Interleukin-37 (IL-37) has been identified as a cytokine with potent antiinflammatory and immunosuppressive functions. The aim of this study was to compare levels of IL-37 mRNA in immunological subgroups of chronic human immunodeficiency virus-1 (HIV-1)-infected individuals and noninfected controls, to determine IL-37’s association with biomarkers of inflammation and reservoir size. This was a cross-sectional study. The HIV-1-infected patients were categorized in three subgroups depending on their combination antiretroviral therapy (cART) treatment status and CD4+ T-cell count. Quantitative RT-PCR was used for the detection of IL-37 mRNA and HIV-1 DNA in peripheral blood mononuclear cells (PBMCs). Biomarkers in plasma were quantified by enzyme-linked immunosorbent assay (ELISA), whereas T-cell activation was determined by flow cytometry. Lastly, lipopolysaccharide (LPS) stimulations of patients PBMCs were carried out to determine differences in IL-37 mRNA response between the subgroups. Sixty HIV-1-infected patients and 20 noninfected controls were included in the study. Steady-state IL-37 mRNA levels in PBMCs were significantly higher in HIV-1-infected individuals compared with noninfected controls: 2.4-fold (p ≤ 0.01) cART-naïve subjects; 3.9-fold (p ≤ 0.0001) inadequate immunological responders; and 4.0-fold (p ≤ 0.0001) in immunological responders compared with noninfected controls. Additionally, levels of the monocyte inflammatory marker sCD14 correlated with IL-37 mRNA (p = 0.03), whereas there was no association with T-cell activation. Finally, we observed a significant correlation between total viral HIV-1 DNA and IL-37 mRNA in PBMCs (p < 0.0001). Collectively, our data shows that the level of IL-37 mRNA is affected by chronic HIV-1-infection. A relationship with the activation of the monocyte compartment is suggested by the correlation with sCD14 and, interestingly, IL-37 could be related to the size of the total viral HIV-1 reservoir.

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larity and intracellularly, where it is translocated to the nucleus and suppresses TLR-agonist-induced cytokines by a caspase-1-dependent mechanism (12,13). In addition, neutralizing antibodies to IL-37 have demonstrated an effect of extracellular IL-37, resulting in a higher proinflammatory load (12). Therefore, due to these antiinflammatory and immunosuppressive functions of IL-37 and to the potential for a future therapeutic use of this cytokine, diseases dominated by excess inflammation are becoming a subject of great interest. For instance, studies have reported higher levels of IL-37 expression in melanoma patients, systemic lupus erythematosus, colitis, rheumatoid arthritis, atopic dermatitis and morbid obesity (14–19). In addition, several studies are showing correlation between both increased and decreased amounts of IL-37 to the severity of the disease (reviewed in [20]). In a mouse model, a marked protection against LPS-induced shock was observed with transgenic expression of human IL-37 (IL-37tg) (17). In addition, IL-37tg mice subjected to chemically-induced colitis exhibited a lower level of colonic inflammation, reduced IL-1β and tumor necrosis factor alpha (TNFα) production, but increased levels of IL-10; effects of which proved to be myeloid-derived rather than epithelial cell-derived (16). IL-37 presumably mediates suppression of acquired immunity by the inhibition of dendritic cell maturation, thereby affecting the functional link between innate and adaptive immunity (17,21).

HIV-1 infection is characterized by excess immune activation (22,23). Although cART effectively suppresses viral replication, persistent HIV-1-associated immune activation is believed to lead to impaired immune function and premature immunologic aging, as well as an increased risk of cardiovascular disease and cancer (23–29). The underlying mechanisms are still poorly understood, but the persistence of low-level viremia despite effective cART and translocation of microbial products, such as LPS, across a compromised gastrointestinal mucosal surface has been suggested to play important roles (30–32).

Notably, HIV-1-infected patients with inadequate reconstitution of the CD4+ T-cell compartment upon initiation of cART, termed inadequate immunological responders (IIRs), exhibit higher levels of inflammatory biomarkers, greater T-cell activation and increased mortality compared with immunological responders (33–40). Yet, how innate immune responses influence these pathological processes remains unclear (41).

Thus, as HIV-1-associated inflammation negatively influences the health of infected patients despite suppressive cART and as IL-37 has emerged as a cytokine with unique immune regulatory effects, assessing IL-37 expression in the context of chronic HIV-1 infection is an important and unexplored area of research. Therefore, we determined IL-37 mRNA expression, inflammation and persistent HIV-1 DNA in an immunological mixed cohort of chronically HIV-1-infected patients.

**MATERIALS AND METHODS**

**Study Design and Inclusion**

This was a cross-sectional study in which three groups of HIV-1-infected patients were examined: (1) cART-naïve with no history of antiretroviral treatment; (2) cART-treated IIRs defined as having CD4+ T-cell counts continuously below 500 mm3 despite viral suppression with plasma HIV RNA <50 copies/mL for >3 years; (3) cART-treated immunological responders defined as having reached a CD4+ T-cell count of >500 mm3 within 3 years of cART-induced viral suppression with plasma HIV-1 RNA <50 copies/mL. Healthy non–HIV-1-infected persons were included as control population. Data on CD4 T-cell count, plasma HIV-1 RNA and use of cART were obtained from hospital databases and medical records. Subjects known to be pregnant, coinfected with Hepatitis B or C or diagnosed with any autoimmune or autoinflammatory disease were excluded. The study was conducted at the Department of Infectious Diseases, Aarhus University Hospital, Denmark. Written informed consent was obtained from each participant. The study was approved by The Regional Research Ethics Committee for the Region of Midtjylland and The Danish Data Protection Agency for the Region of Midtjylland.

Serum and plasma samples were obtained from each participant. Samples were stored at –80°C until analyses. PBMCs were isolated using Ficoll-Paque PLUS (GE Healthcare, Pittsburgh, PA USA) and stored at –180°C.

**IL-37 mRNA in PBMCs**

For each participant, total RNA was extracted from 1 million PBMCs to standardize input, using the High Pure Isolation kit (Roche, Basel, Switzerland) as described by the manufacturer. Synthesis of cDNA was performed using an Omniscript Reverse Transcription kit (Qiagen, Venlo, the Netherlands) with 5 μL RNA as template and a final volume of 20 μL. A mixture of 1 μL oligo dT primer (0.4 μg/L) and 1 μL random hexamers (0.4 μg/L) were used in addition to the standard protocol. The gene U6 snRNA (Table 1) was measured by real-time polymerase chain reaction (RT-PCR) as a quality control of the cDNA and for further use as an endogenous normalization control.

A nested-PCR containing two amplification rounds was used to measure IL-37 levels in the cDNA samples. We used a full-length cloned IL-37 cDNA transcript.

**Table 1. Primer sequences.**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Forward (5′→3′)</th>
<th>Reverse (5′→3′)</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-37 (1 round)</td>
<td>CTCCTGGGGGTCTCTAAAGG</td>
<td>GATGAACCATCCGGGGTGAG</td>
<td>204 bp</td>
</tr>
<tr>
<td>U6 snRNA</td>
<td>GCTTGGCAGCACGATATACTAAA</td>
<td>CGCITCAGGAATTGGCTGT CAT</td>
<td>84 bp</td>
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</tr>
</tbody>
</table>
in serial dilutions as positive control producing a final standard curve. Nontemplate controls and RNA samples not reverse transcribed were run alongside patient samples on every plate to ensure optimal control for possible contamination. Patient samples were mixed on all plates to ensure samples from each of the four groups were represented in every run.

The first amplification round was limited to 10 cycles with the following conditions (GeneAmp PCR System 9700, Applied Biosystems [Thermo Fisher Scientific Inc., Waltham, MA, USA]): 95°C for 10 min, 10 cycles of 94°C for 20 s, 55°C for 40 s and 72°C for 40 s and maintained at 4°C. We used 5 μL of cDNA from each participant completed with a PCR mixture consisting of 25 μL AmpliTaq Gold PCR Master Mix (Applied Biosystems [Thermo Fisher Scientific]), 2 μL of each 20 μmol/L IL-37 primer (see Table 1) and 16 μL RNase free water to complete a final reaction volume of 50 μL. All samples were run in duplicates. The IL-37 primer pair was designed to cover each of the five isoforms of IL-37(a–e). Once amplified, the product was 204 bp, crossing the exon(5)–exon(6) junction.

In the second round of nested-PCR, we used an IL-37 FAM-labeled Taqman Gene Expression Assay (Applied Biosystems [Thermo Fisher Scientific]) covering all five isoforms. All samples from the first round were assayed in duplicates, making a total of quadruplicate determinations per patient. The PCRmix consisted of 10 μL 2× TaqMan Gene Expression MasterMix, 1 μL 20× TaqMan Gene Expression Assay (Hs00367201m1, Applied Biosystems [Thermo Fisher Scientific]) and 5 μL RNase free water. 4 μL template was added from the previous amplification, making a final 20 μL reaction volume. The RT-qPCR was performed using the following conditions: 95°C for 10 min, 45 cycles of 95°C for 15 s and 60°C for 1 min on a Bio-Rad CFX96 Real-Time system (Bio-Rad, Hercules, CA, USA). The relative ratio of IL-37 mRNA in the PBMCs was determined by the Pfaffl method using a standard curve. All patient values were related to the U6 snRNA as the reference control. Seventy-three patient samples were analyzed. The missing data on the last seven patients were due to a limited amount of cells.

**Stimulation of PBMCs**

We investigated the induction of IL-37 mRNA in PBMCs in response to 24 h of stimulation with LPS (100 ng/mL). Cryopreserved PBMCs were rapidly thawed and rested 3 h at 37°C, 5% CO2 in complete medium (RPNI 1640 supplemented with 10% Hi-FBS, 1% l-glutamine and 1% Penicillin-Streptomycin [BioWest, Nuaillé, France]) in 96-well plates (250,000 cells/100 μL/well). After 3 h, quadruplicate wells were stimulated with 100 μL of LPS (final concentration 100 ng/mL) or control medium, resulting in a final volume of 200 μL per well. After 24 h at 37°C, 5% CO2, supernatants were collected, and the PBMCs were washed and lysed directly in lysis buffer in the wells. The samples were frozen at –80°C. The RNA was purified using the High Pure Isolation kit (Roche). cDNA and subsequent nested PCR were carried out as above. Data are missing on eight patients in the RPMI and six patients in the LPS stimulation due to a limited amount of cells.

**Soluble Markers**

We measured the levels of soluble CD14, IL-6 and soluble CD163 in plasma. sCD14 and IL-6 were quantified using Quantikine High Sensitivity ELISA, both from R&D Systems (Minneapolis, MN, USA). Plasma levels of sCD163 were determined using an in-house assay. This sandwich ELISA assay is using a polyclonal rabbit anti-CD163 IgG as capture antibody and a monoclonal anti-CD163 as detection, described in more details previously (42). Data from one patient in the sCD163 analysis were excluded as an outlier.

**T-Cell Markers**

Cryopreserved PBMCs were rapidly thawed and transferred to 13 mL cold phosphate buffered saline solution (PBS). After washing, 10^6 cells were resuspended in FACS tubes with a staining buffer containing bovine serum albumin and incubated in the dark for 20 min with the following antibodies: α-CD3 conjugated PE-Cy7 (BD Biosciences, San Jose, CA, USA), α-CD4 conjugated APC-H7 (BD Biosciences) and α-CD8 conjugated PerCP-Cy5.5 (BioLegend, San Diego, CA, USA). Samples were washed with 2 mL FACS flow buffer (BD Biosciences) and analyzed on a FACSCanto 2 (BD Biosciences). The CD3^+CD4^+ population was used as an approximation for CD8^+ cells. Monocyte percentages were estimated with forward and side scatter. Data were analyzed using FlowJo v.7.6.5 (Tree Star, Ashland, OR).

**Total Viral Reservoir**

The total viral reservoir was determined in IIRs and Responders as copies of integrated HIV-1 DNA per 10^6 PBMCs using quantitative PCR. The frequency of cells carrying HIV-DNA was calculated from a standard curve of serially diluted DNA from 8E5 cells (43). Lower limit of detection in the assay was defined as 25 copies/10^6 PBMCs, below which the quantification was not considered reliable. Patients with lower HIV-DNA levels were assigned a random value around 25 ± 1.

**Statistical Analysis**

Characteristics for the groups were compared using ordinary one-way analysis of variance (ANOVA) or Kruskall-Wallis test. When only data from two groups were available, Rank sum test (Mann-Whitney) or Student t test were used as appropriate. Differences in laboratory results for the four groups were compared using Holm-Sidak multiple comparisons test or Dunn multiple comparisons test in relation to distribution of data. Paired data were analyzed using Wilcoxon signed rank test. Data distribution was assessed by inspection of histograms and normal quantile-quantile (q–q) plots. Pearson correlation and linear regression were used to explore cor-
relations between parameters. Two-tailed \( P \) values below 0.05 were considered significant. Statistical analyses and graphical presentations were performed using GraphPad Prism, version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) and Stata 12 (StataCorp, College Station, TX, USA).

All supplementary materials are available online at www.molmed.org.

RESULTS

Study Population

We included a total of 60 HIV-1-infected patients (20 cART-naïve, 20 IIRs and 20 responders) as well as 20 noninfected healthy subjects. Their characteristics are shown in Table 2.

Levels of IL-37 mRNA in PBMCs from HIV-1-Infected Patients

The steady state, constitutive levels of IL-37 mRNA expression per U6 copy in PBMCs were significantly higher among HIV-1-infected patients compared with noninfected controls. The difference was 2.4-fold (\( p \leq 0.01 \)) in cART-naïve subjects, 3.9-fold (\( p \leq 0.0001 \)) in IIRs and 4.0-fold (\( p \leq 0.0001 \)) in responders when compared with the levels in noninfected controls. However, there were no statistically significant differences in IL-37 mRNA levels between the HIV-1-infected groups (Figure 1). There were no significant differences in the proportions of monocytes between the subgroups (see Table 2). Further, when the levels of IL-37 mRNA were normalized to the monocyte proportion, we observed the same pattern of IL-37 mRNA distribution as in Figure 1, indicating that the increase in PBMC IL-37 mRNA reflected an increase in the amount of IL-37 mRNA per monocyte rather than increased numbers of monocytes (Figure 2).

![Figure 1](image1.png)

![Figure 2](image2.png)

Table 2. Characteristics for all participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>cART-naïve (( n = 20 ))</th>
<th>cART-treated inadequate responders (( n = 20 ))</th>
<th>cART-treated responders (( n = 20 ))</th>
<th>Noninfected controls (( n = 20 ))</th>
<th>( P ) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (IQR(^b))</td>
<td>40.5 (34.3–52.8)</td>
<td>52.0 (43.0–64.5)</td>
<td>46.5 (43.0–51.0)</td>
<td>47.5 (35.0–55.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, no.</td>
<td>17</td>
<td>14</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Female, no.</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CD4(^+) cell count inclusion date, median cells/( \mu L ) (IQR)</td>
<td>555 (385–743)</td>
<td>320 (280–378)</td>
<td>790 (640–1000)</td>
<td>—</td>
<td>( &lt;0.0001 )</td>
</tr>
<tr>
<td>Nadir CD4(^+) cell count, median cells/( \mu L ) (IQR)</td>
<td>480 (385–613)</td>
<td>63 (20–139)</td>
<td>197 (119–340)</td>
<td>—</td>
<td>( &lt;0.0001 )</td>
</tr>
<tr>
<td>HIV RNA level, median log(copies/mL) (IQR)</td>
<td>4.2 (3.6–6.0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Duration of cART, median years (IQR)</td>
<td>5.6 (4.4–7.2)</td>
<td>10.1 (7.7–14.5)</td>
<td>5.0 (4.7–5.8)</td>
<td>—</td>
<td>0.0005</td>
</tr>
<tr>
<td>Previremic index, median log(copies/mL) (IQR)</td>
<td>4.9 (4.3–6.1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.96</td>
</tr>
<tr>
<td>Monocyte percentage, % (IQR)</td>
<td>18.9 (12.2–25.6)</td>
<td>22.4 (16.2–29.0)</td>
<td>19.4 (15.4–22.9)</td>
<td>20.2 (15.1–23.4)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

\(^a\) \( P \) values determined by ordinary ANOVA.

\(^b\) IQR, interquartile range.
Next, we examined the induction of IL-37 mRNA in response to LPS stimulation in PBMCs. After stimulation, all HIV-1-infected groups showed significantly higher levels of IL-37 mRNA as compared with noninfected controls, both with and without LPS. Though the relative induction of IL-37 mRNA did not differ between groups, the absolute increase in IL-37 mRNA was higher in the HIV-1-infected groups (Figure 3).

Also, the IIRs showed significantly higher levels of IL-37 than the cART-naive group, when stimulated with LPS ($p \leq 0.01$). The IL-37 mRNA induction in response to LPS stimulation compared with media alone was statistically significant in all groups, except for responders ($p = 0.07$), using Wilcoxon signed rank test (see Figure 3).

**IL-37 mRNA in Relation to sCD14, IL-6 and sCD163**

We observed significantly higher levels of circulating sCD14 in IIRs compared with noninfected controls. The other HIV-1-infected groups showed higher levels as well, though not significant (Table 3 and Figure 4A). Moreover, we identified...
a statistically significant positive correlation between IL-37 mRNA and sCD14 ($p = 0.03$; Figure 4B). Levels of sCD163 were significantly higher in cART-naïve and IIRs compared with noninfected controls ($p \leq 0.001$; $p \leq 0.05$), with the highest levels in the cART-naïve group. The cART-naïve group exhibited significantly higher levels than the responders ($p = 0.01$) (see Table 3 and Figure 5A). As expected, sCD163 correlated with sCD14 ($p = 0.03$), but there was no correlation between sCD163 and IL-37 mRNA in PBMCs (Figure 5B). We found a 1.4-fold higher level of IL-6 in the plasma of HIV-1-infected individuals compared with noninfected controls, however, using multiple comparisons, no individual significant differences were observed between the groups (see Table 3). In contrast to sCD14, there was no correlation between circulating IL-6 and mRNA levels of IL-37 in PBMCs ($p = 0.10$).

**IL-37 and T-Cell Activation**

To investigate T-cell activation, we analyzed the expression of CD38 on CD4$^+$ and CD8$^+$ T cells. As shown in Table 3, CD38 expression (both in CD4$^+$ and CD8$^+$ T cells) followed the pattern: cART-naïve > IIRs > noninfected controls > responders. We observed no correlation between IL-37 mRNA levels and CD38 expression when assessed in the total T-cell pool or in individual T-cell subtype (Supplementary Figures S1, S2).

**IL-37 mRNA and the Size of the Total Viral Reservoir**

We identified a significant positive correlation between the size of the total viral reservoir as measured by HIV-1 DNA and IL-37 mRNA levels in the PBMCs. This association was present for both LPS-induced IL-37 mRNA expression and unstimulated IL-37 mRNA expression ($p < 0.0001$ and $p = 0.04$; Figures 6A, B). There was no difference in HIV-1 DNA per 10$^6$ PBMCs between IIRs and responders (436.1, [95% CI: 148–724] for IIRs and 591.1, [95% CI: 137–1046] for responders; $p = 0.95$).

**DISCUSSION**

To our knowledge, this study is the first to investigate the expression of IL-37 in HIV-1 infection. That the observed increased expression of IL-37 could play a regulatory role in HIV-1 by limiting in-
flammation is consistent with the role of other antiinflammatory members of the IL-1 family. For instance, elevated levels of the IL-1 receptor antagonist, soluble IL-1 receptor type 2 and IL-18 binding protein are often present in autoimmune and autoinflammatory diseases, and serve as indicators of disease severity.

We know that IL-37 is immunosuppressive and that it imposes a tolerogenic state on dendritic cells (21). However, trying to link the increased expression of IL-37 in HIV-1 infected patients. In this study, we observed a positive correlation between sCD14 and IL-37 mRNA. As sCD14 has formerly been associated with increased morbidity and mortality in HIV-1 infection (51–53), the correlation between IL-37 mRNA production and sCD14 levels might also indicate an important role of IL-37 in response to the ongoing low-level inflammation on cART, although this correlation was weak and obviously limiting the conclusions to be made here. Signs of a prognostic relevance for this cytokine does require further attention in future studies as a faulty inflammatory regulation has been observed to have prognostic implications with other members of the IL-1 family in different conditions (54–56).

That sCD14 burden is not lower in cART-naïve and cART-treated patients mimics the pattern of IL-37 mRNA, that is, monocyte activation is not directly affected by plasma viral load. Instead, other mechanisms such as microbial translocation from the intestines con-
plasma and serum levels in a cohort of healthy human subjects (ages 20 to 72). In addition, we observed an inability of the ELISA to detect IL-37 in LPS-stimulated monocyte supernatants and lysates, with the same samples being positive on a validated Western blotting with the same antibody used in the ELISA. Therefore, we must conclude that levels of mRNA are the most reliable data at present to evaluate the cytokine.

Lastly, we defined IIRs and responders based on the available literature (33,34). However, other studies have used lower cutoffs of CD4⁺ T-cell counts to define those who have been termed immunological nonresponders (40,62) as a subgroup of the IIRs. This reduces the immunological proximity between the groups and is likely to enhance differences between these subgroups of HIV-1 patients.

In conclusion, steady-state levels of IL-37 mRNA in PBMCs of HIV-1-infected individuals, both with and without LPS stimulation, were significantly higher than in noninfected controls. IL-37 mRNA correlated positively with circulating levels of the monocyte inflammatory marker sCD14, which could suggest a functional link between monocyte activation and IL-37. Moreover, a significant positive correlation between the size of the HIV-1 reservoir and mRNA levels of IL-37 in PBMCs was observed. Collectively, these data add to the understanding of the inflammatory processes observed with chronic HIV-1 infection and its possible relation to IL-37.

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DISCLOSURE

The authors declare they have no competing interests as defined by Molecular Medicine, or other interests that might be perceived to influence the results and discussion reported in this paper.

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