Research paper

Persistence of monocyte activation under treatment in people followed since acute HIV-1 infection relative to participants at high or low risk of HIV infection

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1. Introduction

The introduction of antiretroviral therapy (ART) has substantially improved the life expectancy of people living with HIV (PLHIV). However, overall rates of non-AIDS morbidities and mortalities remain
Research in Context

Evidence before this study

Many studies have assessed changes in inflammatory biomarkers after antiretroviral therapy (ART) initiation and reported only partial recovery to levels close to those seen in HIV-negative people. We searched PubMed with no language restrictions until September 01, 2020 with the terms: “Inflammation” [tiab] AND (“markers” [tiab] OR “biomarkers” [tiab]) AND (“HIV-negative” OR “HIV-uninfected” [tiab]) AND (“treatment” [tiab] OR “therapy” [tiab] OR “HAART” [tiab]). This search yielded 122 items. Among them, we identified only six studies that reported comparisons between virally-suppressed and HIV-negative individuals adjusted for exposures other that HIV that contribute to systemic immune activation (e.g., smoking, alcohol, substance abuse or coinfections) and/or had enrolled an appropriate group of HIV-negative participants. We also found limited data on women, and on people treated at a low level of immunodeficiency or from acute and early HIV infection (AHI). This is particularly important when considering people diagnosed in AHI, in whom restoration to levels close to HIV-negative subjects may be easier to achieve.

Added value of this study

We studied a large prospective cohort of both men and women diagnosed in acute and early HIV-1 infection and characterized their inflammatory profile under long-term ART (median 6-1 years, range, 3.2 – 17.0 years). Besides, we included two age- and sex-matched HIV-negative control groups, with contrasting profiles, in terms of risk of HIV infection and inflammatory cofactors (e.g., smoking, alcohol and drugs use). The first comparison group, comprising 102 men who have sex with men (MSM) at high risk for HIV infection, from the ANRS IPERGAY trial, can be seen as a sample of the uninfected source population from which most of the HIV-infected MSM enrolled in the PRIMO cohort could have originated. The second comparison group, comprising 141 volunteers for HIV preventive vaccine trials with a very low-risk profile for HIV infection, aimed at providing information on standard levels of inflammation in a population of the same sex and age as the HIV-infected participants in our study. We compared long-term ART-treated participants with these two HIV-uninfected control groups, for the levels of ten biomarkers that we selected to integrate the most described sources of inflammation, i.e. monocyte activation (soluble CD14 [sCD14], sCD163, CXCL10), mucosal inflammation (intestinal fatty-acid binding protein [I-FABP], interleukin 17 [IL-17]), and fibrosis (hyaluronic acid), in addition to standard non-specific markers of inflammation (ultrasensitive C-reactive protein [us-CRP], IL-6, tumor necrosis factor α [TNF-α], soluble TNF receptor II [sTNFRII]). Our virally-suppressed participants showed higher levels of soluble markers associated with monocyte activation and gut epithelial dysfunction, compared with both control groups. The inflammatory profiles of HIV-uninfected IPERGAY and COHVAC men were similar for markers associated with monocyte activation (sCD14, sCD163, CXCL10), but differed on some other markers. IPERGAY men showed higher levels of IL-17, TNF-α, and I-FABP, and lower levels of sTNFRII than COHVAC men. The differences in IL-17 and TNF-α levels persisted after adjusting for age, smoking and alcohol use, while those for sTNFRII or I-FABP levels were explained by these cofactors. Interestingly, we identified a small subset of 15 PRIMO participants with particularly low inflammatory profile under ART and also at the diagnosis of AHI, which was not explained by the HIV- or non-HIV-related factors we measured. This suggests that persistent inflammation under treatment may be related to an increased inflammatory profile since AHI.

Implications of all the available evidence

Monocyte activation and gut epithelial dysfunction appeared to be important drivers of inflammation in HIV-infected individuals. Exploring factors that determine activation levels prior to treatment would be of great interest to the development of therapeutic strategies to reduce persistent immune activation and inflammation in treated people living with HIV.

Factors in the perspective of AHI could have originated. The second comparison group, comprising 102 men who have sex with men (MSM) at high risk for HIV infection, from the ANRS IPERGAY trial, can be seen as a sample of the uninfected source population from which most of the HIV-infected MSM enrolled in the PRIMO cohort could have originated. The second comparison group, comprising 141 volunteers for HIV preventive vaccine trials with a very low-risk profile for HIV infection, aimed at providing information on standard levels of inflammation in a population of the same sex and age as the HIV-infected participants in our study. We compared long-term ART-treated participants with these two HIV-uninfected control groups, for the levels of ten biomarkers that we selected to integrate the most described sources of inflammation, i.e. monocyte activation (soluble CD14 [sCD14], sCD163, CXCL10), mucosal inflammation (intestinal fatty-acid binding protein [I-FABP], interleukin 17 [IL-17]), and fibrosis (hyaluronic acid), in addition to standard non-specific markers of inflammation (ultrasensitive C-reactive protein [us-CRP], IL-6, tumor necrosis factor α [TNF-α], soluble TNF receptor II [sTNFRII]). Our virally-suppressed participants showed higher levels of soluble markers associated with monocyte activation and gut epithelial dysfunction, compared with both control groups. The inflammatory profiles of HIV-uninfected IPERGAY and COHVAC men were similar for markers associated with monocyte activation (sCD14, sCD163, CXCL10), but differed on some other markers. IPERGAY men showed higher levels of IL-17, TNF-α, and I-FABP, and lower levels of sTNFRII than COHVAC men. The differences in IL-17 and TNF-α levels persisted after adjusting for age, smoking and alcohol use, while those for sTNFRII or I-FABP levels were explained by these cofactors. Interestingly, we identified a small subset of 15 PRIMO participants with particularly low inflammatory profile under ART and also at the diagnosis of AHI, which was not explained by the HIV- or non-HIV-related
not consider individuals of non-white ethnicity or those who died within a year after the selected sample or had a history of an AIDS-event or with a current B or C hepatitis coinfection (positive Hbs antigenemia; positive HCV PCR). Participants were selected regardless of their time of treatment initiation, based on the results of a previous study of our group which did not show any difference in inflammatory levels after more than three years of treatment depending on the time to ART initiation, immediate at AHI diagnosis versus deferred during chronic infection [14]. We pragmatically set at 150 the number of PRIMO participants enrolled in this study. We had previously studied 97 participants who met the criteria mentioned above [14]. Therefore, we selected 53 additional participants, comprising all 27 eligible female participants, to best represent women, and 26 male participants randomly selected from the 244 eligible men. All selected participants were enrolled in the PRIMO cohort between 1997 and 2012, i.e. at a time when ART initiation in AHI was based on presence of symptoms and CD4+ T-cell count [15].

The PRIMO participants were compared with two contrasted HIV-uninfected groups, originating from the ANRS IPERGAY preexposure prophylaxis trial [16] and the ANRS COHVAC postvaccine trial cohort [17]. IPERGAY participants were MSM at high risk for HIV infection, defined as a history of unprotected anal sex with at least two partners during the previous six months, and exhibited high frequencies of non-HIV-related factors of inflammation: at enrolment in the trial, 28% were diagnosed with syphilis, gonorrhea, or chlamydia, 23% reported > 5 alcoholic drinks per day in the month, and 44% the use of recreational drugs in the past 12 months [16]. In contrast, COHVAC participants were volunteers for ANRS HIV preventive vaccine trials who were selected for trials because they were in good health and had a very low-risk profile for HIV infection. At enrolment in the COHVAC cohort, a low percentage (< 10%) of participants reported unprotected sex with partners of unknown HIV status [17].

Cisgender participants from the IPERGAY and COHVAC studies who did not acquire HIV nor HCV or HBV and with available frozen samples during follow-up were eligible to be controls. For IPERGAY participants, the selection was restricted to European individuals, whereas no data on ethnicity or geographical origin was collected in the COHVAC cohort. IPERGAY and COHVAC participants were matched 1:1 with PRIMO participants for sex and age (by five-year strata of current age). The sample size was pragmatically set at 150 HIV-positive PRIMO participants and 1:1 matched IPERGAY and COHVAC controls. No formal sample size calculation was performed. This sample size was considered to be sufficient to allow estimation of parameters with sufficient precision based on previous reports [10,14,18].

2.2. Ethics

The PRIMO and COHVAC cohorts were approved by the ethics committee (Comité de Protection des Personnes Ile-de-France III, n. 1157 and 2522 respectively). The IPERGAY trial protocol was approved by public health authorities and by ethics committees in France and Canada (Comité de Protection des Personnes Ile-de-France IV, Comité d’Ethique de la Recherche de Montreal, n. 2011/26). All participants gave their written informed consent to participate.

2.3. Measures

We centrally measured plasma levels of ten soluble biomarkers of all participants. sTNFRII, sCD14, sCD163, CXCL10, IL-FABP, and hyaluronic acid were measured by specific ELISA (Human TNF RII/TNFRSF1B DuoSet ELISA, Human CD14 DuoSet ELISA, Human CD163 DuoSet ELISA, Human CXCL10/IP10 DuoSet ELISA, Human FABP2/I-FABP DuoSet ELISA, and Hyaluronan DuoSet ELISA, R&D Systems). IL-17, IL-6, and TNF-α were measured by single-molecule array (SiMoA) assay (Quanterox), and CRP by immunochemistry (CRP LX HS, Cobas C, integra, Roche Diagnostics). Samples with undetectable levels were attributed half the threshold value.

We measured plasma HIV RNA levels of PRIMO participants, using an ultrasensitive real-time PCR technique (GENERIC HIV, Biocentric, France) and total HIV DNA levels from whole blood samples using a real-time PCR assay (GENERIC Biocentric, France) [19].

The data that support the findings of this study are available on request to the corresponding author. The data are not publicly available due to privacy restrictions.

2.4. Statistics

We compared the levels of each biomarker of the PRIMO, IPERGAY and COHVAC participants using multiple linear regression models stratified by sex. We compared the levels of each biomarker of the PRIMO, IPERGAY and COHVAC participants using multiple linear regression models stratified by sex and adjusted for age, smoking, and alcohol use (Multivariate.1). We additionally adjusted the comparisons for BMI in further models restricted to men from the PRIMO and IPERGAY groups, where information on BMI was available (Multivariate.2). Because of the high percentage of individuals with undetectable CXCL10 levels (from 69 to 87% in each group), we transformed CXCL10 into a binary variable (undetectable versus detectable CXCL10 level) and used logistic regression models for this marker.

We also plotted radar charts to visualize the inflammatory profiles of each group, separately for men and women. To do this, for each marker we divided individuals into low and high-producers, depending on whether they had a level below versus equal or above the overall median level of all groups combined. The radar chart represents the percentage of high-producers in each group for the ten biomarkers. Finally, we performed a principal component analysis (PCA) and ascendant hierarchical clustering to identify individuals with similar inflammatory profiles. PCA allows to visualize proximities between individuals in a two-dimensional map. Hierarchical clustering aggregates similar individuals in clusters. We assessed to what extent participants of the three groups, PRIMO, COHVAC and IPERGAY, clustered together.

Given the very low percentage of missing data, all models were run in participants with complete data. Analysis was conducted in R (R Core Team, 2018).

2.5. Role of funders

This work was supported by the French Agency for Research on AIDS and Viral Hepatitis (ANRS) and a doctoral grant from Paris-Saclay University to S.N.

The funders had no role in the analyses, interpretation of the data, or decision to submit results.

The corresponding author has full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Participant characteristics

We analysed 150 participants of the PRIMO cohort, 42 women and 108 men, with a median age of 47 years (IQR, 41–53). They had been under ART for a median of 6–1 years (IQR, 5.0–7.8; range, 3.2–17.0). The median CD4+ T-cell count was 733 cells/μL and 40% still had a CD4:CD8 ratio < 1. The ultrasensitive viral load was undetectable for 64% of participants (median threshold: 3 copies/ml). We compared them to 41 women and 100 men of the COHVAC cohort and 102 men of the IPERGAY trial. Despite the matching, the COHVAC men tended
to be older than their IPERGAY counterparts, likely due to the width of the 5 year-strata of age chosen for matching with the PRIMO participants. The COHVAC participants particularly differed from the IPERGAY and PRIMO participants in that they were less likely to report tobacco and alcohol use, whereas the PRIMO and IPERGAY individuals were similar in terms of smoking, alcohol use and BMI (Table 1).

### 3.2. Impact of HIV-1 infection

In univariate analyses, PRIMO men and women differed from both their IPERGAY and COHVAC counterparts by higher levels of sCD163, sCD14, sTNFRII and I-FABP (Fig. 1, Supplementary Table 1). The differences for these four markers remained statistically significant after adjusting for age, current smoking and alcohol use, and also after a further adjustment for BMI in a model restricted to the PRIMO and IPERGAY men (Table 2).

Some other differences between the ART-treated and HIV-uninfected participants depended on the control group. Indeed, PRIMO and COHVAC participants had similar IL-17 levels, both among men and women, whereas the IPERGAY men had higher IL-17 levels. Moreover, PRIMO participants had higher TNF-α levels than their COHVAC counterparts, but similar levels to their IPERGAY counterparts (Supplementary Table 2). The PRIMO and IPERGAY men had similar us-CRP levels, and elevated compared to the COHVAC men. Of note, this difference was no longer statistically significant after adjustment for smoking and alcohol. Finally, there was no difference between groups for hyaluronic acid levels. All these results are summarized in terms of high (versus low) levels for each marker and depicted in Fig. 1.

Certain other differences were sex-specific: IL-6 levels were higher in HIV-infected women than HIV-uninfected women, but not between the men, regardless of the control group. HIV-infected men showed higher CXCL10 levels than HIV-uninfected men, whereas no difference was observed among the women.

We then performed a PCA to visualize correlations between biomarkers and identify participants with similar inflammatory profiles. We removed CXCL10 from the following analyses because 80% of the participants had undetectable levels of this marker. Those with complete data for the nine other markers were 133, 138, and 93 participants from the PRIMO, COHVAC, and IPERGAY groups, respectively. Principal components PC1 and PC2 explained 41% of the total variance (Fig. 2a). PC1 was mainly defined by sTNFRII and sCD163, plus us-CRP and TNF-α. PC2 was defined by the opposition between IL-17 and I-FABP. sCD14 contributed to both components. The concentration ellipses (Fig. 2b) showed that the IPERGAY ellipse comprised all the COHVAC participants and only one-third of the PRIMO participants; the remaining two-thirds PRIMO participants were predominantly located in the lower right quadrant and were those who showed higher levels of all inflammatory markers than the other participants.

We also observed that the COHVAC participants and only one-third of the PRIMO participants; the remaining two-thirds PRIMO participants were predominantly located in the lower right quadrant and were those who showed higher levels of all inflammatory markers than the other participants. The other differences were sex-specific: IL-6 levels were higher in HIV-infected women than HIV-uninfected women, but not between the men, regardless of the control group. HIV-infected men showed higher CXCL10 levels than HIV-uninfected men, whereas no difference was observed among the women.
have lower levels for other inflammation markers, although the differences were not always statistically significant (Fig. 3).

### 3.3. Cofactors of inflammation and the IPERGAY/COHVAC comparison

In the PRIMO participants, no inflammatory marker after a median of six years of ART was associated with the duration of treatment, time to ART initiation, or markers of HIV infection (CD4+ T-cell count, CD4/CD8 ratio, ultrasensitive viral load, and HIV DNA levels), except for sTNFRII levels which slightly correlated with the CD4:CD8 ratio (Spearman rho = -0.22, P = 0.01).

We then evaluated associations of non-HIV related factors (smoking, alcohol consumption and BMI) with inflammatory levels, first in the PRIMO participants only. We ran univariate regression models and then multivariate regression models adjusted for age and sex. Secondly, we looked for similar associations in the group of uninfected COHVAC and IPERGAY participants. We proceeded this way for each of the 10 markers (Fig. 4).

In the PRIMO participants, smoking was associated with lower sCD163 and IL-17 levels (likelihood-ratio test, multiple regression, P = 0.02 and 0.05, respectively), alcohol consumption with lower sTNFRII and hyaluronic acid levels (P = 0.002 and P = 0.007, respectively), and obesity with higher IL-6 levels (P = 0.002 and P = 0.007, respectively). Women had higher sCD14 levels than men, although the difference was not statistically significant (+201 ng/mL, P = 0.07). Age was associated with increase in TNF-α levels (P = 0.04).

The associations between sCD163 and smoking and between sTNFRII and alcohol consumption were also found in the COHVAC participants (Fig. 4).

The inflammatory profiles of IPERGAY and COHVAC men were similar for markers associated with monocyte activation (sCD14, sCD163, CXCL10), but not for some other markers. IPERGAY men showed higher levels of IL-17, TNF-α, and I-FABP, and lower levels of sTNFRII than COHVAC men. The differences in IL-17 and TNF-α levels persisted after adjusting for age, smoking and alcohol use, but not those for sTNFRII or I-FABP levels (Fig. 1, Table 4, Supplementary Table 3).

### 4. Discussion

Here we compared long-term ART-treated participants with two HIV-uninfected control groups, with either a low or high risk of HIV acquisition, for the levels of ten biomarkers that we selected to integrate the most described sources of inflammation, i.e. monocyte activation (sCD14, sCD163, CXCL10), mucosal inflammation (I-FABP, IL-17), and fibrosis (hyaluronic acid), in addition to standard non-specific markers of inflammation (us-CRP, IL-6, TNF-α, sTNFRII). Among these markers, sTNFRII, sCD14, sCD163, and I-FABP were the most discriminant between ART-treated participants and HIV-uninfected controls: they differed between both ART-treated men and women and their HIV-uninfected sex-matched counterparts, and the differences persisted after adjusting for age, smoking, alcohol use, and BMI.

Our findings are consistent with those of previous studies that, in mainly chronically-infected patients, compared treated PLHIV to appropriate controls [11,18,21]. Interestingly, a recent study from the MACS cohort reported abnormally elevated concentrations of certain inflammatory biomarkers including sCD14, sTNFRII, but also CXCL10 and TNF-α, sTNFRII. Among these markers, sTNFRII, sCD14, sCD163, and I-FABP were the most discriminant between ART-treated participants and HIV-uninfected controls: they differed between both ART-treated men and women and their HIV-uninfected sex-matched counterparts, and the differences persisted after adjusting for age, smoking, alcohol use, and BMI.

In an older population, with a median age 59 years, Booiman et al. did not observe any difference in sCD14 according to HIV status, but still reported elevated levels of sCD163 and I-FABP in PLHV after a median of eight years of ART [10]. Monocyte activation thus appears to be an important driver of inflammation in HIV-infected patients under ART. Increased levels of sCD14 can also be associated with microbial translocation [23]. Similarly, high levels of...
Table 2
Impact of HIV-1 infection on each inflammatory biomarker among men and women

| Biomarker | Men Univariate Estimate (95% CI) | P-value | Men Multivariate Estimate (95% CI) | P-value | Women Univariate Estimate (95% CI) | P-value | Women Multivariate Estimate (95% CI) | P-value |
|-----------|----------------------------------|---------|-----------------------------------|---------|-----------------------------------|---------|-------------------------------------|---------|
| sCD14, ng/mL | | | | | | | | |
| PRIMO | Ref. | – | Ref. | – | | | | |
| COHIV | –507 (–622, –392) | < 0.0001 | –469 (–633, –365) | < 0.0001 | | | | |
| IFPREG | –544 (–655, –430) | < 0.0001 | –535 (–651, –420) | < 0.0001 | | | | |
| Age, years | 4 (–2, 10) | 0.24 | 4 (–1, 10) | 0.10 | 7 (0, 14) | 0.05 | | |
| Alcohol consumer | 110 (–1, 221) | 0.05 | –16 (–128, 95) | 0.77 | –20 (–170, 129) | 0.79 | | |
| Current smoker | 143 (29, 257) | 0.01 | 52 (–56, 159) | 0.34 | 37 (–92, 166) | 0.57 | | |
| BMI | | | | | | | | |
| Normal | Ref. | – | Ref. | – | | | | |
| Overweight | –97 (–271, 77) | 0.27 | | | | | | | |
| Obesity | –216 (–602, 159) | 0.12 | | | | | | | |
| COHIV | –647 (–897, –396) | < 0.0001 | –626 (–906, –346) | < 0.0001 | | | | |
| Age, years | 3 (–8, 14) | 0.57 | 4 (–6, 14) | 0.41 | | | | |
| Alcohol consumer | 275 (–17, 567) | 0.06 | 6 (–302, 314) | 0.97 | | | | |
| Current smoker | 271 (–28, 570) | 0.08 | 63 (–253, 384) | 0.70 | | | | |
| sCD163, ng/mL | | | | | | | | |
| PRIMO | | | | | | | | |
| COHIV | –91 (–144, –38) | 0.001 | –110 (–171, –48) | 0.001 | | | | |
| Age, years | 1 (–1, 3) | 0.38 | 1 (–2, 2) | 0.47 | –1 (–4, 4) | 0.77 | | |
| Alcohol consumer | 33 (–12, 78) | 0.15 | 17 (–34, 68) | 0.52 | 81 (–63, 78) | 0.83 | | |
| Current smoker | –3 (–8, 5) | 0.11 | 6 (–118, –19) | 0.01 | –52 (–92, 100) | 0.06 | | |
| BMI | | | | | | | | |
| Normal | Ref. | – | | | | | | |
| Overweight | 39 (–32, 109) | 0.28 | | | | | | | |
| Obesity | 70 (–42, 181) | 0.22 | | | | | | | |
| COHIV | –117 (–195, –38) | 0.004 | –156 (–242, –71) | 0.001 | | | | |
| Age, years | –1 (–4, 3) | 0.69 | –1 (–4, 2) | 0.56 | | | | |
| Alcohol consumer | –25 (–110, 61) | 0.57 | –55 (–148, 39) | 0.25 | | | | |
| Current smoker | –25 (–112, 62) | 0.57 | –63 (–161, 34) | 0.20 | | | | |
| sTNFR1, pg/mL | | | | | | | | |
| PRIMO | | | | | | | | |
| COHIV | –1013 (–1387, –639) | < 0.0001 | –1171 (–1609, –733) | < 0.0001 | | | | |
| Age, years | 5 (–13, 23) | 0.58 | 5 (–12, 23) | 0.53 | 1 (–24, 24) | 0.97 | | |
| Alcohol consumer | –114 (–455, 228) | 0.51 | –421 (–786, –57) | 0.02 | –463 (–971, 44) | 0.07 | | |
| Current smoker | 321 (–28, 670) | 0.07 | 199 (–150, 548) | 0.26 | 280 (–146, 718) | 0.19 | | |
| BMI | | | | | | | | |
| Normal | Ref. | – | | | | | | |
| Overweight | 29 (–519, 576) | 0.92 | | | | | | | |
| Obesity | 93 (–765, 990) | 0.83 | | | | | | | |
| COHIV | –1189 (–1727, –651) | < 0.0001 | –1490 (–2064, –915) | < 0.0001 | | | | |
| Age, years | 9 (–14, 32) | 0.44 | 8 (–13, 29) | 0.45 | | | | |
| Alcohol consumer | –131 (–753, 490) | 0.68 | –541 (–1175, 93) | 0.09 | | | | |
| Current smoker | –115 (–752, 523) | 0.72 | –362 (–1020, 297) | 0.28 | | | | |
| 1-FABP, pg/mL | | | | | | | | |
| PRIMO | | | | | | | | |
| COHIV | –1171 (–1364, –977) | < 0.0001 | –1053 (–1279, –827) | < 0.0001 | | | | |
| Age, years | –4 (–15, 7) | 0.51 | 0 (–9.9) | 0.96 | 2 (–14, 10) | 0.79 | | |
| Alcohol consumer | 478 (281, 674) | < 0.0001 | 135 (–53, 323) | 0.16 | 182 (–68, 433) | 0.15 | | |
| Current smoker | 407 (203, 610) | < 0.0001 | 108 (–73, 289) | 0.24 | 106 (–108, 321) | 0.33 | | |
| BMI | | | | | | | | |
| Normal | Ref. | – | | | | | | |
| Overweight | 29 (–258, 315) | 0.84 | –30 (–286, 226) | 0.82 | | | | |
| Obesity | –210 (–659, 238) | 0.36 | –235 (–605, 135) | 0.21 | | | | |
| COHIV | –1259 (–1540, –977) | < 0.0001 | –1224 (–1533, –915) | < 0.0001 | | | | |
| Age, years | 6 (–10, 21) | 0.48 | 7 (–5, 18) | 0.24 | | | | |
| Alcohol consumer | 485 (84, 893) | 0.02 | 15 (–321, 351) | 0.93 | | | | |
| Current smoker | 476 (59, 893) | 0.03 | 105 (–248, 459) | 0.55 | | | | |

* Results from linear regression models.

a Multivariate 1: results from a multiple linear regression adjusted for age, alcohol, and smoking.
b Multivariate 2: results from a multiple linear regression adjusted for age, alcohol, smoking and BMI and restricted to men of the PRIMO and IFPREG groups.

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval; Ref., reference
See Supplementary Table 2 for us-CRP, IL-6, TNF-α, IL-17, CXCL10 and hyaluronic acid.

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**Note:** The table above contains the impact of HIV-1 infection on each inflammatory biomarker among men and women, including results from univariate and multivariate linear regression analyses adjusted for age, alcohol, and smoking. The table also includes BMI categories (Normal, Overweight, Obesity) and their respective values. The data is presented in a structured format, with each biomarker listed across the top, followed by the results for men and women separately. The table notes the significance levels for each result, with asterisks indicating statistical significance. Additional abbreviations and references are provided at the bottom of the table.
**Table 3**

Comparison of PRIMO participants between the two clusters revealed by hierarchical clustering.

| Characteristics                        | Cluster 1, n = 15 Low inflammatory levels on ART | Cluster 2, n = 118. Elevated inflammatory levels on ART | P-valuea |
|----------------------------------------|-------------------------------------------------|-------------------------------------------------------|----------|
| Sex, men                               | 73.3 (11)                                       | 72.0 (85)                                             | 1        |
| Age, years                             | 46.4 (41, 53.8)                                 | 48.2 (42.9, 53.7)                                     | 0.67     |
| **Under ART**                          |                                                 |                                                       |          |
| Current smoker                         | 46.7 (7)                                        | 49.2 (58)                                             | 0.87     |
| Alcohol consumer                       | 73.3 (11)                                       | 70.3 (83)                                             | 1.00     |
| BMI, kg/m²                             | 25.2 (23.0, 28.5)                               | 23.8 (21.4, 25.5)                                     | 0.17     |
| ART duration, months                   | 66.9 (59.9, 71.8)                               | 75.8 (60.3, 94.9)                                     | 0.17     |
| CD4+ T-cell count, cells/μL            | 776 (637, 844)                                  | 712 (590, 872)                                        | 0.50     |
| CD4:CD8 Ratio                          | 1.3 (1.0, 1.5)                                  | 1.2 (0.9, 1.7)                                        | 0.75     |
| Ultrasensitive HIV RNA levels          | Undetectable                                    |                                                       | 0.89     |
|                                       | 60.0 (9)                                        | 61.9 (73)                                             |          |
| Detection threshold, copies/mL         | 2 (2, 4)                                        | 3 (2, 3)                                              | 0.89     |
| Detectable samples, copies/mL          | 46 (14, 32)                                     | 11 (4, 32)                                            | 0.20     |
| Total HIV DNA level, log₁₀ copies/10⁶ PBMCs | 2.8 (2.6, 3.1)                                | 2.5 (2.1, 2.8)                                        | 0.02     |
| us-CRP, ng/mL                          | 1.47 (0.78, 2.47)                               | 1.59 (0.83, 3.35)                                     | 0.53     |
| IL-6, pg/mL                            | 1.25 (0.88, 1.86)                               | 1.23 (0.78, 1.94)                                     | 0.91     |
| IL-17, pg/mL                           | 0.07 (0.05, 0.16)                               | 0.09 (0.06, 0.17)                                     | 0.78     |
| TNF-α, pg/mL                           | 2.79 (2.29, 3.40)                               | 3.15 (2.62, 3.98)                                     | 0.08     |
| CXCL10 - 37 pg/mL                      | 867 (13)                                       | 68.6 (81)                                             | 0.23     |
| sTNFRIIL, pg/mL                        | 2595 (2115, 3532)                               | 3455 (2764, 4232)                                     | 0.02     |
| Hyaluronic acid, ng/mL                 | 16.3 (10.6, 27.3)                               | 13.4 (8.5, 21.4)                                      | 0.21     |
| sCD163, ng/mL                          | 404 (203, 485)                                  | 476 (379, 643)                                        | 0.02     |
| sCD14, ng/mL                           | 1554 (1401, 1770)                               | 2205 (1937, 2616)                                     | < 0.0001 |
| I-FABP, pg/mL                          | 1547 (1154, 2212)                               | 2587 (1999, 2961)                                     | < 0.0001 |
| **At AHI diagnosis**                   |                                                 |                                                       |          |
| Symptomatic AHI                        | 73.3 (11)                                       | 89.0 (105)                                            | 0.10     |
| CD4+ T-cell count, cells/μL            | 636 (428, 852)                                  | 523 (371, 681)                                        | 0.19     |
| Plasma HIV RNA levels, log₁₀ copies/mL | 5.1 (3.9, 5.8)                                 | 5.1 (4.5, 5.6)                                        | 0.83     |
| CD4:CD8 ratio                          | 0.9 (0.5, 1.2)                                  | 0.5 (0.3, 0.8)                                        | 0.004    |
| Total HIV DNA level, log₁₀ copies/10⁶ PBMCs | 3.3 (2.9, 3.5)                                | 3.3 (3.0, 3.6)                                        | 0.52     |
| Protective HLA I allele                | 33.3 (3)                                       | 25.0 (20)                                             | 0.69     |
| ART initiated in the month following AHI diagnosis | 13.3 (2)                                      | 47.5 (56)                                             | 0.01     |

Data are presented as the median (interquartile range) or percentage (No.).

- Wilcoxon Mann–Whitney test for continuous variables and x² test for categorical variables.
- detection threshold depended on the available plasma volume.
- HIV DNA levels measured within a year before the measurement of inflammatory markers.
- HLA class I alleles associated with slow progression of HIV disease [20]: (HLA-A*25, HLA-A*32, HLA-A*74, HLA-B*14, HLA-B*27, HLA-B*51, HLA-B*52, HLA-B*57) Data available for 9 and 80 participants.

Abbreviations: AHI, acute and early HIV infection; ART, antiretroviral therapy; BMI, body mass index; PBMCs, peripheral blood mononuclear cells.
I-FABP, a marker commonly associated with mucosal homeostasis, may reflect ongoing enterocyte damage, although epithelial cell regeneration under effective ART has also been suggested [24,25]. sTNFRII, sCD14, and I-FABP have been shown to be predictive for morbidity and mortality in ART-treated PLHIV [26,29], and sCD163 has been related to subclinical atherosclerosis [30]. Further studies are needed to address the long-term clinical relevance of the differences that we and others have reported.

Our cluster analysis revealed a subset of 15 PRIMO participants with a reduced inflammatory profile under ART, comparable to HIV-uninfected participants. Of note, these individuals already had a particularly favourable CD4:CD8 ratio in AHI. Accordingly, most of them had initiated ART at distance of AHI diagnosis. In addition to better immunological characteristics, they also had lower levels of inflammatory markers during AHI than other PRIMO participants. This is consistent with the results of Gandhi et al., who reported that pre-ART levels of several inflammatory markers significantly correlated with on-therapy levels of the same biomarkers, even after years of suppressive ART, and not with markers of HIV persistence [31]. Taken together, these findings suggest that persistent inflammation under treatment may be related to an increased inflammatory profile since AHI; the low inflammatory profile under treatment observed in...
few participants might be explained by viral and host factors, including genetic ones.

This study had some limitations. First, there were unmeasured factors, including some comorbidities, medications or measurement of waist circumference. These factors could contribute to explain the differences we observed between the PRIMO participants and their IPERGAY and COHVAC HIV-uninfected counterparts. Nevertheless, this study was designed to compare the levels of inflammation in HIV-infected participants with those observed in sex and age-matched HIV-uninfected participants, at either low or high risk for HIV acquisition. The presence of comorbidities, drug treatments and visceral fat, which are often more common in HIV-infected participants than in uninfected subjects [32], would then be more likely to be explanatory factors for the observed differences than confounding factors that should be adjusted for. Secondly, our selection of ten biomarkers did not allow a complete integration of all inflammatory sources, in particular the contribution of metabolic inflammation. Thirdly, we restricted our study population to HCV and HBV uninfected individuals. Our results may therefore not be generalizable to other populations in a different context of the HIV epidemic.

Fourthly, we also probably did not have sufficient statistical power to identify a sex-modifying effect on associations between certain markers of inflammation and non-HIV-related factors.

![Fig. 4](image_url)

Fig. 4. Inflammatory levels and associations with non-HIV-related factors. (a) from multivariate linear (or logistic for CXCL10) regression models adjusted for sex. (b) from multivariate linear (or logistic for CXCL10) regression models adjusted for age. (c) from multivariate linear (or logistic for CXCL10) regression models adjusted for age and sex. Summary table of the associations between inflammatory levels and non-HIV-related factors, obtained from multiple linear (or logistic for CXCL10) regression models, by cohort. For each marker, the direction of the association is symbolized by a sign positive (+) or negative (-). P-values are estimated from likelihood-ratio test. Empty box is used to indicate a P-value > 0.15.

|                | Age a         | Women versus men b | Alcohol Consumer c | Current Smoker c | Overweight or obesity c |
|----------------|---------------|---------------------|--------------------|------------------|------------------------|
| **PRIMO**      |               |                     |                    |                  |                        |
| CRP-us         |               |                     |                    |                  |                        |
| IL-6           | (+) P = 0.08  |                     |                    |                  | (+) P = 0.003          |
| TNF-α          | (-) P = 0.04  |                     |                    |                  |                        |
| sTNFRII        |               | (-) P = 0.02        |                    |                  |                        |
| sCD163         |               |                     | (-) P = 0.02       |                  |                        |
| sCD14          | (+) P = 0.07  |                     |                    |                  | (-) P = 0.11           |
| CXCL10         |               |                     |                    |                  |                        |
| I-FABP         |               |                     |                    | (-) P = 0.14     |                        |
| IL-17          |               | (-) P = 0.05        |                    |                  |                        |
| Hyaluronic acid|               | (-) P = 0.007       |                    |                  | (-) P = 0.11           |

| **COHVAC**     |               |                     |                    |                  |                        |
| CRP-us         |               |                     |                    |                  |                        |
| IL-6           | (+) P = 0.05  |                     |                    |                  | (-) P = 0.13           |
| TNF-α          | (-) P = 0.01  |                     |                    |                  |                        |
| sTNFRII        | (-) P = 0.01  |                     | (-) P = 0.06       |                  |                        |
| sCD163         | (+) P = 0.05  |                     | (-) P = 0.04       |                  |                        |
| sCD14          | (+) P = 0.05  |                     |                    |                  |                        |
| CXCL10         |               | (+) P = 0.001       |                    |                  |                        |
| I-FABP         |               |                     |                    |                  |                        |
| IL-17          | (+) P = 0.13  |                     |                    |                  |                        |
| Hyaluronic acid| (+) P = 0.01  |                     |                    |                  |                        |

| **IPERGAY**    |               |                     |                    |                  |                        |
| CRP-us         |               |                     |                    |                  |                        |
| IL-6           | (+) P = 0.07  | (+) P = 0.10        | (+) P = 0.05       |                  |                        |
| TNF-α          | (+) P = 0.08  |                     |                    |                  |                        |
| sTNFRII        |               |                     | (-) P = 0.14       |                  |                        |
| sCD163         |               | (-) P = 0.13        |                    |                  |                        |
| sCD14          | (+) P = 0.13  | (+) P = 0.13        | (+) P = 0.10       |                  |                        |
| CXCL10         |               |                     |                    |                  |                        |
| I-FABP         |               |                     |                    |                  |                        |
| IL-17          |               |                     |                    |                  |                        |
| Hyaluronic acid|               |                     |                    |                  |                        |
Among the strengths of this study were the use of multiplex assays that measured biomarker levels, even at low concentrations, the enrolment of both men and women, and the choice of two control groups with contrasting lifestyles and health behaviour profiles, and with information collected on the main cofactors of inflammation, which are age, sex, smoking, alcohol consumption, and BMI. The comparison group of participants from the IPERGAY trial can be seen as a sample of the uninfected source population from which most of the MSM of the PRIMO cohort could have originated, while the second comparison group from the COHVAC cohort provided information on standard levels of inflammation in a population of the same sex and age as the HIV-infected participants in our study. We had hypothesized that these two control groups would have different inflammatory profiles, given their differences in their health behaviours. And in fact, PRIMO men no longer had significantly higher levels of us-CRP than COHVAC men, after adjusting for alcohol and smoking, whereas the differences for the other more specific markers remained significant after adjustment. IPERGAY men had levels of soluble markers associated with monocyte activation (sCD14, sCD163, CXCL10) similar to those of COHVAC men, but higher TNF-α and IL-17 levels. These higher levels of IL-17 in IPERGAY men, even higher than those observed in PRIMO men, suggest different responses to various mucosal/epithelial infections [33] and may be linked to a higher exposure of these participants with high-risk behaviours to diverse infectious agents that trigger the innate immune system. Finally, we identified different inflammatory profiles depending on the sex; PRIMO men, but not women, exhibited higher CXCL10 levels than their uninfected counterparts. Conversely, PRIMO women, but not men, exhibited higher IL-6 levels. The production of CXCL10 and IL-6 being associated with different sources (IFN pathway versus metabolic pathway respectively), it is thus possible that these two pathways make a different contribution in male and female participants.

In conclusion, after many years of suppressive ART, participants followed since AHI in the PRIMO cohort still showed elevated monocyte/macrophage activation and persistent gut epithelial dysfunction, relative to two groups of age- and sex-matched HIV-negative participants with either a low or high prevalence of cofactors of inflammation. Persistent inflammation under treatment may be related to an increased inflammatory profile since AHI. Comparisons of inflammation/activation levels between HIV-infected and uninfected participants should consider exposures other than HIV that contribute to systemic immune activation.

### Table 4

Higher inflammatory levels in IPERGAY men compared to COHVAC men

|                      | Univariate * | Multivariate b |
|----------------------|-------------|---------------|
|                      | Estimate (95%CI) | P-value | Estimate (95%CI) | P-value |
| **TNF-α, pg/mL**     |             |               |                 |
| COHVAC               | Ref.        | --            | Ref.            | --       |
| IPERGAY              | 0.83 (0.42, 1.24) | < 0.0001 | 0.73 (0.22, 1.23) | 0.01     |
| Age, years           | 0.01 (0.00, 0.003) | 0.96  | 0.02 (0.00, 0.04) | 0.14     |
| Alcohol consumer     | 0.63 (0.15, 1.03) | 0.01  | 0.25 (0.02, 0.73) | 0.30     |
| Current smoker       | 0.38 (0.10, 0.86) | 0.12  | 0.07 (0.44, 0.57) | 0.79     |
| **sTNFRII, pg/mL**   |             |               |                 |
| COHVAC               | Ref.        | --            | Ref.            | --       |
| IPERGAY              | −3.34 (−6.30, −5.99) | 0.02  | −2.86 (−6.40, 68) | 0.11     |
| Age, years           | 13 (−3.29)  | 0.12          | 10 (−7.26)      | 0.26     |
| Alcohol consumer     | −2.25 (−5.15, 64) | 0.13  | −0.67 (−4.06, 272) | 0.70     |
| Current smoker       | −1.16 (−4.45, 213) | 0.49  | 4.44 (−308, 396) | 0.80     |
| **IL-17, pg/mL**     |             |               |                 |
| COHVAC               | Ref.        | --            | Ref.            | --       |
| IPERGAY              | 0.48 (0.21, 0.76) | 0.001 | 0.48 (0.18, 0.80) | 0.001    |
| Age, years           | −0.01 (−0.02, 0.01) | 0.43  | −0.00 (−0.02, 0.02) | 0.87     |
| Alcohol consumer     | 0.30 (0.02, 0.58) | 0.04  | 0.09 (−0.23, 0.42) | 0.57     |
| Current smoker       | 0.04 (−0.28, 0.37) | 0.80  | −0.19 (−0.53, 0.15) | 0.28     |

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* Results from linear regression models.

b Results from a multiple linear regression adjusted for age, alcohol, and smoking

Abbreviations: 95%CI, 95% confidence interval; Ref. Reference

See Supplementary Table 3 for us-CRP, IL-6, sTNFRII, CXCL10, sCD14, sCD163 and hyaluronic acid.

### Contributors

C.G. and L.M. were the main investigators of the ANRS PRIMO cohort.

O.L. and J-M. M. were the main investigators of the ANRS COHVAC cohort and the ANRS IPERGAY trial, respectively.

C.B., C.G. and L.M. designed the study. A.E., A.V., C.L., J.R., L.B., and V.A-F contributed the data.

S.N. performed the statistical analyses and L.M. supervised her.

S.N., L.M., C. B. and C. G. contributed to the interpretation of the results.

S.N. wrote the first version of the manuscript.

All authors read the manuscript, provided critical feedback and approved the final manuscript.

### Data sharing statement

Data are not owned by the authors. The data of the ANRS PRIMO, COHVAC and IPERGAY studies are owned by the Institut National de la Santé et de la Recherche Médicale (Inserm). French law requires that everyone who wants to share cohort data or clinical study data on humans must ask permission from the French data protection authority, the Commission Nationale de l’Informatique et des Libertés (CNIL). The request for access to the data must be made to the corresponding author and the sponsor.
Declaration of Competing Interest

Dr. Avettand-Fenoël reports grants from ANRS, during the conduct of the study; grants and personal fees from ViVi, grants from Janssen, outside the submitted work. Dr. Reyne reports personal fees and non-financial support from Gilead Science, personal fees and non-financial support from ViVi Healthcare, personal fees and non-financial support from MD France, personal fees and non-financial support from Janssen, personal fees and non-financial support from Pfizer, outside the submitted work. Dr. Molina reports personal fees from Gilead Sciences, personal fees from Merck, personal fees from ViVi Healthcare, outside the submitted work. Dr. Launay reports grants from Assistance Publique - Hôpitaux de Paris (AP-HP), during the conduct of the study. Dr. Novelli, Dr. Lécouroux, Dr. Villemant, Dr. Essat, Dr. Blum, Dr. Bourgeois, Dr. Goujard and Dr. Meyer have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ebiom.2020.103129.

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