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Early Combination Antiretroviral Therapy Initiation During Primary HIV Infection Restricts HIV Reservoirs and Gut-Driven Inflammation but Fails to Rewire the Systemic Cytokine Landscape

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Background. HIV reservoirs, dysregulated cytokine profile, and gut barrier damage persist despite suppressive combination antiretroviral therapy (cART). Whether initiating cART during primary HIV infection (PHI) mitigates these pathological processes remains unclear.

Methods. We studied 55 individuals with PHI at baseline (T0), after 12 (T12), and 48 weeks (T48) of cART, 18 individuals with chronic HIV infection (CHI) and 10 sex-matched people without HIV (PWOH). Total HIV DNA was measured in peripheral blood mononuclear cells (PBMCs) using ddPCR, while cytokines profiles (IL-2, IL-4, TNF-α, IFN-γ) were measured in plasma by Luminex and antigen-specific T-cell responses were assessed in PBMCs of a subset of participants by intracellular cytokine staining. Microbial translocation markers (EndoCab, 1,3-β-D-glucan, lipopolysaccharide-binding protein [LBP], soluble CD14 [sCD14]) and gut barrier integrity markers (E-cadherin, I-FABP) were measured in plasma by ELISA, at each corresponding time point. Statistical analyses included Friedman tests with Dunn's multiple comparisons, Wilcoxon paired tests, and Mann–Whitney tests, as appropriate.

Results. At baseline, both groups displayed a cytokine profile characterized by elevated IL-4 levels compared with PWOH, with individuals with PHI showing significantly higher IL-2 levels and comparable IFN-γ and TNF-α levels to individuals with CHI. Over 48 weeks of cART, IL-4 and IL-2 declined only in individuals with PHI, yet, remained elevated compared with PWOH, whereas cytokine levels remained largely stable in individuals with CHI. Conversely, antigen-specific $CD4^+$ T-cell responses remained mainly Th1-skewed, with minimal IL-4 production. Individuals with PHI showed lower baseline sCD14, comparable to PWOH, which further declined during cART, whereas sCD14 remained elevated in individuals with CHI compared with PWOH. Markers of microbial translocation (LBP, 1,3-β-D-glucan) remained stable in individuals treated in PHI and comparable to PWOH but increased in individuals treated in CHI over time. E-cadherin levels were consistently lower in individuals with PHI, similar to PWOH. In contrast, I-FABP showed a non-significant decline over time only in individuals with PHI, while remaining higher in both individuals with PHI and CHI compared with PWOH.

Conclusions. Early cART initiation in individuals with PHI reduces viral reservoirs and limits gut barrier disruption and microbial translocation but fails to restore the systemic cytokine landscape compared with PWOH. These findings support the benefits of prompt treatment initiation during acute infection to limit HIV reservoir size and preserve mucosal integrity.

Keywords. cytokines; gut barrier damage; HIV reservoir; microbial translocation; primary HIV infection.

Received 08 July 2025; accepted 09 February 2026; published online 16 March 2026

Presented in part at 15° ICAR Italian Conference on AIDS and Antiviral Research, 14–16 June 2023, Bari, Italy, oral presentation; 19th European AIDS Conference, 19–21 October 2023, Warsaw, Poland, oral presentation.

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https://doi.org/10.1093/ofid/ofag077

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Primary HIV infection (PHI) represents a key pathogenic event for the establishment of viral reservoirs in cells and tissues [1]. At this stage, the HIV-1 virus integrates into the host cell genome, generating cells infected with latent proviral DNA. Combination antiretroviral therapy (cART) has radically improved the lives of people living with HIV (PWH), turning HIV/AIDS into a chronic disease [2]. Nevertheless, cART cannot eradicate HIV, as it persists in cellular and anatomical reservoirs of infected individuals, representing the main obstacle to achieving a definitive cure [3].

Cytokines are central regulators of the immune response and play a critical role in shaping the outcome of HIV infection. HIV infection is associated with profound alterations in circulating cytokine levels, with both pro-inflammatory and anti-inflammatory cytokines showing abnormal expression patterns from the earliest stages of infection [4]. This cytokine dysregulation contributes to T-cell dysfunction, chronic inflammation, and the establishment and maintenance of viral reservoirs despite effective cART [5]. Notably, while cART suppresses viral replication and restores CD4⁺ T-cell counts, systemic cytokine levels often remain elevated compared with people without HIV (PWOH), indicating persistent immune perturbation [5]. Early initiation of cART during PHI has been associated with a partial normalization of some cytokines, but full restoration of the systemic cytokine milieu is rarely achieved, highlighting the importance of early therapeutic intervention in limiting immune dysregulation.

The gastrointestinal tract is the earliest and principal site of inflammation and immune activation during HIV infection. In particular, HIV leads to a profound architectural disruption of the gut epithelial barrier, resulting in increased intestinal permeability and subsequent microbial translocation. This process contributes to enduring immune activation and inflammation despite effective cART [6, 7]. Microbial translocation is defined as the systemic release of lipopolysaccharide (LPS), a major immunostimulatory component of Gram-negative bacteria. LPS stimulation leads CD14⁺ monocytes/macrophages to secrete soluble CD14 (sCD14), which binds to LPS [8]. Evidence suggests that levels of sCD14, lipopolysaccharide-binding protein (LBP), and EndoCAb may be elevated since the earliest phases of HIV infection compared with levels in uninfected individuals [9]. The compromised integrity of the intestinal barrier exacerbates this phenomenon, leading to increased microbial translocation and inflammation. Interestingly, observations from intestinal biopsies of individuals with acute infection revealed higher expression of E-cadherin, a protein within the intestinal junctional complex, compared with chronic HIV infection [10]. This finding underscores the importance of early cART initiation to preserve mucosal integrity, limit microbial translocation, and mitigate systemic immune activation associated with disease progression.

In addition to LPS, 1,3-beta-D-glucan, a major component of fungal cell walls, serves as a marker of microbial translocation. Its elevated plasma levels in HIV individuals are associated with intestinal epithelial damage, immune activation, inflammation, and the risk of developing non-AIDS–related events [11].

While HIV reservoirs, cytokine dysregulation, and gut barrier damage persist in cART-treated individuals, it remains unclear whether early initiation of cART during PHI can reverse these phenomena. With this question in mind, we investigated total HIV DNA, circulating cytokine profiles, antigen-specific Th1- and Th2-type responses in CD4⁺ T-cells in a subgroup of participants, markers of monocyte activation, microbial translocation, and gut barrier damage in PWOH, individuals with PHI and chronic HIV infection (CHI) during cART.

MATERIALS AND METHODS

Study Population

We consecutively enrolled individuals with PHI from the INACTION (Italian Network of Acute HIV Infection) trial, a multicentric open-label randomized study and compared them to age and sex-matched individuals starting cART during chronic HIV infection with CD4+ T-cell counts ≥ 500/µL (CHI) from the Clinic of Infectious Diseases and Tropical Medicine in San Paolo Hospital, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy. PHI diagnosis was established based on a positive p24 antigenemia or detectable HIV-RNA with a negative/indeterminate Western Blot confirmation assay; staging of HIV infection was made according to Fiebig classification [12]. Ten sex-matched PWOH were included as controls.

Individuals with PHI had a stored biological samples collected prior to cART (T0), after 12 (T12) and after 48 weeks of cART (T48); individuals with CHI at T0 and T48 weeks from cART. Blood samples were obtained following the provision of informed consent, which was approved by the Institutional Review Board at the ASST Santi Paolo e Carlo, Milan, Italy. All research was performed in accordance with the Declaration of Helsinki.

Quantification of Total HIV DNA

Total DNA was extracted from the peripheral blood mononuclear cells (PBMCs) previously isolated, using Qiamp DNA Mini Kit, following the manufacturer's protocol. Extracted DNA was digested using the restriction enzyme MSCII (Thermo Fischer Scientific) at 37 °C for 1 h. Primer/probe set to conserved regions of HIV-gag and an RPP30 (RNAse P) primer/probe set were used for HIV DNA quantification. Samples were diluted 10-fold for RPP30 assay. Total HIV DNA was measured in duplicate on ddPCR with the QX100 Droplet Digital PCR platform (Bio-Rad). The ddPCR reaction mix consisted of 10 µL 2XddPCR super mix for probes (Bio-Rad), 750 nM primers, 250 nM probes, and 5 µL of

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digested DNA. ddPCR amplification reactions consisted of initial denaturation at 95 °C for 10 minutes, followed by 39 cycles of 94 °C for 30 seconds denaturation, 55 °C for 1 minute annealing, and 98 °C for 10 minutes elongation. Droplets were read by the QX100 droplet reader, and the data were analyzed using the QuantaSoft analysis software (Bio-Rad Quanta Soft v 1.7). Results are reported as copies/10^6 PBMCs, and the quantities of total HIV DNA were normalized to the reference gene RPP30 measured by ddPCR.

Quantification of Circulating Cytokine Profile

Circulating cytokine profile, ie, TNF-α, IFN-γ, IL-2, and IL-4, was assessed by Luminex technology (Austin, TX, USA), according to the manufacturer's instructions.

Intracellular Cytokine Staining and Antigen-Specific T-Cell Stimulation Assay

In a subgroup of individuals (n = 5 individuals in PHI at T0 and T 48 and n = 5 individuals in CHI at T0 and T 48), HIV- and CMV-specific T-cells were evaluated using intracellular cytokine staining following antigen-specific stimulation.

Briefly, cryopreserved PBMCs were thawed and 1.5×10^6 cells were plated in complete RPMI containing 10% human serum supplemented with 1% penicillin–streptomycin–glutamine. After 3 hours resting, PBMCs were stimulated with PepMix™ HIV (GAG) Ultra (1 µg/mL, JPT) and with PepTivator CMV pp65 (15-mer peptides with 11 aa overlap covering the complete sequence of the pp65 protein of human cytomegalovirus) (1 µg/mL, Miltenyi Biotec). Staphylococcus enterotoxin B (SEB) (1 µg/mL) was used as positive control, while unstimulated controls received equivalent volume of sterile H_2O. All conditions were left for 18 hours at 37 °C, with addition of 1 × Golgi Stop and Golgi Plug (BD Biosciences) one hour after stimulation to allow intracellular cytokine detection. The staining was performed as follow: viability staining (15 minutes, RT) (Viobility Fixable Dye, Miltenyi Biotec), surface antigens staining (20 minutes, RT), fixation/permeabilization (Cytofix/Cytoperm, BD Biosciences), and intracellular cytokines staining (30 minutes, RT). Unspecific activation in unstimulated controls was subtracted from stimulated samples to account for specific activation. Immunophenotype was assessed evaluating the frequency of cells in the unstimulated control expressing the surface markers. An example of gating strategy used is represented in Supplementary S1.

Quantification of Plasma Markers of Monocyte Activation, Microbial Translocation, and Gut Barrier Damage

sCD14, EndoCab IgG Human, human lipolysaccharide binding protein LBP, human 1,3-beta-D-glucan, I-FABP and E-cadherin markers were measured by ELISA (EndoCab IgG cod HYC-HK504-IGG, Hycult Biotech, Uden, The Netherlands; LBP cod E0360HU-96; 1,3-beta-D-glucan cod E4111hu-96, BT LAB, Shanghai, China; Human sCD14 Immunoassay cod DC140; Human I-FABP Immunoassay cod DFBP20 and Human E-cadherin Immunoassay cod DCADE0B, R&D Systems, Minneapolis, MN, USA), following the manufacturer's instructions. The optical density of each well was measured using the microplate reader set to 450 nm (EnSight™ multimode plate reader, PerkinElmer Inc. Canada).

Statistical Analysis

Descriptive and statistical analyses were performed using GraphPad Prism 10.4.2 (GraphPad Inc., La Jolla, CA, USA).

Categorical variables were reported as percentages (Fisher's exact test) and continuous variables were reported as median (interquartile range). Comparisons among groups were performed by Mann–Whitney *U* test. The non-parametric paired Friedman with Dunn's multiple comparisons test was used for longitudinal analyses between T0, T12, and T48 in individuals with PHI. Wilcoxon matched-pairs signed rank test was used for longitudinal analyses between T0 and T48 in individuals with CHI. Mann–Whitney *U* test was used for cross-sectional analyses comparing different study groups and to compare each group with PWOH. Spearman's correlation test was used to correlate HIV DNA and plasma inflammation markers. A P-value < .05 was considered statistically significant.

RESULTS

Study Population

Fifty-five individuals with PHI (19/55 in Fiebig stages I–III; 36/55 in Fiebig stages IV–V) and 18 individuals with CHI were studied (Table 1). No significant differences were observed between the groups in terms of demographics. However, before starting cART (T0), individuals with PHI had significantly higher HIV-RNA levels and significantly lower absolute and percentage CD4+ T-cells compared with individuals with CHI. Additionally, we observed a significant difference in the antiretroviral therapy regimen at study enrollment, as individuals treated in PHI were treated according to therapy allocation per randomization arm [13].

We first assessed changes in viro-immunological parameters following treatment in both study groups (Figure 1). As expected, a reduction of HIV-RNA levels was observed in both groups (PHI T0–T12 < 0.0001, PHI T0–T48 < 0.0001, CHI T0–T48 < 0.0001; Figure 1*A*). Additionally, cART led to CD4+ T-cell reconstitution, with a significant increase of the percentage of CD4+ T-cell (PHI T0–T12 < 0.0001, PHI T0–T48 < 0.0001, CHI T0–T48 < 0.0001; Figure 1*B*), absolute numbers of CD4+ T-cell (PHI T0–T12 < 0.0001, PHI T0–T48 < 0.0001, CHI T0–T48 = 0.0008; Figure 1*C*), and consequently an increase of CD4/CD8 ratio in individuals with PHI and CHI (PHI T0–T12 < 0.0001, PHI T0–T48 < 0.0001, CHI T0–T48 = 0.01; Figure 1*D*) after cART.

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Table 1. Demographic and Clinical Features of the Study Population Before Starting cART (T0)

	PHI T0 (n = 55)	CHI T0 (n = 18)	*P* Value
Age, y, median (IQR)	34 (27–45)	31 (26–45)	.6
Sex, n (%)			
Male	53 (96.36%)	16 (88.89%)	.2
Female	2 (3.64%)	2 (11.11%)	
Previous AIDS diagnosis, n (%)	0 (0%)	1 (5.56%)	.2
Viro-immunologic parameters, median (IQR)			
%CD4 at T0	21.6 (15–29)	29.5 (25–35.25)	.0003
CD4 at T0, cells/μL	551 (395–653)	645.5 (576.3–756.3)	.007
%CD8 at T0	53.1 (47.4–67.6)	46 (37–50.25)	.001
CD8 at T0, cells/μL	1301 (836–2376)	986.5 (786.3–1558)	.1
CD4/CD8 ratio at T0	0.39 (0.22–0.58)	0.6 (0.49–0.85)	.001
HIV-RNA, copies/mL, median (IQR)	676 722 (55 375–4 547 657)	22 534 (5262–86 524)	<.0001
Fiebig stage, n (%)			
I-III	19 (34.54%)	NA	NA
IV-VI	36 (65.45%)	NA	
M between HIV diagnosis and cART initiation, median (IQR)	NA	2.5 (0.66–5.42)	NA
cART regimen, n (%)			
INSTI-based (3DR)	20 (36.36%)	10 (55.5%)	
INSTI-based (2DR)	0 (0%)	3 (16.6%)	
NNRTI-based (3DR)	0 (0%)	5 (27.7%)	<.0001
PI-based (3DR)	19 (34.54%)	0 (0%)	
INSTI + PI-based (4DR)	16 (29%)	0 (0%)	
HBsAg, n (%)	0 (0%)	0 (0%)	>.9999
HCV, n (%)	2 (3.77%)	2 (11.76%)	.2

cART, combination antiretroviral therapy; *INSTI*, integrase strand transfer inhibitor (INSTI-based 3DR: PHI = 20 emtricitabine/tenofovir alafenamide fumarate TAF/dolutegravir; CHI = 6 dolutegravir/abacavir/lamivudine, 1 emtricitabine/TAF/bictegravir, 2 emtricitabine/TAF/dolutegravir, 1 emtricitabine/tenofovir disoproxil fumarato TDF/dolutegravir; INSTI-based 2DR: CHI = 3 dolutegravir/lamivudine); *NNRTI*, non-nucleoside reverse transcriptase inhibitor (NNRTI-based 3DR: CHI = 5 emtricitabine/TAF/rilpivirine); *PI*, protease inhibitor (PI-based 3DR: PHI = 19 TAF/emtricitabine/darunavir); INSTI + PI-based 4DR: PHI = 16 TAF/emtricitabine/dolutegravir/darunavir).

**Statistical analyses*, Mann–Whitney *U* test, Fisher exact test, Chi-square test, as appropriate.

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Individuals With PHI Exhibit Greater HIV DNA Reduction During cART Compared with Individuals With CHI

We first investigated the levels of total HIV DNA during cART in the 2 study groups.

Despite comparable HIV DNA levels at T0 (Figure 1*E*), a significant contraction of HIV DNA during cART was observed in individuals with PHI (PHI, T0: 4.6 $\log_{10}$ copies/10^6 PBMCs [4.2–5], T12: 4.2 $\log_{10}$ copies/10^6 PBMCs [3.9–4.5], $P = .003$; T48: 3.7 $\log_{10}$ copies/10^6 PBMCs [3.3–4], $P < .0001$ and $P = .01$ for T48 vs T0 and T12, respectively) yet not individuals treated in CHI, who showed only a non-significant trend toward HIV DNA reduction (CHI, T0: 4.5 $\log_{10}$ copies/10^6 PBMCs [4.2–4.9]; T48: 4 $\log_{10}$ copies/10^6 PBMCs [3.7–4.7], $P = .09$; Figure 1*E*), with the net result of substantially lower HIV DNA in individuals in PHI versus CHI at week 48 ($P = .007$; Figure 1*E*). Furthermore, in individuals treated in PHI, cART was able to reduce HIV DNA levels in both Fiebig Stages I–III and IV–VI (Fiebig I–III T0–T48: 4.4 $\log_{10}$ copies/10^6 PBMCs [4–5] vs 3.5 $\log_{10}$ copies/10^6 PBMCs [3.1–3.8], $P = .0002$; Fiebig IV–VI T0–T48: 4.6 $\log_{10}$ copies/10^6 PBMCs [4.2–5] vs 3.8 $\log_{10}$ copies/10^6 PBMCs [3.4–4.1], $P < .0001$; Supplementary Figure 2*A*). Finally, no statistically significant difference in HIV DNA levels was noted between Fiebig I–III and Fiebig IV–VI at all time points.

Systemic Cytokine Profile in Individuals With PHI and Individuals With CHI

Next, we assessed the levels of circulating cytokines IL-2, IFN-γ, TNF-α, and IL-4.

Figure 2*A* and *B* shows the proportion of the cytokine profile in the 2 study groups, before and after antiretroviral therapy.

At T0, both individuals treated in PHI and CHI displayed a predominance of the cytokine IL-4, which persisted after 48 weeks of cART (Figure 2*A* and *B*). Individuals with PHI had significantly higher plasma IL-4 levels at baseline compared with individuals with CHI (T0: 1.5 $\log_{10}$ pg/mL [1.3–1.6] vs 1.2 $\log_{10}$ pg/mL [1.1–1.4] in CHI; $P = .01$), which decreased significantly after 48 weeks of cART (1.5 $\log_{10}$ pg/mL, [1.3–1.6] vs 1.3 $\log_{10}$ pg/mL [1.1–1.6] $P = .02$, Figure 2*C*). People without HIV showed significantly lower IL-4 plasma levels compared with individuals with PHI at all 3 time points ($P < .0001$) and compared with individuals with CHI at both T0 and T48 ($P < .0001$, Figure 2*C*). At baseline (T0), individuals with PHI

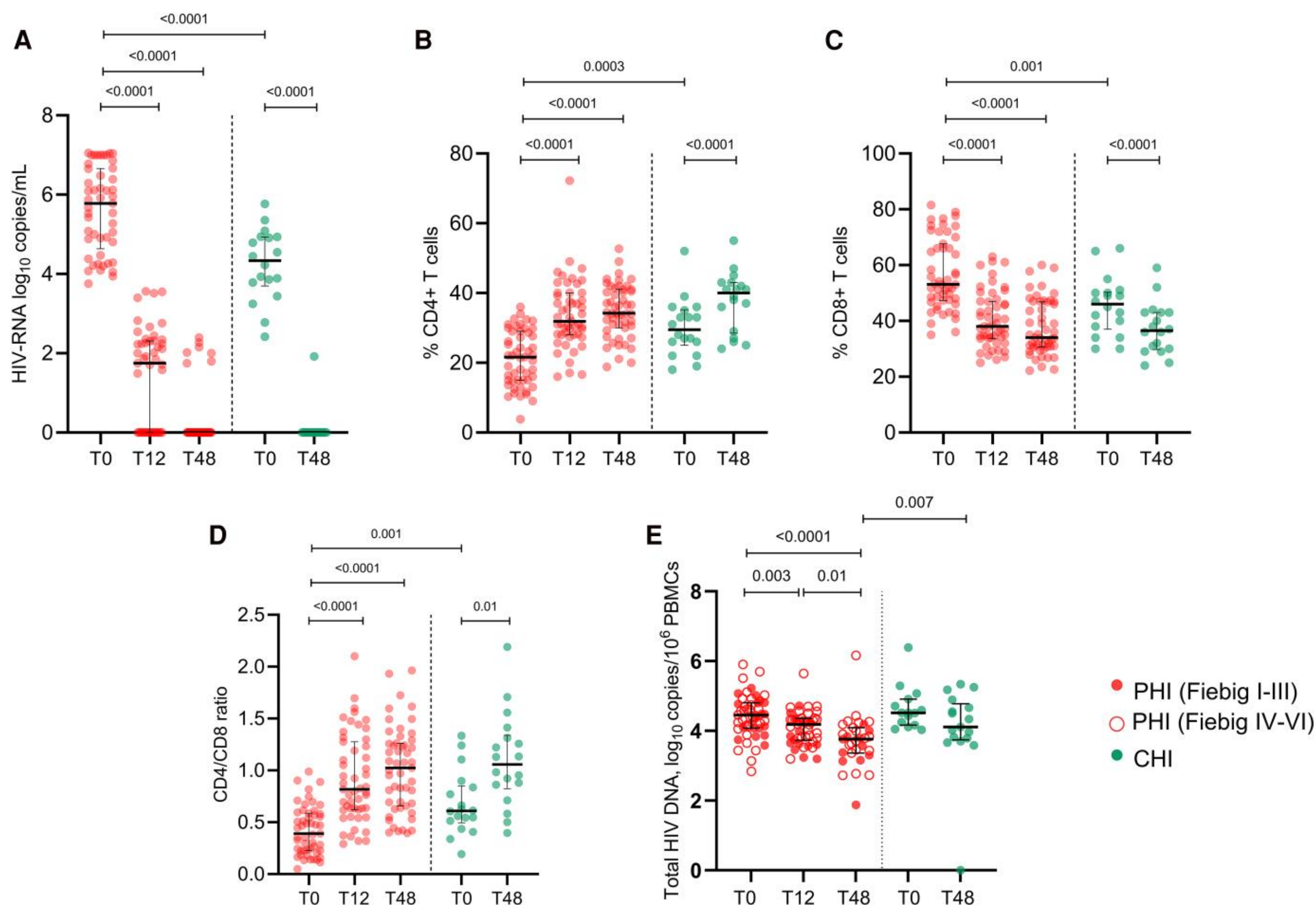

Figure 1. Viro-immunological parameters during cART in individuals with PHI and in individuals with CHI. HIV-related parameters in individuals with PHI and CHI at T0, T12, and T48. Friedman with Dunn's multiple comparisons test (PHI T0-T12-T48), Wilcoxon matched-pairs signed rank test (CHI T0-T48) and Mann–Whitney test (PHI-CHI at T0 and T48) (*A*–*D*). Total HIV DNA reported as copies/10^6 was quantified in PBMCs from individuals with PHI and individuals with CHI at T0, T12, and T48 (*E*). Friedman with Dunn's multiple comparisons test (PHI T0-T12-T48), Wilcoxon matched-pairs signed rank test (CHI T0-T48) and Mann–Whitney *U* test (PHI-CHI at T0 and T48). Full red dots indicate individuals with PHI in Fiebig Stages I–III, empty red dots indicate individuals with PHI in Fiebig Stages IV–VI. Friedman with Dunn's multiple comparisons test (Fiebig I–III T0-T12-T48 and Fiebig IV–VI T0-T12-T48).

had significantly higher levels of IL-2 (0.8 $\log_{10}$ pg/mL [0.6–1] vs 0.5 pg/mL [0.4–0.8]; $P = .007$) versus individuals with CHI, with a significant reduction after 48 weeks of cART (0.8 $\log_{10}$ pg/mL [0.6–1] vs 0.6 $\log_{10}$ pg/mL [0.4–1]; $P = .04$, Figure 2*D*). People without HIV displayed significantly lower IL-2 levels compared with both PHI and CHI groups at all corresponding time points ($P < .0001$, Figure 2*D*).

Despite no major differences in IFN-γ and TNF-α between groups before starting cART, at T48, individuals with PHI showed significantly lower IFN-γ plasma levels (0.1 $\log_{10}$ pg/mL [0–0.8] vs 0.8 $\log_{10}$ pg/mL [0.4–0.9]; $P = .004$) compared with individuals with CHI (Figure 2*E* and *F*). Moreover, PWOH exhibited significantly lower levels of IFN-γ (T0: $P = .04$, T48 $P = .04$, Figure 2*E*) and TNF-α (T0: $P = .05$, T48 $P = .02$, Figure 2*F*) compared with individuals with CHI at both T0 and T48, consistent with the lower systemic immune activation observed in controls.

No significant correlations were observed between HIV DNA levels and any of the inflammatory markers analyzed (data not shown).

No major differences were observed between Fiebig I–III and Fiebig IV–VI at any time point (Supplementary Figure 2*C*–*E*). However, IL-4 levels decreased significantly over time in Fiebig I–III participants at T48 (1.6 $\log_{10}$ pg/mL [1.4–1.7] vs 1.3 $\log_{10}$ pg/mL [1–1.58]; $P = .009$; Supplementary Figure 2*B*), whereas no significant changes were observed in Fiebig IV–VI.

To evaluate the potential contribution of T-cells to the unbalanced plasma cytokine profile, we measured antigen-specific cytokine production following stimulation with HIV Gag or CMV pp65 peptide pools in a subgroup of participants (n = 5 PHI at T0 and T48; n = 5 CHI at T0 and T48). At baseline, HIV-specific $CD4^+$ T-cell responses were predominantly Th1-oriented in both individuals with PHI and CHI, with IL-2 comprising the largest fraction at T0 and decreasing by

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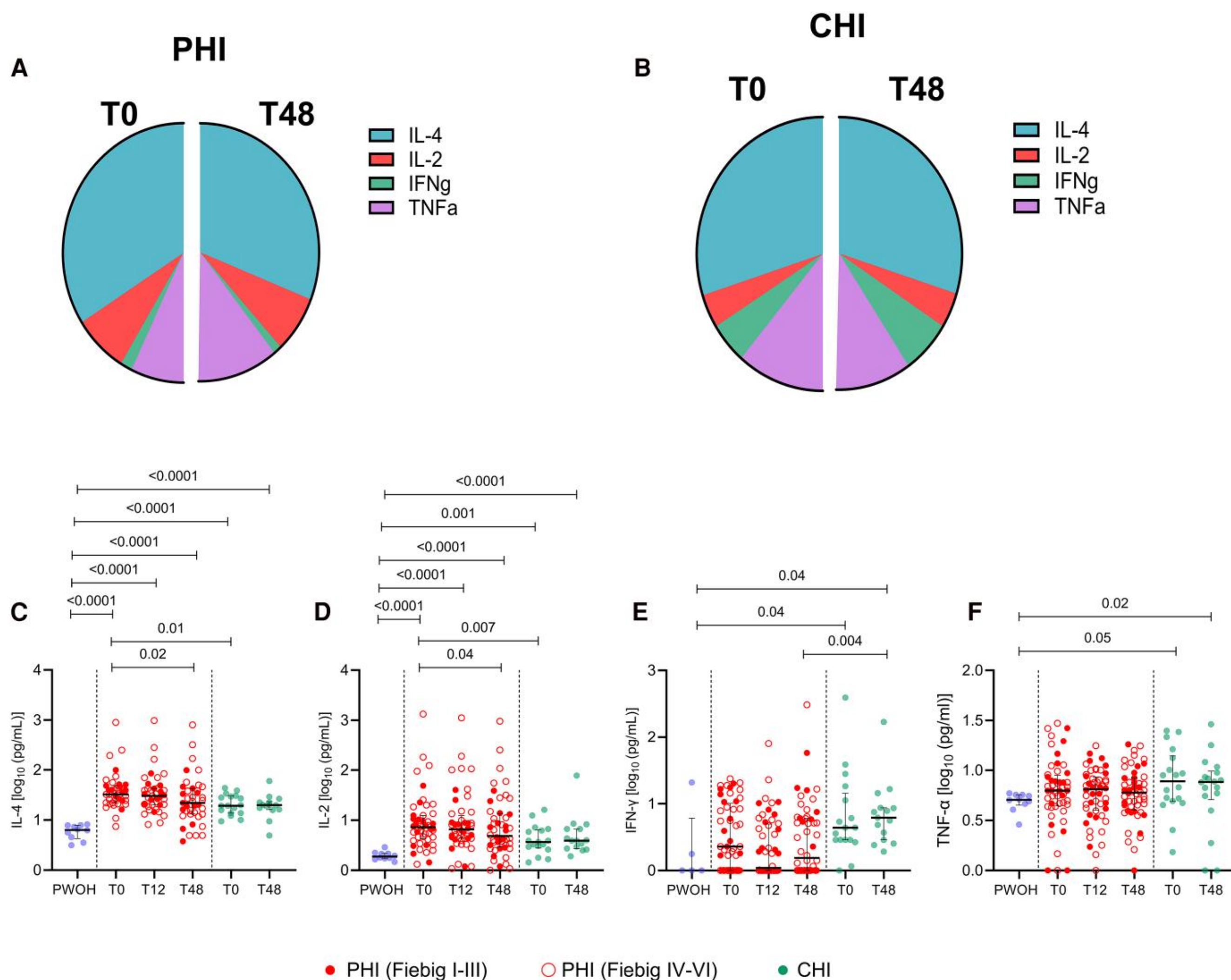

Figure 2. Circulating cytokine profile in individuals with primary HIV infection (PHI) and in individuals with chronic HIV infection (CHI). Pie charts: proportion of cytokines expressed as percentage in individuals with PHI and CHI, before and after combination antiretroviral therapy (cART) (*A–B*). Levels of circulating cytokines (IL-4, IL-2, IFN-γ, and TNF-α) were measured in plasma samples from individuals with PHI and CHI during cART and from age- and sex-matched PWOH (*C–F*). Friedman with Dunn's multiple comparisons test (PHI T0-T12-T48), Wilcoxon matched-pairs signed rank test (CHI T0-T48) and Mann–Whitney *U* test (PHI-CHI at T0 and T48, and to compare each group with PWOH). Full red dots indicate individuals with PHI in Fiebig Stages I–III, empty red dots indicate individuals with PHI in Fiebig Stages IV–VI. Friedman with Dunn's multiple comparisons test (Fiebig I–III T0-T12-T48 and Fiebig IV–VI T0-T12-T48).

T48 in both groups (Supplementary Figure 3*A* and *B*). Similarly, CMV-specific responses were also primarily Th1-biased across all groups (Supplementary Figure 3*C* and *D*).

Individuals With PHI Display Higher sCD14 Decline and Limited Microbial Translocation

After describing the cytokine profile in individuals treated in PHI and CHI, we evaluated the levels of sCD14, a marker of monocyte activation.

At T0, individuals with PHI showed a significantly lower circulating sCD14 (0.4 $\log_{10}$ μg/mL [0.3–0.45] vs 0.6 μg/mL [0.56–0.63]; $P < .0001$; Figure 3*A*) compared with individuals with CHI. Forty-eight weeks of cART further reduced sCD14 levels in PHI (0.4 $\log_{10}$ μg/mL [0.3–0.45] vs 0.37 $\log_{10}$ μg/mL [0.34–0.4]; $P = .008$), yet, not in individuals with CHI, resulting in significantly lower circulating sCD14 in PHI (vs 0.37 $\log_{10}$ μg/mL [0.34–0.4] vs 0.6 $\log_{10}$ μg/mL [0.55–0.61]; $P < .0001$; Figure 3*A*) with no differences according to Fiebig stage (Supplementary Figure 2*F*). When compared with PWOH, no significant differences in sCD14 levels were observed between PWOH and individuals with PHI at any time point, whereas PWOH displayed significantly lower sCD14 levels compared with individuals with CHI both at T0 and T48 ($P < .0001$, Figure 3*A*).

Since CD14 has been associated to monocyte activation driven by intestinal damage [14], we next sought to investigate possible differences in microbial translocation between the

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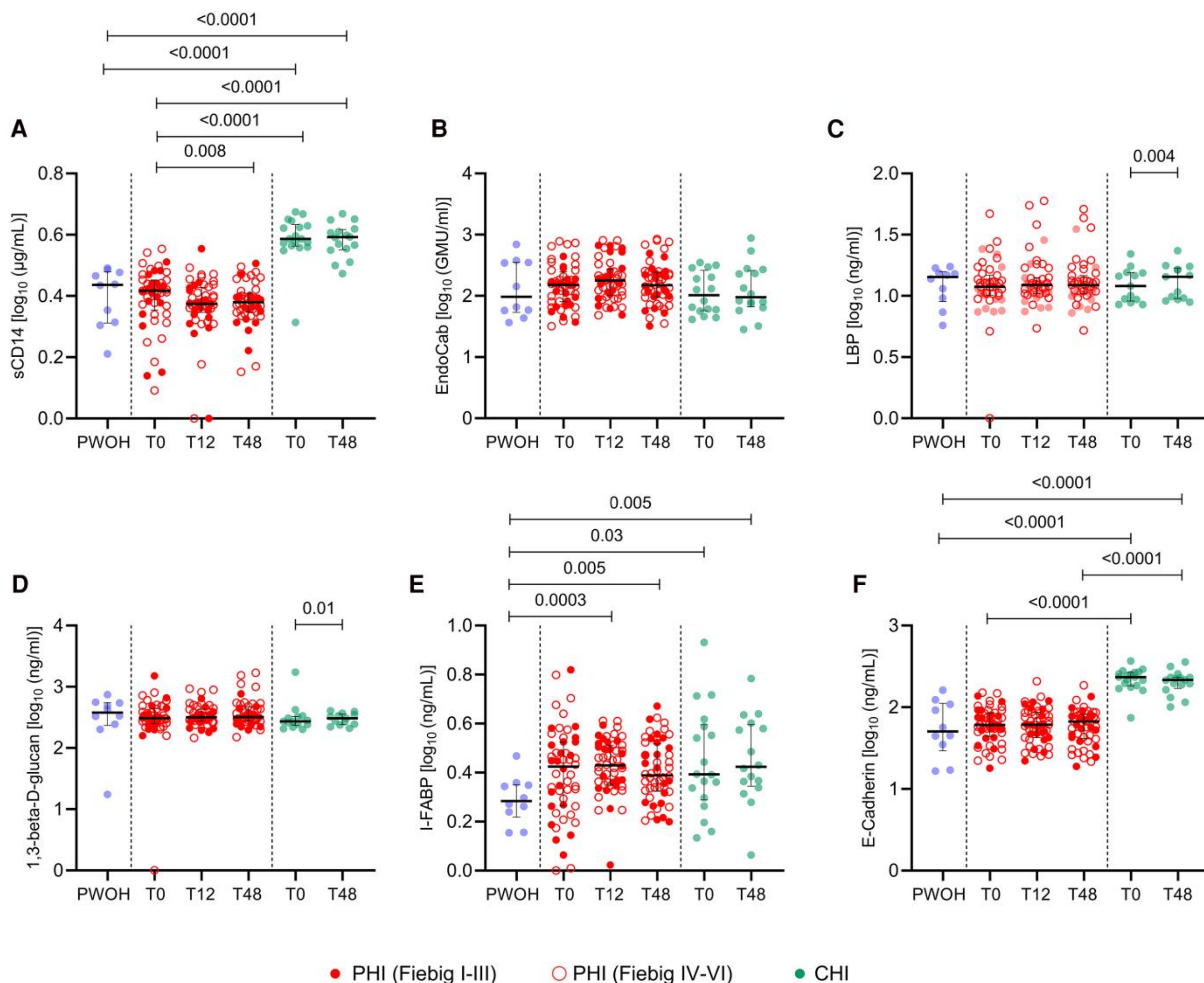

Figure 3. Circulating markers of monocyte activation, microbial translocation, and gut barrier integrity in individuals with PHI and in individuals with CHI. Markers of monocyte activation (sCD14) (*A*), microbial translocation (EndoCab, LBP, 1,3-beta-D-glucan) (*B–D*), and intestinal barrier integrity damage (I-FABP, E-cadherin) (*E–F*) were measured in plasma samples from individuals with PHI and CHI during cART and from age- and sex-matched PWOH. Friedman with Dunn's multiple comparisons test (PHI T0-T12-T48), Wilcoxon matched-pairs signed rank test (CHI T0-T48) and Mann–Whitney *U* test (PHI-CHI at T0 and T48 and to compare each group with PWOH). Full red dots indicate individuals with PHI in Fiebig Stages I–III, empty red dots indicate individuals with PHI in Fiebig Stages IV–VI. Friedman with Dunn's multiple comparisons test (Fiebig I–III T0-T12-T48 and Fiebig IV–VI T0-T12-T48).

2 groups by assessing circulating EndoCab, LBP and 1,3-β-D glucan. Despite no significant differences in both EndoCab and LBP levels at baseline, the latter demonstrated a significant rise at T48 in individuals with CHI only (1 $\log_{10}$ ng/mL [0.9–1.1] vs 1.1 $\log_{10}$ ng/mL [0.9–1.2] $P = .006$, Figure 3C). Interestingly, Fiebig I–III individuals displayed lower LBP than Fiebig IV–VI, at T48 (Fiebig I–III 1 $\log_{10}$ ng/mL [0.9–2] vs Fiebig IV–VI 1.1 $\log_{10}$ ng/mL [1–1.2], $P = .01$; Supplementary Figure 2H). A similarly pattern was shared by 1,3-β-D glucan plasma levels with a significant increase only in individuals treated in CHI at T48 (2.43 $\log_{10}$ ng/mL [2.36–2.5] vs 2.48 $\log_{10}$ ng/mL [2.38–2.55] $P = .01$, Figure 3D). No significant differences in EndoCab, LBP, or 1,3-β-D-glucan levels were detected between PWOH and either PHI or CHI groups.

Individuals With PHI Show Reduced Epithelial Disruption and Enterocyte Damage vs CHI

Having shown a raising trend in biomarkers of microbial translocation in individuals with CHI, we asked whether this might be fueled by damage to the intestinal barrier and whether early initiation of cART could maintain intestinal barrier integrity by measuring circulating IFABP and E-cadherin.

Although prior to cART, start I-FABP levels were comparable between individuals treated in PHI and CHI, individuals

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with PHI displayed a non-significant reduction in I-FABP levels at T48 (0.42 log_{10} ng/mL [0.2–0.5] vs 0.38 log_{10} ng/mL [0.32–0.51]; $P = .08$; Figure 3E), which was not observed in individuals with CHI, with no differences according to Fiebig stages (Supplementary Figure 2J). When compared with controls, PWOH exhibited significantly lower I-FABP levels than individuals with PHI at T12 ($P = .0003$) and T48 ($P = .005$, Figure 3E), as well as lower levels than individuals with CHI at both T0 ($P = .03$) and T48 ($P = .005$, Figure 3E).

Interestingly, individuals with PHI displayed significantly lower circulating E-cadherin than individuals with CHI at both T0 and T48 (T0: 1.78 log10 ng/mL [1.64–1.93] vs 2.36 [2.26–2.42]; $P < .0001$; T48: 1.82 log10 ng/mL [1.61–1.91] vs 2.33 log10 ng/mL [2.23–2.36]; $P < .0001$; Figure 3F), with no further changes in both individuals with PHI and CHI during cART, suggesting that early initiation of cART may prevent cell junction damage. PWOH showed comparable E-cadherin levels to PHI at both time points but significantly lower levels compared with CHI at T0 ($P < .0001$) and T48 ($P < .0001$; Figure 3F). Finally, no differences were noted when stratifying according to Fiebig stage (Supplementary Figure 2K).

DISCUSSION

In this study, we evaluated total HIV DNA, circulating cytokines profiles, antigen-specific T-cell responses in a subset of participants, markers of monocyte activation, microbial translocation, and gut barrier damage in PWOH, individuals with primary (PHI) and chronic (CHI) HIV infection undergoing cART, with the specific aim to determine whether early cART initiation during PHI helps contain these pathological processes.

As expected, cART effectively reduced HIV viral load and promoted reconstitution of the CD4+ T-cell compartment, increasing both percentages and absolute counts, as well as the CD4/CD8 ratio, in participants with PHI at 12 and 48 weeks as well as in participants with CHI at 48 weeks [15]. Both groups achieved virological suppression and significant immune recovery after treatment [16]. The greater magnitude of change observed in the PHI group likely reflects their lower baseline CD4 counts and higher CD8 percentages and viral loads at treatment initiation, rather than an inherently stronger viro-immunologic response to early therapy.

Although baseline HIV DNA levels were comparable between the 2 groups prior to cART initiation, a significant reduction in total HIV DNA was observed only in participants with primary HIV infection at both early (3 months) and later (1 year) timepoints on cART. In contrast, individuals with CHI showed only a non-significant trend toward HIV DNA decline, altogether confirming the role of early ART start in enhancing immune recovery and limiting viral reservoir establishment [15–19].

These results are in line with literature data demonstrating that PLWH who initiate cART in primary infection maintain smaller reservoirs on suppressive cART than those starting therapy during chronic infection [20–22]. Notably, early initiation of cART during the earliest Fiebig I/II stages has been shown to reduce total HIV DNA levels by 20-fold after just 2 weeks and by up to 316-fold after 3 years [23].

In line with previous reports, our data demonstrated a systemic cytokine imbalance in people living with HIV, characterized by elevated baseline plasma cytokine levels compared with PWOH [4]. Specifically, both individuals with primary (PHI) and chronic (CHI) HIV infection exhibited elevated plasma IL-4 at baseline, which declined significantly over time only in PHI, while remaining persistently high in individuals with CHI. Similarly, IL-2 levels decreased over 48 weeks of cART only in PHI, remaining relatively stable in individuals with CHI. In contrast, no major differences in IFN-γ and TNF-α levels were observed between individuals with PHI and CHI at baseline or during cART, except for a lower IFN-γ level in individuals with PHI at 48. These findings suggest that early treatment may partially restore the balance of systemic cytokines; yet, levels remain elevated compared with PWOH, indicating persistent immune activation despite effective therapy [4, 24, 25].

In order to investigate whether the elevated plasma IL-4 cytokines reflected $CD4^+$ T-cell polarization, we performed HIV- and CMV-antigen–specific responses on a subgroup of participants, given that CMV is highly prevalent in people living with HIV and contributes to chronic immune activation [26].

Our results indicated that antigen-specific $CD4^+$ T-cells contribute negligibly to the elevated plasma IL-4 levels, as responses to both HIV and CMV were predominantly Th1-type cytokines [27].

Therefore, the Th2-biased plasma cytokine environment did not mirror $CD4^+$ T-cell polarization. Growing evidence suggests that IL-4 could be produced by innate immune cells, including type 2 innate lymphoid cells (ILC2 seconds), basophils, and eosinophils [28]. ILC2 seconds secrete IL-4, IL-5, and IL-13 upon activation by innate signals (eg, IL-33, IL-25, leukotrienes) [29, 30], while basophils rapidly produce IL-4 independently of T-cell antigen specificity [31, 32], contributing to systemic Th2-type environments in inflammatory conditions, including HIV infection.

Taken together, our findings suggest that, although plasma IL-4 was elevated, antigen-specific $CD4^+$ T-cells retained a Th1-dominant profile, particularly during primary infection.

We next investigated the plasmatic levels of sCD14, a marker of monocyte activation [33] that has been shown to be a surrogate marker for the extent of subclinical atherosclerotic disease in cART-treated PLWH with chronic infection. Accordingly, elevated sCD14 has been shown to predict disease progression also during primary HIV, being associated with a more rapid CD4 decline and an increased risk of death from coronary

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artery disease [14]. Interestingly, our data show significantly lower circulating sCD14 in individuals treated in PHI versus individuals with CHI at T0, with a further decrease upon cART only in participants with PHI, resulting in significantly lower levels in individuals with PHI versus CHI after 1 year of cART.

Because circulating sCD14 has been shown to be mainly driven by microbial translocation [4, 8], we next asked whether individuals with PHI and CHI might feature a different modulation of systemic translocation of microbial biomarkers [34, 35]. Unexpectedly, pre-therapy EndoCab, LBP, and 1,3-β-D glucan levels were comparable between the 2 groups, suggesting similar microbial translocation despite different timing of cART start. Interestingly enough, however, a divergent trend was shown after 1 year of successful therapy: while LBP and β-glucan levels remained unchanged in individuals with PHI, both markers increased significantly in individuals with CHI. Our data are in agreement with other studies and clearly suggest that the duration of infection before therapy does indeed affect the degree of microbial translocation during cART, at the advantage of individuals who have the chance to start early [11, 36].

We subsequently explored whether such differential microbial translocation could be attributed to differences in the extent of intestinal barrier damage. We therefore assessed plasma levels of I-FABP, a specific and abundant protein in the epithelial cells of the small intestine [37], which is released into the bloodstream following mucosal injury. Because elevated I-FABP plasma levels have been shown to correlate with the severity of intestinal damage [38, 39], it can be considered an indicator of intestinal damage in PLWH [40, 41]. In our cohort, no major differences were found in I-FABP levels between participants with PHI and CHI apart from a trend toward I-FABP reduction after 48 weeks of cART exclusively in individuals with PHI.

Finally, we proceeded by evaluating the levels of E-cadherin, a member of the cadherin (calcium-dependent adhesion molecules) family of type I transmembrane proteins that forms tight intracellular connections between cells within epithelial surfaces [42]. Being expressed at high levels within the gastrointestinal epithelium, disruption of the integrity of mucosal membranes can lead to the release of a soluble form of E-cadherin into the plasma [43, 44]. Consistent with sCD14 data, we observed significantly lower circulating E-cadherin in individuals treated in PHI compared with individuals with CHI prior to cART initiation, suggesting that intestinal damage occurs later in the course of chronic infection. These findings align with prior research from our group on intestinal biopsies, demonstrating higher E-cadherin expression during the acute compared with the chronic phase [10]. Moreover, after 48 weeks of treatment, E-cadherin levels were significantly reduced in PHI compared with CHI individuals, highlighting the beneficial effect of starting cART in the acute phase of infection.

A limitation of our study is that PWOH were only sex-matched. Although age may influence biomarkers of microbial translocation and intestinal damage, our PWOH controls were all under 50 years of age (median 45 years) and not substantially older than the individuals with PHI and CHI, minimizing the potential impact of age on the observed differences.

In conclusion, early initiation of cART in primary HIV infection has the clear advantage of reducing the size of the HIV reservoir but fails to restore the systemic cytokine landscape. Furthermore, monocyte activation and intestinal integrity damage are limited during primary infection and are contained by cART treatment compared with chronic infection, thus suggesting that early initiation of cART during primary infection might limit gut barrier damage and maintain intestinal homeostasis by preventing microbial translocation-driven inflammation.

Data availability. The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. The study was supported in part by the Italian Ministry of Health (Ricerca Finalizzata) (number NET-2013–02355333-3) to G.M.

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

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