

The Interplay Between Host Genetic Variation, Viral Replication, and Microbial Translocation in Untreated HIV-Infected Individuals

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Systemic immune activation, a major determinant of human immunodeficiency virus (HIV) disease progression, is the result of a complex interplay between viral replication, dysregulation of the immune system, and microbial translocation due to gut mucosal damage. Although human genetic variants influencing HIV load have been identified, it is unknown how much the host genetic background contributes to interindividual differences in other determinants of HIV pathogenesis such as gut damage and microbial translocation. Using samples and data from 717 untreated participants in the Swiss HIV Cohort Study and a genome-wide association study design, we searched for human genetic determinants of plasma levels of intestinal fatty acid-binding protein (I-FABP/FABP2), a marker of gut damage, and of soluble CD14 (sCD14), a marker of lipopolysaccharide bioactivity and microbial translocation. We also assessed the correlations between HIV load, sCD14, and I-FABP. Although we found no genome-wide significant determinant of the tested plasma markers, we observed strong associations between sCD14 and both HIV load and I-FABP, shedding new light on the relationships between processes that drive progression of untreated HIV infection.

Keywords. HIV; host genomics; genome-wide association study; immune activation; microbial translocation; sCD14; I-FABP.

Human immunodeficiency virus (HIV) infection is characterized by systemic immune activation, which persists even with viral suppression by antiretroviral therapy, and this immune activation is associated with HIV pathogenesis and disease progression in treated and untreated individuals [1,2]. One cause of immune activation is microbial translocation, which occurs when

microbial products from the lumen of the gastrointestinal (GI) tract translocate into the systemic circulation through a damaged GI tract barrier [3]. Immune activation and gut damage are cyclically linked, with immune activation leading to damage of the structural and immune barriers of the GI tract, and translocated microbial products stimulating the systemic immune system. This interplay is complex, and multiple factors affect each aspect of this vicious cycle, with the virus initiating and driving the process in the absence of treatment.

Soluble CD14 (sCD14) is a biomarker found at the heart of this interaction. Because it is a secreted sensor of bacterial lipopolysaccharide (LPS), sCD14 acts as an indirect marker of microbial translocation. The plasma sCD14 levels were associated with mortality rates in 2 studies of HIV-infected individuals who were receiving

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antiretroviral therapy [4, 5]. Intestinal fatty acid-binding protein (I-FABP encoded by *FABP2*) is a marker of GI tract enterocyte damage [6] and thereby makes it possible to indirectly measure structural damage to the GI tract, which would be prohibitive to sample in a large cohort. The plasma levels of I-FABP also showed some association with mortality rates in treated HIV-infected populations and were inversely correlated with CD4⁺ T-cell counts [4, 5]. These plasma markers allow the large-scale measurement of GI tract damage and microbial translocation.

Human genetic variation is known to play a modulating role in the host response to HIV infection. Multiple genome-wide association studies (GWASs) have been performed in cohorts with HIV control phenotypes, primarily in individuals of European ancestry and mostly focusing on HIV load or disease progression (CD4⁺ T-cell decline or time to AIDS) [7–10]. These studies consistently identified a small number of genetic variants associated with viral control, including single-nucleotide polymorphisms (SNPs) mapping to the HLA class I region on chromosome 6 and a 32-base pair deletion in the *CCR5* gene (*CCR5Δ32*) on chromosome 3. On the other hand, to our knowledge, there have been no reported GWASs of GI tract damage or microbial translocation, so it is unknown to what extent these essential aspects of HIV pathogenesis are influenced by host genetic variation and whether they also correlate with the *HLA-B*, *HLA-C*, and *CCR5* variants associated with viral load.

Of note, early candidate gene studies reported the existence of SNPs affecting sCD14 and I-FABP plasma levels, but these associations have yet to be confirmed in HIV-infected populations and in larger cohorts. The minor allele of rs2569190, a SNP mapping to the *CD14* promoter region, was associated with higher plasma levels of sCD14 [11]. The same SNP was associated with significant differences in secretion of sCD14 and interleukin 6 in LPS-stimulated peripheral blood mononuclear cells [12]. Two haplotypes have also been identified in the *FABP2* promoter (built from rs1799883, rs10034579, rs2282688, and rs6857641) associated with I-FABP expression differences in vitro [13, 14].

To elucidate how genetic factors may affect the interrelated processes of viral replication, gut damage, and microbial translocation leading to systemic immune activation, we measured the plasma levels of sCD14 and I-FABP in 717 untreated, clinically and genetically well-characterized HIV-infected subjects from the Swiss HIV Cohort Study (SHCS), and we used a GWAS design to search for human genetic variants associated with these biomarkers. We did not identify any significant genetic associations with sCD14 or I-FABP plasma levels, and we found that the human genetic variants known to be associated with HIV viremia are not associated with sCD14 or I-FABP levels. On the other hand, we observed independent associations between sCD14 and both HIV load and I-FABP, demonstrating the intricate relationships that exist between the various pathogenic mechanisms involved in HIV disease progression.

METHODS

Study Participants

The study subjects are part of the SHCS, a nationwide cohort study with continuous enrollment and semiannual study visits (www.shcs.ch [15]). The SHCS has been approved by the ethics committees of all participating institutions. Each study participant provided written informed consent for genetic testing. HIV-infected individuals were eligible if they had (1) genome-wide genotyping data generated in the context of a previous GWAS; (2) a stored plasma sample collected 3–6 years after estimated date of seroconversion, in the absence of antiretroviral treatment, and with a CD4⁺ T-cell count of $\geq 350/\mu\text{L}$ of blood; and (3) ≥ 3 stable plasma HIV RNA results, obtained in the absence of antiretroviral treatment, ≥ 6 months after the known or presumed date of infection, and with a CD4⁺ T-cell count of $\geq 350/\mu\text{L}$ of blood. The set point viral load was calculated as the mean of all log₁₀-transformed viral results fitting these conditions.

Plasma Biomarker Measurements

The I-FABP and sCD14 plasma levels were measured as described elsewhere using commercially available enzyme-linked immunosorbent assays [5]. The I-FABP assay (Cell Sciences) was performed on plasma diluted to 50%, and the sCD14 assay (R&D Systems) on plasma diluted to 0.5%. All analyses were performed with blinding to clinical and genetic status. Each test was determined in duplicate, and the mean value of each marker was calculated and used in the downstream analyses.

Genotyping and Imputation

Genotyping was performed using the Illumina HumanHap550 array, as described elsewhere [8]. After quality control of the genotyping data and exclusion of population outliers by principal component analysis [16], 686 individuals with complete phenotype and genotype data were available for downstream analysis. Genotypes were imputed using the 1000 Genomes Project CEU reference panel: we used Mach1 software (v. 1.0.17) for prephasing [17] and MiniMAC software for imputation [18]. Imputed SNPs with a minor allele frequency of $\geq 1\%$ and an imputation quality score (r^2) of ≥ 0.3 were kept for association testing. The *CCR5Δ32* variant, which is not represented directly or indirectly on the genome-wide chip, was independently genotyped with a TaqMan assay.

Association Testing

We use GWAPower software (v. 1.0) for power calculation [19]. Association tests were carried out by linear regression using PLINK software (v. 1.07) [20], and by linear mixed model regression using FaST-LMM software (v. 2.0) [21]. The FaST-LMM kernel matrix was computed from 69 000 randomly selected SNPs (corresponding to 1% of the total number of tested SNPs).

Regressions were performed against log₁₀-normalized HIV load at set point, log₁₀-normalized sCD14 plasma levels, and log₁₀-normalized I-FABP plasma levels. Age, sex, and the coordinates of the top 3 principal component analysis axes were included as covariates in all regression models. We used Bonferroni correction for multiple testing. Statistics for the associations between sCD14, I-FABP, viral load at set point, and the SNPs were computed by means of linear regression using R software (v. 3.0).

RESULTS

Lack of Association Between Common Human Genetic Variants and Markers of GI Tract Damage or Microbial Translocation

We analyzed HIV-infected patients that had been genotyped in the context of a previous GWAS [8]. A total of 6 982 014 SNPs, directly genotyped on Illumina arrays or imputed using the 1000 Genomes Project CEU population as reference, were available for association testing. Stored plasma samples were obtained from eligible treatment-naïve subjects, and the plasma levels of I-FABP and sCD14 were measured using enzyme-linked immunosorbent assay. A total of 717 participants had complete genetic and phenotypic data, of whom 31 were identified as population outliers by principal component analysis of the genotyping data and excluded. Therefore, the final study population included 686 individuals of European ancestry. Demographic and laboratory information for all study participants is shown in Table 1.

No associations were found between any human SNP and the plasma levels of I-FABP or sCD14 during early chronic, untreated HIV infection, after correction for multiple testing (Figure 1). Our study was powered to detect genetic variants that explain ≥4% of the variability in sCD14 or I-FABP plasma levels.

We also specifically looked at the SNPs that were reported elsewhere to be associated with sCD14 and I-FABP plasma levels. We did not observe any association between sCD14 plasma

levels and the *CD14* promoter SNP rs2569190 (*P* = .46) or between I-FABP plasma levels and the *FABP2* promoter SNPs rs1799883, rs10034579, rs2282688, and rs6857641, alone or in haplotype combinations (all *P* > .30).

Association of I-FABP Plasma Levels and HIV Load With sCD14 Plasma Levels

We next examined the correlations between several factors known to play a role in HIV pathogenesis: HIV load at set point, CD4⁺ T-cell count, plasma sCD14 level, and plasma I-FABP level. CD4⁺ T-cell counts were not associated with sCD14 or I-FABP plasma levels (*P* > .50 and *r*² < 0.01 for both), and this parameter was excluded from subsequent analyses. Of note, the distribution of CD4⁺ T-cell counts was truncated owing to the inclusion criterion that all study participants have CD4⁺ T-cell counts >350/μL; the median cell count was 452/μL in the study population (interquartile range, 390–566/μL).

We observed a moderate correlation between plasma levels of I-FABP and sCD14 (*P* = 7.1 × 10^{−16}; *r*² = 0.09; Figure 2A), confirming the obvious link between GI tract damage and microbial translocation. This correlation was largely independent of HIV load (*P* = 3.5 × 10^{−15} when viral load was included as a covariate in the regression model).

The HIV plasma load at set point was strongly associated with sCD14 but not with I-FABP plasma levels (*P* = 7.1 × 10^{−8} and *P* = .20, respectively; Figure 2B and 2C). The strong association observed between viral load and sCD14 plasma levels during chronic untreated infection is consistent with a cyclical relationship between HIV replication and immune activation due to microbial translocation. On the other hand, the absence of correlation between viral load and I-FABP concentration suggests that the virus is not a major driver of GI tract damage during the chronic phase of infection. This finding is consistent with the fact that this marker of enterocyte damage can still be detected in individuals receiving suppressive antiretroviral therapy [2].

Human Genetic Variants Associated With HIV Control but Not With sCD14 or I-FABP Plasma Levels

Three genetic variants have been consistently shown to be associates with HIV control in previous GWAS: rs2395029, a near-perfect proxy for HLA-B*57:01 in Europeans; rs9264942, an indirect marker of HLA-C expression levels; and the CCR5Δ32 deletion in its heterozygous form. We tested them for association with viral load at set point in linear regression models that included sex, age, and the coordinate of the top 3 principal component axes as covariates. The associations were again significant for all 3 variants in our study population (Table 2). However, there was no association with sCD14 or I-FABP plasma levels (all *P* > .05).

To further explore the potential interactions between HIV load at set point, host genetic variants and sCD14 plasma levels, we performed multivariate regression analyses on viral loads,

Table 1. Demographic and Laboratory Characteristics

| Characteristic | Eligible Participants (n = 717) | Final Study Population (n = 686) |
|---|---------------------------------|----------------------------------|
| Male sex, No. (%) | 543 (75.7) | 520 (75.8) |
| Age, median (IQR), y | 33 (27–40) | 34 (28–40) |
| HIV load at set point, mean (SD), log ₁₀ copies/mL | 3.81 (0.96) | 3.81 (0.96) |
| CD4 ⁺ T-cell count, median (IQR), cells/μL | 460 (390–571) | 452 (390–556) |
| sCD14, mean (SD), log ₁₀ pg/mL | 6.23 (0.13) | 6.24 (0.13) |
| I-FABP, mean (SD), log ₁₀ pg/mL | 2.70 (0.61) | 2.70 (0.60) |

Abbreviations: HIV, human immunodeficiency virus; I-FABP, intestinal fatty acid-binding protein; IQR, interquartile range; sCD14, soluble CD14; SD, standard deviation.

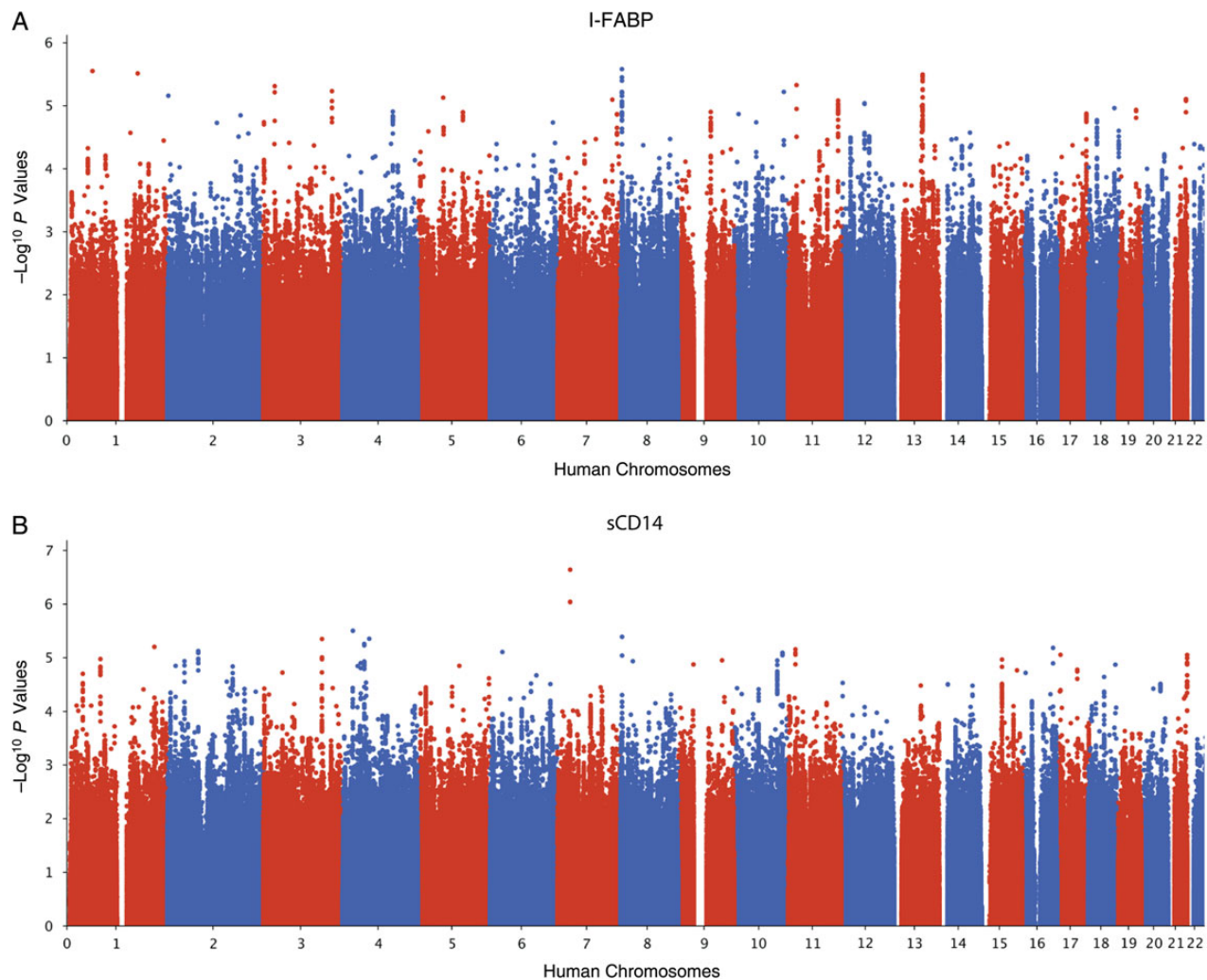


Figure 1. No single-nucleotide polymorphisms are significantly associated with intestinal fatty acid-binding protein (I-FABP) or soluble CD14 (sCD14) plasma levels. Manhattan plots show the distribution of results for the 2 genome-wide association studies, for I-FABP (A) and sCD14 (B) plasma levels. Horizontal axes represent human chromosomes in linear order; vertical axes, association strengths as $-\log_{10} P$ values.

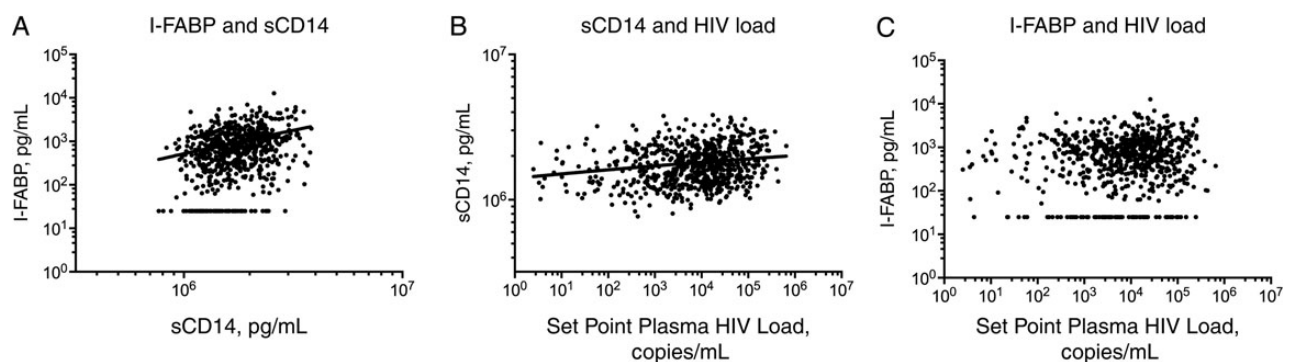


Figure 2. Intestinal fatty acid-binding protein (I-FABP) and human immunodeficiency virus (HIV) load at set point are independently associated with soluble CD14 (sCD14). Correlations are shown between plasma levels of I-FABP and sCD14 ($P = 7.1 \times 10^{-16}$; $r^2 = 0.09$) (A), sCD14 and HIV load ($P = 7.1 \times 10^{-8}$; $r^2 = 0.04$) (B), and I-FABP and HIV load ($P = .2$; $r^2 < 0.01$) (C).

Table 2. P Values for Association With HIV Load at Set Point in Linear Regression Models Including Sex, Age, and Coordinates of the Top 3 Principal Components Axes as Covariates

| Variant | P Value | | |
|--------------|-----------------------|-----------------------|-----------------------------|
| | Univariate Models | Multivariate Models | |
| | | Genetic Variants Only | Genetic Variants Plus sCD14 |
| rs2395029 | 5.4×10^{-8} | 9.6×10^{-6} | 6.7×10^{-6} |
| rs9264942 | 1.3×10^{-10} | 3.3×10^{-7} | 5.40×10^{-7} |
| CCR5Δ32 | .02 | .02 | .02 |
| sCD14 levels | 7.1×10^{-8} | . . . | 1.90×10^{-7} |

Abbreviations: HIV, human immunodeficiency virus; sCD14, soluble CD14.

including the 3 genetic variants as independent variables, with or without sCD14 plasma levels in the model: rs2395029, rs9264942, and CCR5Δ32 remained significant predictors of viral load, and the strength of the association did not change significantly when the regressions included sCD14 plasma levels (Table 2). Thus, the previously described genetic variants in the *HLA-B*, *HLA-C*, and *CCR5* regions and the sCD14 plasma levels are independently associated with HIV load at the set point.

DISCUSSION

HIV pathogenesis is the result of a complex interaction between the virus and the host response, which results in immune dysregulation. Many factors have been identified that independently contribute to pathogenesis, but their intricate relationships have yet to be fully elucidated. In particular, host genetic factors and systemic immune activation due to the translocation of microbial products from the gut have both been shown to have a strong impact on HIV control and disease progression, but these have not been studied in relation to each other. We therefore sought to measure plasma markers of GI tract damage and microbial translocation in clinically and genetically well-characterized patients from the SHCS.

We performed a GWAS searching for human genetic determinants of sCD14 or I-FABP plasma levels, and we failed to identify significantly associated variants after correction for multiple testing. Because our study was powered to detect variants that explain $\geq 4\%$ of sCD14 or I-FABP variability, we conclude that the plasma levels of these biomarkers are not primarily determined by common genetic variants with moderate to high effects.

We did not observe any association between a previously reported *CD14* promoter variant and sCD14 plasma levels, which strongly suggests that in untreated HIV-infected individuals,

this biomarker primarily reflects LPS bioactivity or microbial translocation rather than underlying genotype, in keeping with the demonstrated strength of this measurement as a predictive biomarker of disease progression. Of note, in the original report [11], homozygosity for the rs2569190 minor allele was associated with only a 0.04 \log_{10} -transformed sCD14 increase, whereas the range of \log_{10} -transformed sCD14 values was 5.9–6.6 ($\Delta = 0.7$) in our study population. Similarly, we did not identify any association between *FABP2* genotypic variation [13, 14] and plasma levels of I-FABP, which suggests that enterocyte damage, rather than genetically determined expression differences in I-FABP, drives the plasma level of I-FABP in HIV-infected patients.

We then searched for associations between sCD14 and I-FABP plasma levels and the degree of spontaneous HIV control (as reflected in viral load) during the chronic phase of HIV infection, and we found that sCD14 strongly associates with both I-FABP and viral load. Much of the previous work on sCD14 and I-FABP has focused on treated HIV infection, because gut damage, microbial translocation and systemic inflammation are the focus of current therapeutic efforts to decrease the non-AIDS morbid effects and premature death observed in patients with suppressed viremia receiving antiretroviral therapy. In a cohort of mostly treated HIV-infected individuals, Sandler et al [5] found a large increase in the risk of death with higher plasma sCD14 levels and an inverse association between plasma I-FABP level and CD4⁺ T-cell counts. A recent study by Hunt et al [4] found a significant correlation between I-FABP and sCD14 levels in treated subjects with advanced disease, and each marker strongly predicted mortality independently of CD4⁺ T-cell count [4]. In fact, a similar correlation between gut damage and LPS-induced monocyte activation has also been observed in HIV-negative subjects [22].

To date, only a single study has examined the predictive value of sCD14 for mortality in untreated chronic HIV infection [23]: sCD14 levels were correlated with both viral load and CD4⁺ T-cell count, and the association of sCD14 with disease progression was not independent of these parameters. Our study adds to this important area of research by also including a marker of enterocyte damage and testing the relationships between all these parameters in a larger, genetically homogeneous group of untreated individuals.

Our observation that I-FABP is associated with sCD14 but not with viral load during chronic untreated infection suggests that, although the virus itself begins and reinforces the vicious cycle of enterocyte damage, translocation of microbial products, and immune activation, these processes may become largely independent of viral replication in the chronic phase of untreated infection. This would be consistent with the high levels of immune activation that can still be observed in some individuals during fully suppressive antiretroviral therapy [2]. The interaction between these measures is likely to be bidirectional, because

enterocyte damage allows microbial translocation and sCD14 increase due to LPS-induced monocyte activation, whereas chronic immune activation is likely to further damage the GI tract barrier. Interestingly, this correlation between I-FABP and sCD14 plasma levels was not observed in primary HIV infection, suggesting that microbial translocation is not the primary driver of monocyte activation during the acute phase of infection [24].

The strong association that we found between sCD14 and viral load, which had already been described in a small group of untreated patients [5], is most likely indirect. The presence in plasma of microbial products, including LPS, leads not only to higher sCD14 levels but also to systemic inflammation, which is known to increase HIV load [25].

Considering the negative results of our genetic scan, specific limitations of the study design need to be highlighted. Some variability in sCD14 and I-FABP measurements was inevitable, which probably had a negative impact on study power. Each sample was tested in duplicate to deal with potential assay variability, but owing to the lack of suitable samples we did not repeat the measurements at different time points, which would have allowed a precise estimation of biological variability. Another potential confounder is the variable duration of HIV infection (3–6 years) before sampling, potentially leading to interindividual differences in disease progression. The exclusion of patients with moderate to severe immunosuppression (CD4⁺ T cell count, <350/μL of blood) aimed at mitigating this issue.

The absence of genetic associations with plasma I-FABP or sCD14 allows better interpretation of microbial translocation data and demonstrates that the previously identified genetic variants associated with HIV load are independent of sCD14. Our finding of associations between sCD14 and both I-FABP and viral load reinforces the centrality of microbial translocation in the pathogenesis of untreated HIV infection.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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