?

Plasma GDF-15 levels were independently associated with age, multimorbidity, and tobacco smoking across two PWH cohorts.

GDF-15 may serve as an integrative biomarker of comorbidity burden and lifestyle factors, supporting its use in future longitudinal and intervention studies.

INTRODUCTION

Advances in antiretroviral therapy (ART) have significantly improved the life expectancy of people with HIV (PWH), approaching that of the general population [1]. Despite effective ART and immune restoration, PWH experience persistent immune activation and systemic inflammation [2–4], contributing to a higher burden of comorbidities occurring more frequently and at younger ages than in HIV-negative individuals [4, 5]. Frailty and multimorbidity are common in older PWH, though mechanisms of accelerated aging remain unclear [6–9].

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Biomarkers offer insight into comorbidity development. Inflammatory markers have been linked to higher risks of cardiovascular, pulmonary, and mental health disorders [2, 4, 10–12], while endothelial dysfunction markers, including soluble vascular cell adhesion molecule-1 (sVCAM-1), intercellular adhesion molecule-1 (sICAM-1), and sP-selectin, are associated with cardiovascular risk [12–15]. Metabolic biomarkers, such as growth differentiation factor-15 (GDF-15), correlate positively with age, negatively with body mass and LDL cholesterol, and associate with coronary plaque [16]. However, no biomarker consistently predicts non-AIDS-related multimorbidity in PWH. We focused on markers of endothelial injury and related pathways to capture cumulative multimorbidity risk and clarify the interplay between HIV, ART, and comorbidities.

This study assessed biomarkers associated with multimorbidity in an aging cohort of PWH from the Biobank Infectious Diseases Cohort (B.0000802), including sVCAM-1, sICAM-1, sP-selectin, and GDF-15, and validated the findings in 150 PWH from the Spanish HIV Research Network Cohort (CoRIS). Identifying such biomarkers may inform targeted interventions and support clinical strategies to improve long-term outcomes in aging PWH.

METHODS

Study Design and Participants

This cross-sectional study aimed to identify circulating biomarkers associated with multimorbidity in PWH. The initial analysis was conducted in the Infectious Diseases Cohort from the Galicia Sur Health Research Institute Biobank (IISGS), including PWH receiving care at Álvaro Cunqueiro Hospital (Vigo, Spain). The IISGS Biobank is a biomedical research platform authorized by the Regional Ministry of Health on July 17, 2013, and registered in the National Biobank Registry (B.0000802) [17].

Findings were validated in an independent, gender-balanced cohort of 150 PWH from the Spanish HIV Research Network Cohort (CoRIS). CoRIS is an open, prospective, multicenter cohort of adult subjects with confirmed HIV infection, naïve to ART at study entry, recruited in 47 centers from 14 of 17 Autonomous Regions in Spain from 2004 onwards. Data follow the HIV Cohorts Data Exchange Protocol (HICDEP) (details at https://hicdep.org/) and strict annual quality controls. The CoRIS database collects baseline and follow-up socio-demographic, immunological, and clinical data. Patients are followed periodically [18].

Eligibility criteria for both cohorts included adults (≥ 18 years) with a confirmed HIV diagnosis, on stable ART ≥ 12 months, and virologically suppressed (< 50 copies/ml) for ≥ 6 months. Participants in the discovery cohort were recruited consecutively during routine clinical visits at Álvaro Cunqueiro Hospital between 2020 and 2023 and provided a blood sample for analysis. For the validation cohort, a sex-balanced sample was selected and matched to the discovery cohort by median age. Participants from the validation cohort were required to have an available stored plasma sample. Individuals were excluded if they had insufficient sample volume or missing essential clinical data. A comparator group of ten HIV-negative individuals was included from the IISGS Biobank.

Data Collection and Definitions

Demographic and clinical data were obtained from electronic medical records via REDCap. Variables included age, sex assigned at birth, country of origin, HIV acquisition mode, time since diagnosis and ART, CD4+ counts, ART regimen, and substance use (tobacco, alcohol, cocaine, heroin). Hazardous alcohol use was defined as > 28 drinks/week for men and > 17 drinks/week for women (1 drink = 10 g ethanol) [19]. Multimorbidity was defined as two or more chronic comorbidities, excluding HIV, extracted from clinical records (discovery cohort) or the non-AIDS Events registry (CoRIS) (see Table S1 in the electronic supplementary material for details). Blood samples were collected in EDTA tubes following standard clinical protocols. After venipuncture, samples were processed within 2 h by centrifugation, plasma separation, and

aliquoting. All aliquots were stored at −80 °C until batch testing.

Biomarker Quantification

Plasma concentrations of sVCAM-1, sICAM-1, sP-selectin, and GDF-15 were quantified using a multiplex bead-based immunoassay (MILLIPLEX® Cardiovascular Disease Panel 2; Merck EMD Millipore). GDF-15 levels were independently quantified in the validation cohort (CoRIS cohort) using the Simplex ProcartaPlex Human GDF-15 Panel (EPX010-12258-901; Thermo Fisher Scientific). Measurements were performed in duplicate, and the mean value was used; data with a coefficient of variation > 20% were excluded.

Data Analysis

Categorical variables are presented as frequencies and percentages. Normally distributed continuous variables are expressed as mean and standard deviation (SD), while non-normally distributed variables are expressed as median and interquartile range (IQR). Group comparisons used χ^2, *t* test, or Mann–Whitney *U* test, as appropriate. Spearman's correlation assessed associations, after verifying the absence of a normal distribution. Multiple linear regression identified factors associated with GDF-15; the variable was natural log-transformed. To address multicollinearity between age and multimorbidity, a composite ordinal variable was created: (0) < 50 years without multimorbidity, (1) < 50 years with multimorbidity, (2) ≥ 50 years without multimorbidity, (3) ≥ 50 years with multimorbidity. Regression coefficients (β) were interpreted as percentage change: % Change = $100 \times (e^{\beta-1})$. Analyses were performed with IBM SPSS Statistics, $p < 0.05$ was considered significant.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and all applicable regulatory requirements. The study protocol for the discovery cohort was reviewed and approved by the Ethics Committee of Galicia (CEIm-G; Ref: 2024/315). The CoRIS cohort was approved by the Research Ethic Committee of the Gregorio Marañón Hospital. Written informed consent was obtained from all participants prior to enrollment. Biobank samples and associated data were processed following standardized governance procedures and in full compliance with national legislation on biomedical research and personal data protection. All datasets were pseudonymized before analysis, ensuring the protection of participant confidentiality and data integrity.

RESULTS

Biomarkers Associated with Multimorbidity in PWH: Infectious Disease Cohort

A total of 74 PWH were included from the Infectious Diseases Cohort. The median age was 53 (44–60) years, with two-thirds of participants (49, 66.2%) aged ≥ 50 years. Most were men (55, 74.3%) and of Spanish origin (62, 83.8%) (Table 1). Multimorbidity was observed in nearly half of the participants (36, 48.6%), with details on the types of comorbidities listed in Table 2. Participants with multimorbidity were older and exhibited lower CD4 nadir values compared with those without multimorbidity (Supplementary Table S2). Demographic and clinical characteristics are summarized in Table 1.

Among the biomarkers analyzed, GDF-15 levels were significantly higher in participants with multimorbidity [771.5 (562.8–1187.9) pg/ml] compared to those without [390.0 (308.5–532.5) pg/ml]; $p < 0.001$. This was the only biomarker showing a statistically significant association with multimorbidity. Higher concentrations of sICAM-1, sP-selectin, and sVCAM-1 were observed in participants with multimorbidity, but not statistically significant (Fig. 1). GDF-15 levels showed a moderate positive association with sICAM-1 ($\rho = 0.494$, $p < 0.001$), a weak-to-moderate association with sVCAM-1 ($\rho = 0.315$, $p = 0.008$), and a weak association with sP-selectin ($\rho = 0.250$, $p = 0.041$), as assessed by Spearman's rank correlation. Full biomarker data

Table 1 Socio-demographics and clinical characteristics of the study population

	Infectious Disease Cohort, *N* = 74, *n* (%)	**CoRIS cohort *N* = 150, *n* (%)**
Age (years)	53 (44–60)	53 (45–58)
18–30	5 (6.8)	0 (0.0)
31–49	20 (27.0)	61 (40.7)
≥ 50	49 (66.2)	89 (59.3)
Sex		
Male	55 (74.3)	75 (50.0)
Female	19 (25.7)	75 (50.0)
Origin		
Spanish	62 (83.8)	106 (70.7)
Latin America	8 (10.8)	30 (20.0)
African	2 (2.7)	3 (2.0)
Other	2 (2.7)	11 (7.3)
Alcohol consumption		
Current high-risk alcohol use	24 (32.4)	7 (4.7)
Former high-risk alcohol use	10 (13.5)	6 (4.0)
Unknown	1 (1.4)	119 (79.3)
No high-risk alcohol use	39 (52.7)	18 (12.0)
Tobacco use		
Current smoker	36 (48.6)	55 (36.7)
Former smoker	14 (18.9)	25 (16.7)
Never smoker	24 (32.4)	58 (38.7)
Unknown	0 (0.0)	12 (8.0)
Heroin use		
Current heroin user	1 (1.4)	–
Previous heroin user	21 (28.4)	–
No heroin use	52 (70.3)	–
Cocaine use		
Current cocaine use	3 (4.1)	–
Previous cocaine use	21 (28.4)	–
No cocaine use	50 (67.6)	–

Table 1 continued

	Infectious Disease Cohort, *N* = 74, *n* (%)	**CoRIS cohort *N* = 150, *n* (%)**
Injected drugs		
Current injected drugs user	–	1 (0.7)
Previous injected drug user	–	1 (0.7)
No injected drugs use	–	89 (59.3)
Unknown	–	91 (60.7)
Time since HIV diagnosis (years)	15.1 (7.1–27.1)	12.5 (9.2–16.0)
< 10	18 (30.5)	45 (30.0)
10–19	16 (27.1)	89 (59.3)
> 20	25 (42.4)	16 (10.7)
Time on ART (years)	12.0 (6.9–24.9)	10.5 (± 3.59)
ART		
INSTI-based regimen	70 (94.6)	94 (62.7)
BIC/FTC/TAF	12 (16.2)	27 (18.0)
DTG/3TC	37 (50.0)	37 (24.7)
DTG/RPV	16 (21.6)	7 (4.7)
Other INSTI-based regimen	5 (6.8)	5 (3.3)
PI-based regimen	1 (1.4)	10 (6.7)
NRTI + NNRTI regimen	3 (4.1)	25 (16.7)
Unknown	0 (0.0)	21 (14.0)
HIV transmission category		
Men who have sex with men	29 (39.2)	42 (28.0)
Heterosexual	23 (31.1)	76 (50.7)
Intravenous drug user	21 (28.4)	21 (14.0)
Blood product transfusion	0 (0.0)	2 (1.3)
Unknown	1 (1.4)	9 (6.0)
CD4+ lymphocyte nadir (cells/μl)	234 (102–385)	246 (107–378)
RNA HIV load at diagnosis (copies/ml)	65,950 (13,687–366,500)	52,871 (16,925–171,601)

ART antiretroviral therapy, *INSTI* integrase strand transfer inhibitor, *BIC/FTC/TAF* bictegravir/emtricitabine/tenofovir alafenamide, *DTG/3TC* dolutegravir/lamivudine, *DTG/RPV* dolutegravir/rilpivirine, *PI* protease inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor

"–" indicates data not available

Table 2 Comorbidity-related characteristics of the study population

	Infectious disease cohort ***N*** **= 74,** ***n*** **(%)**	**CoRIS cohort** ***N*** **= 150,** ***n*** **(%)**
Cardiovascular diseases		
Arterial hypertension	17 (23.0)	42 (28.0)
Ischemic heart disease	2 (2.7)	8 (5.3)
Congestive heart failure	1 (1.4)	4 (2.1)
Peripheral arterial disease	3 (4.1)	1 (0.5)
Asymptomatic coronary artery disease	–	1 (0.5)
Cerebrovascular disease		
Stroke/ cerebrovascular events	5 (6.8)	6 (3.2)
Asymptomatic cerebrovascular disease	–	2 (1.1)
Metabolic disorders		
Diabetes mellitus	5 (6.8)	28 (14.8)
Dyslipidemia	21 (28.4)	43 (28.7)
Bone disorders		
Osteopenia	28 (37.8)	–
Osteoporosis	11 (14.9)	–
Liver diseases		
Hepatitis B virus (HBV) infection		
Chronic active HBV infection	1 (1.4)	6 (4.0)
Past HBV infection	26 (35.1)	31 (20.7)
Hepatitis C virus (HCV) infection		
Chronic active HCV infection	0 (0.0)	9 (6.0)
Past HCV infection	22 (29.7)	27 (18.0)
Cirrhosis	–	11 (5.8)
End-stage liver disease	–	6 (3.2)
Renal diseases		
End-stage renal disease	–	7 (3.7)
Tubulopathies/Fanconi's syndrome	–	2 (1.1)
Non-AIDS-defining neoplasm	6 (8.1)	26 (17.3)
Mental health comorbidities		
Psychosis	–	6 (3.2)
Severe depression requiring psychiatric treatment	1 (1.4)	29 (15.3)

Table 2 continued

	Infectious disease cohort $N=74$, n (%)	CoRIS cohort $N=150$, n (%)
Substance use disorders	12 (16.2)	–
Opioids	11 (14.9)	–
Others	4 (5.4)	–
Anxiety disorders	10 (13.5)	–
Sleep disorders	2 (2.7)	–
Other mental health disorders	4 (5.4)	–
Others comorbidities		
Chronic obstructive pulmonary disease	5 (6.8)	–
Avascular necrosis	–	2 (1.1)

"–" indicates data not available

stratified by multimorbidity status are presented in Table 3.

GDF-15 concentrations showed a moderate positive correlation with age ($\rho=0.457$, $p<0.001$, $n=71$), as well as with the time since HIV diagnosis ($\rho=0.337$, $p=0.010$, $n=57$) and duration on ART ($\rho=0.374$, $p=0.005$, $n=55$). A negative correlation was observed with nadir CD4+ T-cell count ($\rho=-0.330$, $p=0.006$, $n=69$). No significant differences in GDF-15 levels were found according to baseline HIV viral load before ART initiation or by type of ART regimen (Supplementary Table S3).

Lifestyle factors were also associated with GDF-15 concentrations. Median levels were significantly lower in never smokers (410.2 pg/ml, $n=24$) than in former smokers (757.6 pg/ml, $n=14$; $p=0.016$) and current smokers (682.7 pg/ml, $n=33$; $p=0.011$). Similarly, non-risk alcohol users had lower levels (452.9 pg/ml, $n=38$) than former users (894.9 pg/ml, $n=10$; $p=0.005$) and current users (549.7 pg/ml, $n=22$; $p=0.013$). Participants with a history of heroin use also had higher GDF-15 levels (1050.1 pg/ml, $n=20$) compared to those without (443.8 pg/ml, $n=50$; $p<0.001$). Elevated levels were further observed among individuals with dyslipidemia, bone disorders, and past HCV infection (Supplementary Table S4). Figure 2 summarizes the behavioral, host, and HIV-related factors associated with elevated GDF-15 levels.

A multiple linear regression model was constructed to assess the associations of nadir CD4+ count, tobacco smoking, and the age-multimorbidity composite variable with GDF-15 levels (log-transformed, lnGDF-15). This analysis identified several significant predictors (Table 4). A significant association was observed for tobacco smoking. Each stepwise increase in the smoking ordinal variable was associated with a 26.1% rise in GDF-15 levels ($\beta=0.232$, $p=0.004$). Likewise, the age-multimorbidity composite variable demonstrated a strong graded association. Each stepwise increase in this category was associated with a 16.0% rise in GDF-15 levels ($\beta=0.148$, $p=0.012$). This indicates that the increase is linked to both the presence of multimorbidity within an age group and advancing to an older age category, with the effects cumulative. In contrast, nadir CD4+ count was not significantly associated with GDF-15 levels in this model.

sP-selectin levels showed a weak negative correlation with age ($\rho=-0.269$, $p=0.026$, $n=69$). No significant associations were found between sICAM-1, sVCAM-1, or sP-selectin and either time since HIV diagnosis or duration on ART. Additionally, sICAM-1 and sVCAM-1 levels did not correlate with any other clinical or

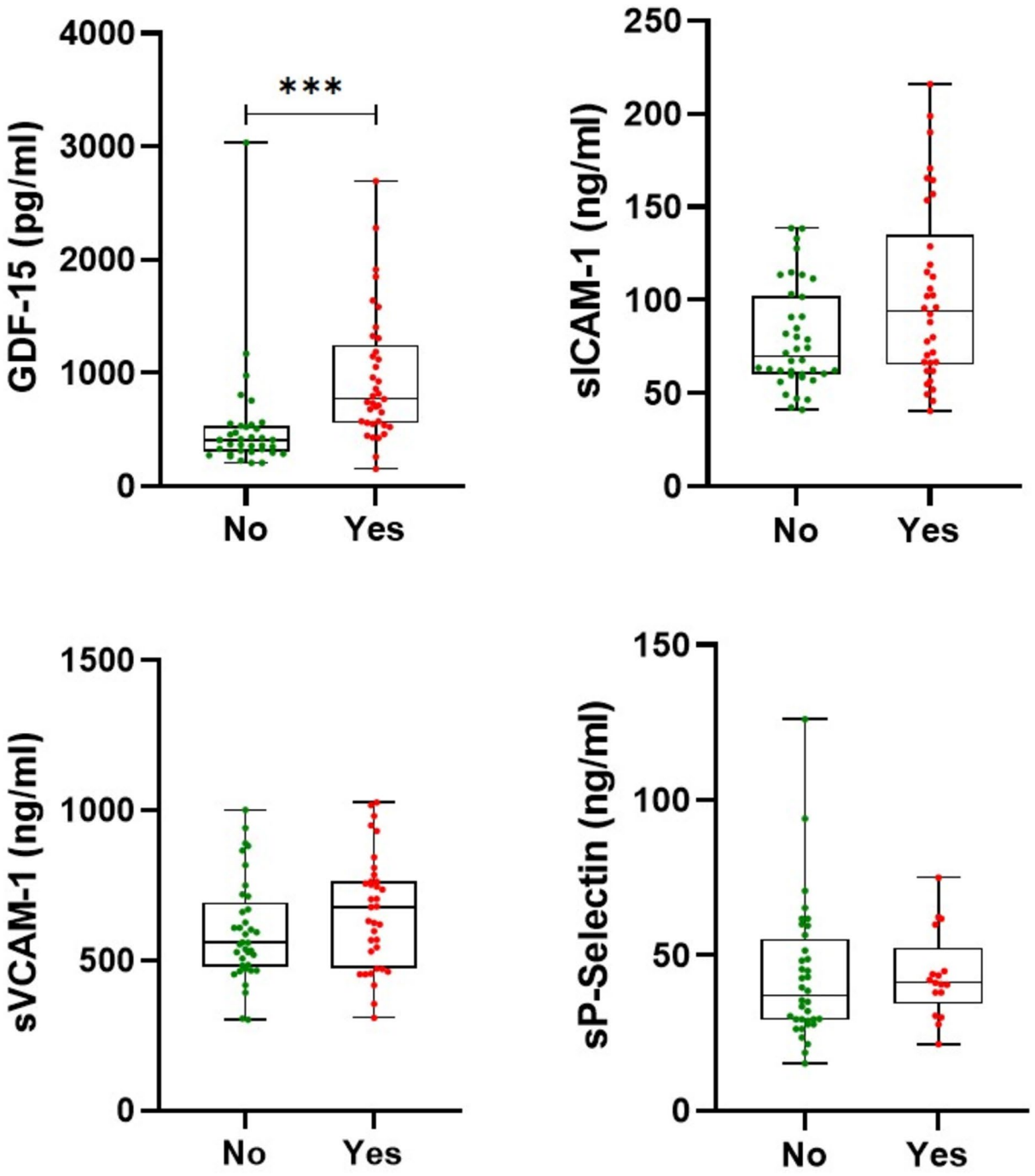

Fig. 1 Plasma levels of GDF-15, sVCAM-1, sICAM-1, and sP-selectin stratified by multimorbidity status (two or more comorbidities) in people with HIV from the Infectious Disease Cohort. [a]GDF-15: growth differentiation factor-15; [b]sICAM-1: soluble intercellular adhesion molecule-1; [c]sIVAM-1: soluble vascular cell adhesion molecule-1; [d]sP-Selectin: soluble platelet selectin. Group comparisons were performed using the Mann–Whitney *U* test or the unpaired *t* test, as appropriate

Table 3 Comparison of biomarker concentrations in people with HIV from the Infectious Disease Cohort according to multimorbidity status

	n	Total	*n*	Without multimorbidity	*n*	Multimorbidity	*p*
GDF-15 (pg/ml)	71	542.7 (361.81–862.6)	36	390.0 (308.5–532.5)	35	771.5 (562.8–1187.9)	**< 0.001**
sICAM-1 (ng/ml)	72	78.2 (61.9–113.4)	38	69.6 (60.6–102.1)	34	94.1 (65.3–135.1)	0.058
sP-Selectin ng/ml)	69	43.1 (30.3–58.2)	36	37.1 (29.1–55.3)	33	44.9 (39.1–59.3)	0.060
sVCAM-1 (ng/ml)	72	628.9 ± 180.9	37	590.2 ± 169.3	35	669.8 ± 186.0	0.062

Bold values indicate statistical significance ($p < 0.05$)

Data are presented as median and interquartile range (IQR) for non-normally distributed biomarkers, and mean ± standard deviation (SD) for normally distributed biomarkers. Group comparisons were performed using the Mann–Whitney *U* test or the unpaired *t* test, as appropriate. All values are rounded to one decimal place

GDF-15 growth differentiation factor-15, *sICAM-1* soluble intercellular adhesion molecule-1, *sP-Selectin* soluble platelet selectin, *sVCAM-1* soluble vascular cell adhesion molecule-1.

demographic variables assessed (Supplementary Table S3).

Validation of GDF-15 Associations in the CoRIS Cohort

We analyzed data from 150 PWH enrolled in the CoRIS cohort. The median age was 53 (45–58) years, and the sex distribution was balanced (75, 50.0% women), allowing for the exploration of associations in a more demographically diverse population. Multimorbidity was present in 82 (54.7%) of participants (see Table 2 for the distribution of comorbidities). Participants with multimorbidity were older compared with those without multimorbidity (Supplementary Table S5). Clinical and demographic characteristics are detailed in Table 1.

As observed in the primary cohort, participants with multimorbidity had significantly higher GDF-15 levels [485.2 (352.3–759.2) pg/ml] compared to those without multimorbidity [360.1 (263.7–523.1) pg/ml]; $p = 0.001$. In bivariate analyses, GDF-15 concentrations demonstrated a moderate positive correlation with age ($\rho = 0.364$; $p < 0.001$) and a weaker but statistically significant correlation with time since HIV diagnosis ($\rho = 0.201$; $p = 0.014$). No significant differences in GDF-15 levels were observed by sex or ART regimen. Regarding lifestyle factors, current smokers exhibited higher GDF-15 levels than never smokers (544.3 vs. 397.9 pg/ml; $p = 0.003$), consistent with the trend observed in the Infectious Disease Cohort. In contrast, GDF-15 levels were not significantly associated with alcohol consumption or history of injection drug use. Similarly, no differences were observed according to ART duration, baseline HIV RNA, or CD4+ nadir.

Analysis of individual comorbidities revealed significantly elevated GDF-15 levels in PWH with arterial hypertension [483.7 (357.5–872.1) vs. 393.0 (254.4–521.9) pg/ml]; $p = 0.032$, prior HBV infection [486.9 (406.9–863.1) vs. 403.7 (262.9–587.1) pg/ml]; $p = 0.002$), and non-AIDS-defining neoplasms [596.7 (431.7–865.6) vs. 410.5 (276.4–590.9) pg/ml]; $p = 0.002$. While no statistically significant differences were found for diabetes mellitus, dyslipidemia, or past HCV infection, a non-significant trend toward higher GDF-15 levels was noted in the latter (Supplementary Table S6). Similarly, GDF-15 levels showed no significant difference between metformin users and non-users (538.6 pg/ml vs. 734.0 pg/ml, respectively; $p = 0.369$), although the sample of metformin users was small ($n = 3$).

A multiple linear regression model, adjusted for the same covariates, was used to validate the significant associations in the independent CoRIS cohort. The results consistently confirmed the initial findings. The ordinal tobacco

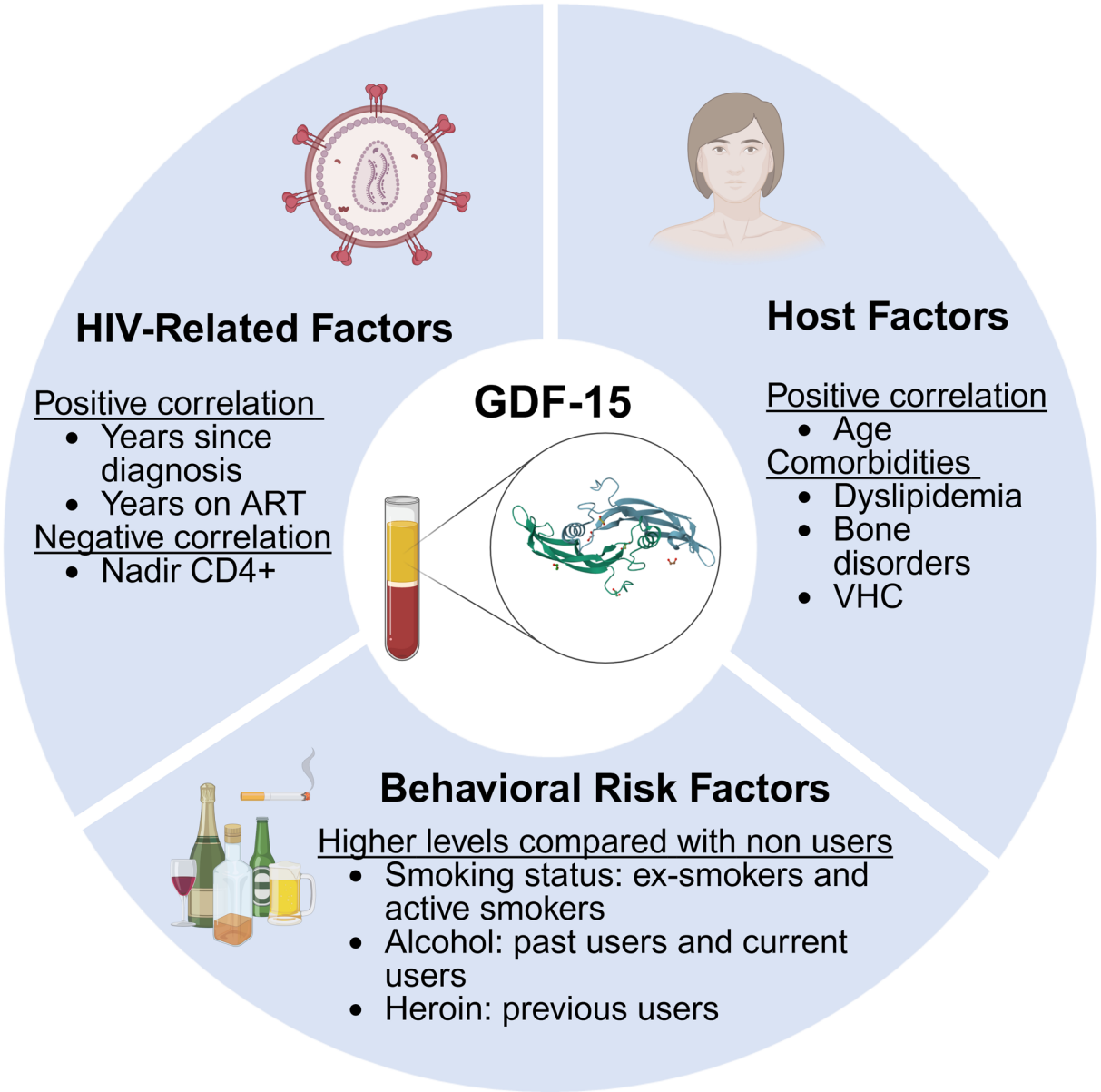

Fig. 2 Factors associated with elevated GDF-15 levels in PWH. Summary of behavioral, host, and HIV-related factors associated with elevated GDF-15 levels in PWH. GDF-15 concentrations were positively correlated with age, time since HIV diagnosis, and duration of ART, and negatively correlated with nadir CD4+ count. Elevated levels were also observed among individuals with certain comorbidities and substance use history. *GDF-15* growth differentiation factor-15, *ART* antiretroviral therapy. The molecular structure was adapted from the Protein Data Bank in Europe, entry 5VT2 (https://doi.org/10.2210/pdb5vt2/pdb), originally described in Science Translational Medicine (https://doi.org/10.1126/scitranslmed.aan8732), and is licensed under CC BY 4.0. Schematic elements were created in BioRender. López, A. (2025). https://BioRender.com/whmkecj

smoking variable remained a significant predictor, with each stepwise increase associated with a 5.44% rise in GDF-15 levels (β = 0.053, $p = 0.007$). The age-multimorbidity composite variable also demonstrated a strong and significant graded association, with each stepwise increase

Table 4 Multiple linear regression of factors associated with log (GDF-15) levels

	β (95% CI)	p	% Change in GDF-15	R^2
Infectious Disease Cohort ($N=74$)				
Tobacco[a]	0.232 (0.079–0.385)	**0.004**	26.1	0.259
CD4+ nadir	0.000 (− 0.001 to 0.000)	0.136	− 0.02	
Age-multimorbidity[b]	0.148 (0.033–0.262)	**0.012**	16.0	
CoRIS cohort ($N=150$)				
Tobacco[a]	0.053 (0.041–0.249)	**0.007**	5.44	0.148
CD4+ nadir	0.000 (0.000–0.001)	0.528	0.00	
Age-multimorbidity[b]	0.174 (0.070–0.278)	**0.001**	19.0	

Bold values indicate statistical significance ($p < 0.05$)

Definition of categorical variables: [a]Tobacco: 1 = Never-smoker, 2 = Former-smoker, 3 = Current-smoker. [b]Age-multimorbidity: 1 = < 50 years without multimorbidity, 2 = < 50 years with multimorbidity, 3 = ≥ 50 years without multimorbidity, 4 = ≥ 50 years with multimorbidity. The percentage change in GDF-15 was calculated as $100 \times (e^{\beta-1})$, where β is the coefficient

corresponding to a 19.0% increase in GDF-15 levels (β = 0.174, $p = 0.001$). As in the primary cohort, nadir CD4+ count was not a significant predictor (Table 4).

DISCUSSION

This study provides a detailed analysis of the factors associated with aging and multimorbidity in PWH, leveraging the complementary strengths of a deeply defined local clinical cohort and a nationally representative validation cohort from CoRIS. Our main finding is the robust association of plasma GDF-15 with aging, multimorbidity, and modifiable lifestyle factors, particularly tobacco smoking, across both cohorts. This positions GDF-15 as an integrative biomarker of comorbidity burden and aging. Beyond its cross-sectional associations, our findings highlight the potential of GDF-15 as a clinically meaningful biomarker for future applications, including early detection of multimorbidity, identification of individuals at higher risk of comorbidity clustering, and longitudinal monitoring of lifestyle-related inflammation such as smoking-related biological stress.

GDF-15 levels were most strongly associated with a composite age-multimorbidity variable, with stepwise increases predicting 16–19% higher levels, consistent with its role as a marker of cellular stress, inflammation, and mitochondrial dysfunction [16, 20]. Tobacco smoking and alcohol consumption were evaluated as lifestyle exposures and interpreted separately. Tobacco smoking emerged as an independent, dose-dependent determinant of elevated GDF-15, and this association persisted after adjustment for age and nadir CD4+, highlighting a modifiable target for intervention. Recent data indicate that tobacco exposure strongly induces GDF-15 expression, which may mediate smoking-related changes in energy balance and body weight [21]. This suggests that smoking cessation could directly mitigate this accelerated aging phenotype, offering a clear, actionable intervention for clinicians and patients. Other lifestyle factors, including hazardous alcohol and heroin use, were also associated with higher GDF-15, though further studies are needed to clarify independent effects. High-risk alcohol consumption has been shown in older populations to correlate with elevated GDF-15 [22]. However, data are lacking for heroin or other substance use disorders, so whether they independently increase

GDF-15 in PWH beyond the effects of co-factors (e.g., hepatitis, liver damage, nutrition) remains to be determined. Together, these findings support the growing recognition that tobacco and alcohol use contribute to chronic inflammation, highlighting their relevance as potentially modifiable drivers of biological aging in PWH. GDF-15 may serve not only as a biomarker of risk but also as a dynamic indicator of response to interventions such as exercise, which has been shown to reduce its levels in the general population [23]. Multicomponent exercise programs have been shown to improve physical function in older adults with HIV [24], and may represent an effective strategy to reduce GDF-15 levels, enhance muscle strength, and mitigate inflammation. In contrast, nadir CD4 + count and current ART regimen were not associated with GDF-15 in adjusted analysis. While past immune damage may have contributed to comorbidity, current health status and behaviors appear to be stronger drivers of the biological aging processes reflected by GDF-15. INSTI-based regimens may exert a less pronounced effect on this pathway of physiological stress, consistent with their more favorable inflammatory and mitochondrial toxicity profiles [25], contrasting with findings from studies of older ART regimens [26]. Nevertheless, ART-related effects on GDF-15 remain biologically plausible, as different drug classes such as PIs and INSTIs may differentially influence mitochondrial stress pathways. Because our analyses were limited to the current regimen and did not capture cumulative historical exposure, drug-specific effects cannot be ruled out and warrant investigation in longitudinal datasets. In addition, GDF-15 is known to be pharmacologically inducible, particularly by metformin [27, 28]. We therefore assessed metformin use within the Infectious Disease Cohort and observed no significant differences in GDF-15 levels between metformin users and non-users, although incomplete medication data in the CoRIS cohort limits a full evaluation of this potential confounding effect.

Traditional endothelial markers (sICAM-1, sVCAM-1, sP-selectin), although established indicators of endothelial activation and cardiovascular risk in PWH[12–15], were not associated with multimorbidity, possibly due to comorbidity heterogeneity or limited cardiovascular disease in our cohort. Interestingly, this finding suggests that GDF-15 captures a broader aspect of systemic aging that extends beyond vascular inflammation. This is supported by emerging literature linking GDF-15 to end-organ damage in diverse systems, including the central nervous system (e.g., neurocognitive impairment [29]) and the liver (e.g., steatosis and fibrosis [30]). Therefore, GDF-15 appears to be a more holistic biomarker of multisystem physiological stress. This interpretation is consistent with the known biology of GDF-15, which is weakly expressed under physiological conditions but strongly induced in response to inflammation and tissue injury [27, 31]. Its induction involves several signaling pathways, including the integrated stress response, which is activated by diverse stress stimuli such as nutrient deprivation and infection[32]. Circulating levels of GDF-15 reflect both acute and chronic cellular stress, which have been associated with aging and disease[27]. Under pathological conditions, GDF-15 can be produced by multiple cardiovascular and non-cardiovascular cell types[27], providing a mechanistic rationale for its elevation in individuals with multiple comorbidities. A key strength of this study is the dual-cohort design, which combines deep clinical phenotyping with robust epidemiological validation. The use of a validated, graded composite variable for age and multimorbidity further strengthens our approach by effectively modeling cumulative comorbidity burden. The cross-sectional nature of our analysis represents a key limitation, as it precludes establishing causal relationships between GDF-15 elevation and multimorbidity. Moreover, the persistence, severity, and treatment status of comorbidities could not be fully captured, which may lead to exposure misclassification. Consequently, our findings should be interpreted as associations reflecting comorbidity burden at the time of assessment. Additional limitations include differences in data collection methods between cohorts, particularly for substance use, which limit direct comparisons in some domains. Multimorbidity was defined as the presence of two or more comorbidities; consequently, individuals with zero or one comorbidity were grouped

as the reference category. Finer stratification was not feasible due to the limited sample size. Medication exposure, including metformin or ART regimen, could not be systematically evaluated. Finally, while we identified strong associations with modifiable factors like smoking, the specific biological mechanisms linking these exposures to GDF-15 elevation warrant further investigation. Longitudinal studies will be required to determine whether elevated GDF-15 reflects cumulative comorbidity burden over time, anticipates the development of multimorbidity, or plays a causal role in aging-related multimorbidity in PWH.

Our findings position GDF-15 as a versatile biomarker with dual utility. Its strong association with aging and multimorbidity suggests its value in risk stratification, potentially helping clinicians identify individuals at the highest risk for accelerated aging. Perhaps more compellingly, its graded response to modifiable risk factors, especially tobacco smoking, reveals its potential role as a quantifiable, biological measure of success in response to lifestyle modifications. This offers a novel tool to evaluate the effectiveness of interventions aimed at promoting healthy aging in PWH.

CONCLUSIONS

In conclusion, our study demonstrates that elevated GDF-15 levels in PWH are strongly associated with older age, multimorbidity, and modifiable lifestyle factors, particularly tobacco smoking. Among the biomarkers analyzed, GDF-15 showed the most consistent association with multimorbidity across both cohorts, whereas traditional endothelial markers (sVCAM-1, sICAM-1, and sP-selectin) did not. These findings highlight the potential future role of GDF-15 as an early indicator of multimorbidity risk and a candidate biomarker for monitoring lifestyle-related inflammation in aging PWH. Further longitudinal research is warranted to confirm its prognostic utility and guide its integration into routine clinical practice and risk-stratification frameworks.

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Data Availability. The individual-level data supporting this study cannot be publicly shared due to privacy restrictions imposed by the ethical approval. Anonymized data are available from the corresponding author (eva.poveda.lopez@sergas.es) upon reasonable request, pending approval from the steering committee and a signed data sharing agreement. Summary data are included in the manuscript and its supplementary files.

Declarations

Conflict of Interest. Aida López López has received support from Gilead to attend the 2024 Spanish National HIV Congress (GeSIDA). Alexandre Pérez González has received fees from Gilead Sciences and ViiV Healthcare outside the submitted work, and support from Gilead Sciences to attend the 2023 Spanish National HIV Congress (GeSIDA). Otilia Bisbal Pardo has received speaker honoraria from Gilead, ViiV Healthcare, and MSD, and has received congress funding from Gilead. Jacobo Alonso Domínguez, Inés Martínez Barros, Antonio Ocampo, Luis Morano, Beatriz Calderón Cruz, Noemí Martínez López de Castro, Mayte Pérez-Olmeda, Jorge Sánchez-Villegas, Víctor Asensi, Marta Montero-Alonso, Rafael Rodríguez-Rosado Martínez-Echevarría, and Eva Poveda have nothing to disclose.

Ethical Approval. This study was conducted in accordance with the principles of the Declaration of Helsinki and all applicable regulatory requirements. The study protocol for the discovery cohort was reviewed and approved by the Ethics Committee of Galicia (CEIm-G; Ref: 2024/315). The CoRIS cohort was approved by the Research Ethics Committee of Gregorio Marañón Hospital. Written informed consent was obtained from all participants prior to enrollment. Biobank samples and associated data were processed following standardized governance procedures and in full compliance with national legislation on biomedical research and personal data protection. All datasets were pseudonymized before analysis, ensuring the protection of participant confidentiality and data integrity.

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REFERENCES

1. Trickey A, Sabin CA, Burkholder G, Crane H, d'Arminio Monforte A, Egger M, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. Lancet HIV. 2023;10:e295-307. https://doi.org/10.1016/S2352-3018(23)00028-0.

2. Zicari S, Sessa L, Cotugno N, Ruggiero A, Morrocchi E, Concato C, et al. Immune activation, inflammation, and non-AIDS co-morbidities in HIV-infected patients under long-term ART. Viruses. 2019;11:200. https://doi.org/10.3390/v11030200.

3. Poveda E, Tabernilla A, Fitzgerald W, Salgado-Barreira Á, Grandal M, Pérez A, et al. Massive release of CD9+ microvesicles in human immunodeficiency virus infection, regardless of virologic control. J Infect Dis. 2022;225:1040–9. https://doi.org/10.1093/infdis/jiaa375.

4. Babu H, Ambikan AT, Gabriel EE, Svensson Akusjärvi S, Palaniappan AN, Sundaraj V, et al. Systemic inflammation and the increased risk of inflamm-aging and age-associated diseases in people living with HIV on long term suppressive antiretroviral therapy. Front Immunol. 2019. https://doi.org/10.3389/fimmu.2019.01965.

5. Van Epps P, Kalayjian RC. Human immunodeficiency virus and aging in the era of effective antiretroviral therapy. Infect Dis Clin North Am. 2017;31:791–810. https://doi.org/10.1016/j.idc.2017.07.007.

6. Womack JA, Murphy TE, Leo-Summers L, Bates J, Jarad S, Gill TM, et al. Assessing the contributions of modifiable risk factors to serious falls and fragility fractures among older persons living with HIV. J Am Geriatr Soc. 2023;71:1891–901. https://doi.org/10.1111/jgs.18304.

7. Collins LF, Palella FJ, Mehta CC, Holloway J, Stosor V, Lake JE, et al. Aging-related comorbidity burden among women and men with or at-risk for HIV in the US, 2008-2019. JAMA Netw Open. 2023;6:e2327584. https://doi.org/10.1001/jamanetworkopen.2023.27584.

8. Guaraldi G, Milic J, Mussini C. Aging with HIV. Curr HIV AIDS Rep. 2019;16:475–81. https://doi.org/10.1007/s11904-019-00464-3.

9. Thomas A, Hoy JF. Challenges of HIV management in an aging population. Curr HIV AIDS Rep. 2025;22:8. https://doi.org/10.1007/s11904-024-00718-9.

10. Mudra Rakshasa-Loots A, Bakewell N, Sharp DJ, Gisslén M, Zetterberg H, Alagaratnam J, et al. Biomarkers of central and peripheral inflammation mediate the association between HIV and depressive symptoms. Transl Psychiatry. 2023;13:190. https://doi.org/10.1038/s41398-023-02489-0.

11. Freeman ML, Hossain MB, Burrowes SAB, Jeudy J, Bui R, Moisi D, et al. Association of soluble markers of inflammation with peri-coronary artery inflammation in people with and without HIV infection and without cardiovascular disease. Open Forum Infect Dis. 2023. https://doi.org/10.1093/ofid/ofad328.

12. Sukumaran L, Kunisaki KM, Bakewell N, Winston A, Mallon PWG, Doyle N, et al. Association between inflammatory biomarker profiles and cardiovascular risk in individuals with and without HIV. AIDS. 2023;37:595–603. https://doi.org/10.1097/QAD.0000000000003462.

13. Kanmogne GD. HIV infection, antiretroviral drugs, and the vascular endothelium. Cells. 2024;13:672. https://doi.org/10.3390/cells13080672.

14. Perkins MV, Joseph SB, Dittmer DP, Mackman N. Cardiovascular disease and thrombosis in HIV infection. Arterioscler Thromb Vasc Biol. 2023;43:175–91. https://doi.org/10.1161/ATVBAHA.122.318232.

15. De Luca A, de Gaetano Donati K, Colafigli M, Cozzi-Lepri A, De Curtis A, Gori A, et al. The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case–control study. BMC Infect Dis. 2013;13:414. https://doi.org/10.1186/1471-2334-13-414.

16. Wang L, Zhao J, Schank M, Hill AC, Banik P, Zhang Y, et al. Circulating GDF-15: a biomarker for metabolic dysregulation and aging in people living with HIV. Front Aging. 2024. https://doi.org/10.3389/fragi.2024.1414866.

17. Instituto de Investigación Sanitaria Galicia Sur. Colección Enfermedades Infecciosas. Biobanco. [cited 2025 Sep 22]. https://www.iisgaliciasur.es/home/biobanco/otras-colecciones/. Accessed 22 Sep 2025.

18. Sobrino-Vegas P, Gutiérrez F, Berenguer J, Labarga P, García F, Alejos-Ferreras B, et al. La cohorte de la red española de investigación en sida y su biobanco: organización, principales resultados y pérdidas al seguimiento. Enferm Infecc Microbiol Clin. 2011;29:645–53. https://doi.org/10.1016/j.eimc.2011.06.002.

19. Ministerio de Sanidad. Límites de Consumo de Bajo Riesgo de Alcohol. Actualización del riesgo relacionado con los niveles de consumo de alcohol, el patrón de consumo y el tipo de bebida. Madrid; 2020. https://www.sanidad.gob.es/areas/promocionPrevencion/alcohol/documentosTecnicos/docs/Limites_Consumo_Bajo_Riesgo_Alcohol_Actualizacion.pdf. Accessed 17 Sep 2025.

20. Ueland T, Nkele I, Hoel H, Lockman S, Michelsen AE, Moshomo T, et al. Markers of extracellular matrix degradation and inflammasome activation are associated with carotid plaques in virally

suppressed people with HIV in Botswana. AIDS. 2025;39:22–30. https://doi.org/10.1097/QAD.0000000000004014.

21. Tinworth AC, Iona A, Yao P, Millwood IY, Fry H, Clarke J, et al. GDF15 and its receptors as pathways mediating smoking related weight change. EBioMedicine. 2025;117:105806. https://doi.org/10.1016/j.ebiom.2025.105806.

22. Ortolá R, García-Esquinas E, Buño-Soto A, Carballo-Casla A, Sotos-Prieto M, Banegas JR, et al. Alcohol consumption patterns and growth differentiation factor 15 among life-time drinkers aged 65+years in Spain: a cross-sectional study. Addiction. 2022;117:1647–57. https://doi.org/10.1111/add.15809.

23. Conte M, Martucci M, Mosconi G, Chiariello A, Cappuccilli M, Totti V, et al. GDF15 plasma level is inversely associated with level of physical activity and correlates with markers of inflammation and muscle weakness. Front Immunol. 2020. https://doi.org/10.3389/fimmu.2020.00915.

24. Brañas F, Díaz-Álvarez J, Fernández-Luna J, Vásquez-Brolen BD, García-Molina R, Moreno E, et al. A 12-week multicomponent exercise program enhances frailty by increasing robustness, improves physical performance, and preserves muscle mass in older adults with HIV: MOVIhNG study. Front Public Health. 2024. https://doi.org/10.3389/fpubh.2024.1373910.

25. Babu H, Sperk M, Ambikan AT, Rachel G, Viswanathan VK, Tripathy SP, et al. Plasma metabolic signature and abnormalities in HIV-infected individuals on long-term successful antiretroviral therapy. Metabolites. 2019;9:210. https://doi.org/10.3390/metabo9100210.

26. Jee A, Sernoskie SC, Uetrecht J. The role of corticosterone in nevirapine-induced idiosyncratic drug-induced liver injury. Toxicol Sci. 2024;200:146–64. https://doi.org/10.1093/toxsci/kfae054.

27. Wollert KC, Kempf T, Wallentin L. Growth differentiation factor 15 as a biomarker in cardiovascular disease. Clin Chem. 2017;63:140–51. https://doi.org/10.1373/clinchem.2016.255174.

28. Isnard S, Lin J, Fombuena B, Ouyang J, Varin TV, Richard C, et al. Repurposing metformin in nondiabetic people with HIV: influence on weight and gut microbiota. Open Forum Infect Dis. 2020. https://doi.org/10.1093/ofid/ofaa338.

29. Boustani A, Ford MK, Kulbe JR, Laird AE, Shu L, Spencer M, et al. Increased growth differentiation factor 15 levels are associated with HIV-associated neurocognitive impairment: a pilot study. Brain Sci. 2025;15:49. https://doi.org/10.3390/brainsci15010049.

30. Debroy P, Pike F, Gawrieh S, Corey KE, Hartig S, Balasubramanyam A, et al. Circulating fibroblast growth factor 21 and growth differentiation factor 15 are associated with severity of hepatic steatosis in people with HIV. HIV Med. 2025. https://doi.org/10.1111/hiv.70060.

31. Rochette L, Zeller M, Cottin Y, Vergely C. Insights into mechanisms of GDF15 and receptor GFRAL: therapeutic targets. Trends Endocrinol Metab. 2020;31:939–51. https://doi.org/10.1016/j.tem.2020.10.004.

32. Reyes J, Yap GS. Emerging roles of growth differentiation factor 15 in immunoregulation and pathogenesis. J Immunol. 2023;210:5–11. https://doi.org/10.4049/jimmunol.2200641.

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