T-Cell Depletion in the Colonic Mucosa of Patients With Idiopathic CD4+ Lymphopenia


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(See the editorial commentary by Lambotte and Bourgeois on pages 1531–3.)

Idiopathic CD4+ lymphopenia (ICL) is a rare syndrome characterized by low peripheral CD4+ T-cell counts that can lead to serious opportunistic infections. The pathogenesis of ICL remains unclear, and whether effector sites are also lymphopenic is unknown. In this study, rectosigmoid mucosal biopsy specimens from patients with ICL and healthy controls were evaluated. Significant T-cell lymphopenia was observed in the mucosal tissue of patients with ICL by flow cytometry and immunohistochemistry, compared with healthy controls. Functional capacity of T cells, assessed by production of interferon γ and interleukin 17, was preserved in the mucosa of patients with ICL. In contrast to T lymphocytes, the frequency of myeloid cells (neutrophils and macrophages) was elevated in the colonic mucosa of patients with ICL. Despite the observed mucosal abnormalities, plasma levels of intestinal fatty acid binding protein, a marker of enterocyte turnover and other inflammatory biomarkers, including interleukin 6, C-reactive protein, and tumor necrosis factor, were not elevated in patients with ICL, compared with healthy controls, whereas soluble CD14 levels were minimally elevated. These data suggest that patients with ICL, despite gut mucosal lymphopenia and local tissue inflammation, have preserved enterocyte turnover and T-helper type 17 cells with minimal systemic inflammation. These observations highlight differences from patients with human immunodeficiency virus infection, with or without AIDS, and may partially explain their distinct clinical prognosis.

Keywords. idiopathic CD4+ lymphopenia; HIV/AIDS; mucosal immunity; biomarkers; inflammation.

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METHODS

Patients
Forty-six patients with ICL and 76 healthy controls were studied. All study participants provided written informed consent under institutional review board–approved protocols (NCT00867269 and NCT00839436). Study participants were not acutely ill at the time of blood sample collection or gut biopsies, and only 2 patients with ICL had a history of intermittent, mild, nonspecific GI complaints. Peripheral blood lymphocyte counts were measured in a clinical laboratory under the Clinical Laboratory Improvement Amendments.

Immunophenotyping
Cryopreserved peripheral blood mononuclear cells from 23 patients with ICL and 31 healthy controls were stained using the antibodies outlined in the Supplementary Materials. Stained samples were acquired using an LSR II flow cytometer with BD FacsDiva software (BD Biosciences). Data were analyzed using FlowJo software (version 9.7.5; Treestar).

Processing of Rectosigmoid Biopsy Specimens
Twelve patients with ICL and 16 healthy controls underwent endoscopic procedures to obtain 24–30 random biopsy specimens from the rectosigmoid colon. Between 16 and 20 of the biopsy specimens were weighed and treated at 37°C for 40 minutes with 0.5 mg/mL collagenase IV (Sigma-Aldrich) and 0.42 U/mL benzonase (Novagen) in Roswell Park Memorial Institute medium (Corning) containing 10% heat-inactivated human serum (Gemini Bio Products), followed by mechanical disruption with a pestle. Cell suspensions were passed through a 40-μm-pore screen. Total viable cells were counted using a Guava PCA flow cytometer (Millipore) with Guava Cytosoft data acquisition and analysis software (version 6.0.2; Millipore), and cell counts were normalized to the number of viable cells per gram of rectosigmoid tissue as previously described [16].

Stimulation of Mucosal Lymphocytes
Between 1 million and 2 million cells obtained from the rectosigmoidal biopsy specimens (obtained from 8 patients with ICL and 6 healthy controls) were stimulated for 6 hours at 37°C with 40 ng/mL phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich) and 1 μM ionomycin (Sigma-Aldrich) in the presence of 10 μg/mL phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich) and 1 μM ionomycin (Sigma-Aldrich) in the presence of 10 μg/mL phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich) and 1 μM ionomycin (Sigma-Aldrich) in the presence of 10 μg/mL phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich) and 1 μM ionomycin (Sigma-Aldrich). After an overnight rest, cells were fixed and stained intracellularly for cytokine production with anti–interleukin 17 (IL-17) phycoerythrin (clone eBio64–DEC17) and anti–interferon γ (IFN-γ) Pacific blue (clone 4S. B3; both from eBioscience) and analyzed using flow cytometry.

Immunohistochemical (IHC) and Quantitative Image Analyses
IHC analysis was performed in 12 patients with ICL and in 16 healthy controls with sufficient tissue (2–3 pieces from rectosigmoid biopsy specimens) as described in the Supplementary Materials. The percentage of the lamina propria that stained for CD3+ cells, CD4+ cells (excluding non-T cells), CD8+ cells, myeloperoxidase (MPO)–positive cells, and cells double stained with CD68 plus CD163 was quantified using Photoshop CS or CS6 (Adobe Systems) and Fovea (Reindeer Graphics) tools as previously described [17].

Measurement of Plasma Biomarker Concentrations
Plasma biomarkers were measured in 32 patients with ICL and 28 healthy controls. Enzyme-linked immunosorbent assays
were performed to measure plasma concentrations of intestinal fatty acid-binding protein (I-FABP; R&D Systems), neopterin (IBL-America), sCD14 (R&D Systems), and sCD163 (Adipobiosciences). Plasma concentration of LPS was determined using a chromogenic assay according to the manufacturer’s protocol, with samples diluted 50-fold in LPS-free water (Lonza). Levels of C-reactive protein (CRP), tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and LPS binding protein (LBP) were measured by electrochemiluminescence (MESO Scale Discovery). D-Dimer levels were measured by enzyme-linked fluorescent assay (VIDAS, BioMerieux).

Statistical Methods
Median values were compared using the Mann–Whitney U test, performed on Prism software (version 6.0c; GraphPad). Because of the exploratory nature of this study, all P values of <.05 are shown.

RESULTS
Study Participants
The characteristics of study participants are shown in Table 1. Patients with ICL and healthy controls did not differ significantly in sex distribution or median age. Both CD4+ and CD8+ T-cell counts were significantly lower in patients with ICL, compared with controls (P < .001). Patients with ICL had a significantly lower ratio of CD4+ to CD8+ T cells in peripheral blood, compared with healthy controls (0.69 vs 2.08; P < .001).

Lymphopenia in Rectosigmoid Mucosa in Patients With ICL
To determine whether the T-cell lymphopenia in ICL is restricted to blood or whether it is also found in peripheral tissues, we used IHC analysis and flow cytometry to investigate the CD3+, CD4+ and CD8+ T-cell populations in colon mucosa from rectosigmoid biopsy specimens. Figure 1A shows that patients with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With ICL (n = 46)</th>
<th>Healthy Controls (n = 76a)</th>
<th>P Value</th>
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<tr>
<td>Male/female sex</td>
<td>25/21</td>
<td>48/26</td>
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<tr>
<td>Age, y</td>
<td>44 (36-57)</td>
<td>45 (39-53)</td>
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<tr>
<td>CD4+ T-cell count, cells/µL</td>
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<td>715 (513-884)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD8+ T-cell count, cells/µL</td>
<td>147 (78-364)</td>
<td>357 (258-454)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD4+/CD8+ T-cell ratio</td>
<td>0.69 (0.21-1.14)</td>
<td>2.08 (1.51-2.89)</td>
<td>&lt;.001</td>
</tr>
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Data are no. of participants or median value (interquartile range).

Figure 1. Patients with idiopathic CD4+ lymphopenia (ICL) are lymphopenic in the colon. Number of lymphocytes found in rectosigmoid tissue specimens from patients with ICL (blue circles) and healthy controls (HCs; red squares). A and B, Results of immunohistochemical analysis, showing the percentage of the area stained for CD3, CD4, or CD8 (A), with an example of CD4 staining in the lamina propria shown in a patient with ICL and a HC in (B). C, Results of flow cytometry, showing the number of CD3+, CD4+, CD8+, or DN (defined as CD3+CD4−CD8−) cells per gram of tissue. Bars represent median values with interquartile ranges. P values are for comparisons between patients with ICL and HCs by the Mann–Whitney U test.
ICL had a significantly lower median surface area of the lamina propria that stained for CD3 (1.50% vs 3.47%; \( P = .036 \)) and for CD4 (1.40% vs 3.63%; \( P < .001 \)), compared with healthy controls (Figure 1B). The median percentage of the surface area that stained for CD8 was also lower for patients with ICL, although the difference did not reach statistical significance (0.90% vs 1.40%; \( P = .053 \)).

Next, we used flow cytometry, which allows quantification of both lamina propria and follicular lymphocytes. Lymphocytes extracted per gram of gut tissue in a pooled sample of 10–15 pieces of rectosigmoid biopsy specimens were analyzed, to increase the probability of analyzing the usually scarce follicles. Figure 1C shows that, similar to IHC findings, levels of all 4 populations analyzed, including CD3\(^{+}\), CD4\(^{+}\), and CD8\(^{+}\) T cells and CD3\(^{+}\)CD4\(^{-}\)CD8\(^{-}\) (DN) lymphocytes, were significantly lower in patients with ICL than in healthy controls. Together, these data show that patients with ICL are also lymphopenic in tissues such as the lamina propria of the colon.

Finally, to see whether the scarcity of lymphocytes in the gut in patients with ICL was the result of a lower expression level of the gut-homing integrin \( \alpha_4\beta_7 \) [18], we measured by flow cytometry expression of \( \beta_7 \) on the surface of CD4\(^{+}\) and CD8\(^{+}\) T cells in PBLs from patients with ICL and healthy controls and found no significant difference in either subset (\( P = .464 \) for CD4\(^{+}\) and \( P = .419 \) for CD8\(^{+}\)). This suggests that depletion of T cells within the colon of patients with ICL is not due to impaired trafficking from aberrant expression of \( \alpha_4\beta_7 \).

**Proportions of Lymphocyte Subsets and Effector/Memory Phenotypes in Patients With ICL**

We next analyzed the proportions of CD4\(^{+}\), CD8\(^{+}\), and DN lymphocytes in the colon and compared them to the proportions found in PBLs from the same individuals (patients with ICL and healthy controls). As previously described, we found that patients with ICL had a lower percentage of CD4\(^{+}\) T cells, a higher percentage of CD8\(^{+}\) T cells, and an overall higher, albeit with wide distribution, percentage of DN T cells with respect to PBLs from healthy controls (Figure 2A–D). In contrast, the percentages of T lymphocytes in the rectosigmoid mucosa of the same patients did not differ from those for healthy controls, with the exception of a higher proportion of CD8\(^{+}\) T cells (Figure 2B and 2E). Figure 2D represents the median proportions of each lymphocyte subset shown in Figure 2A–C.

**Figure 2.** Contrary to peripheral blood, the rectosigmoid mucosa of patients with idiopathic CD4\(^{+}\) lymphopenia (ICL) had proportions of CD4\(^{+}\), CD8\(^{+}\), and DN lymphocytes within the CD3\(^{+}\) population that were similar to those for healthy controls (HCs). A–C, Percentages of CD4\(^{+}\) T cells (A), CD8\(^{+}\) T cells (B), and CD3\(^{+}\)CD4\(^{-}\)CD8\(^{-}\) (DN) lymphocytes (C) among the CD3\(^{+}\) cells found in peripheral blood lymphocytes (PBLs) or rectosigmoid tissue (colon) specimens from patient with ICL (blue circles) and HCs (red squares). D, Median percentages of CD4\(^{+}\), CD8\(^{+}\), and DN lymphocytes among the CD3\(^{+}\) lymphocytes found in PBLs and colon from the individual samples represented in panels A–C. Bars represent median values with interquartile ranges. \( P \) values are for comparisons between patients with ICL and HCs by the Mann–Whitney \( U \) test. Abbreviations: NS, not significant; PB, peripheral blood.
In a subset of participants, we stained PBLs and colon cell suspensions and analyzed the proportions of naive (CD45RO<sup>+</sup>CD27<sup>-</sup>), central memory (CM; CD45RO<sup>+</sup>CD27<sup>+</sup>), and effector memory (EM; CD45RO<sup>-</sup>CD27<sup>-</sup>) cells within the CD4<sup>+</sup> and CD8<sup>+</sup> T cells. The results in PBLs showed a lower percentage of naive cells and higher percentages of both CM and EM populations in patients with ICL, compared with healthy controls, in both T-cell subsets as previously reported [5, 6] (Supplementary Figure 1A). In the rectosigmoid mucosa, the percentages of naive, CM, and EM populations among the CD4<sup>+</sup> T cells from patients with ICL, however, did not differ from those for healthy controls (Supplementary Figure 1B). The mucosal CD8<sup>+</sup> T cells had lower percentages of naive (5.1% vs 19.7%; P = .043) and higher percentages of EM (44.5% vs 21.7%; P = .004) populations than healthy controls (Supplementary Figure 1B). In addition, the proportion of mucosal CD4<sup>+</sup> T cells with a regulatory phenotype did not differ between patients with ICL and healthy controls (P = .328; Supplementary Figure 2). Together, these data show that despite mucosal lymphopenia in patients with ICL, the proportion of different subsets of lymphocytes and the differentiation status of T cells do not differ drastically from those for healthy persons.

**Preserved Functional Th1 and Th17 CD4<sup>+</sup> T-Cell Subsets in the Rectosigmoid Mucosa of Patients With ICL**

We next examined whether the CD4<sup>+</sup> T cells found in the colon of patients with ICL were functionally intact. CD4<sup>+</sup> lymphocytes from rectosigmoid biopsy specimens were stimulated with PMA and ionomycin to determine their capacity to produce IL-17, for Th17 potential, and IFN-γ, for Th1 potential. Th17 cells have been associated with both inflammation in autoimmune colitis [14] and intestinal barrier disruption in HIV/simian immunodeficiency virus (SIV) infections [12, 19]. The proportion of mucosal CD4<sup>+</sup> T cells from patients with ICL producing IL-17 was higher than in healthy controls (5.68% vs 3.39%; P = .013; Figure 3A). The proportion of CD4<sup>+</sup> T cells producing IFN-γ, however, did not differ significantly (51.1% vs 49.0%; P = .632; Figure 3B). Thus, although the colon of patients with ICL contains fewer CD4<sup>+</sup> T cells, these cells have intact functional capacity.

**Increased Numbers of Myeloid Cells in the Lamina Propria of Patients With ICL**

To determine whether the immune depletion found in the gut of patients with ICL affected cells of the innate immune system, we also quantified the surface area stained for polymorphonuclear cells (PMNs) and macrophages. Innate immune cells such as PMNs and macrophages are relevant for gut homeostasis, and their numbers could reflect the health status of the mucosa [20–22]. We found an increased number of both PMNs (stained by MPO) and macrophages (CD68<sup>+</sup>) in the lamina propria of patients with ICL compared with healthy controls (Figure 4A and 4B). Thus, the number of myeloid cells appeared increased overall in the gut of patients with ICL, compared with the number in healthy controls.

**Lower Proportion of CD14<sup>+</sup>CD16<sup>-</sup> Monocytes in the Blood of Patients With ICL**

To test whether the increased population of myeloid cells in the gut of patients with ICL was linked to changes in peripheral monocyte populations, we quantified monocyte subsets by CD14, CD16, CCR2, CX3CR1, and CD163 expression (Supplementary Table 1). The proportion of CD14<sup>+</sup>CD16<sup>-</sup> monocytes, which have been associated with infection and inflammation [23], was significantly lower (3.66% vs 7.35%; P = .008) in patients with ICL as compared to healthy controls, and CD14<sup>-</sup>CD16<sup>+</sup> monocytes were found at a higher proportion (84.4% vs 80.6%; P = .014). Accordingly, the proportion of CCR2<sup>+</sup>CX3CR1<sup>hi</sup> monocytes, a phenotype associated with monocyte recruitment to noninflamed tissues [24], was lower in patients with ICL, although the difference did not achieve significance (8.33% vs 12.8%; P = .059; Supplementary Table 1). The functionality of monocytes was assessed by LPS stimulation. No difference in

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**Figure 3.** CD4<sup>+</sup> T cells in the colon of patients with idiopathic CD4<sup>+</sup> lymphopenia (ICL) are functional. Proportion of mucosal CD4<sup>+</sup> T cells producing interleukin 17 (IL-17; A) or interferon γ (INF-γ; B) after mitogenic stimulation. P values represent comparisons of the 2 groups by the Mann–Whitney U test. Bars are median values with interquartile ranges. Abbreviation: HC, healthy control.
production of TNF (48.3% vs 39.4%; \(P = .410\)), interleukin 1\(\beta\) (34.6% vs 47.6%; \(P = .171\)), IL-6 (33.9% vs 39.5%; \(P = .883\)), or tissue factor (a protein involved in the coagulation pathway; 20.9% vs 14.5%; \(P = .410\)) was observed, suggesting that monocytes found in PBLs from patients with ICL appear functionally intact.

**Preserved Epithelial Integrity and Minimal Systemic Inflammation in Patients With ICL**

To determine whether depletion of lymphocytes and increased number of myeloid cells within the rectosigmoid mucosa were associated with damage to the gut epithelium, we next measured plasma concentrations of I-FABP, a cytoplasmic protein found in intestinal epithelial cells that is released upon enterocyte death [9]. Plasma I-FABP levels did not differ in patients with ICL, compared with healthy controls (1487 vs 1414 pg/mL; \(P = .558\); Figure 5A), suggesting intact enterocyte turnover. In addition, plasma concentrations of LPS and sCD14 were also measured to evaluate microbial translocation directly and indirectly, respectively [25]. Plasma concentrations of LPS were slightly lower in patients with ICL, compared with healthy controls (110 vs 129 pg/mL; \(P = .026\)), and sCD14 levels were slightly higher, compared with healthy controls (1.415 vs 1.212 µg/mL; \(P = .003\); Figure 5C), albeit at values much lower than those reported in patients with HIV infection [25]. LBP levels did not differ between the 2 groups (3734 ng/mL vs 3772 ng/mL; \(P = .966\)). LPS and LBP levels were inversely correlated, as anticipated (\(r = -0.35, P = .007\)).

To further assess systemic inflammation, we measured additional biomarkers, including neopterin and sCD163, which are increased during activation of macrophages and monocytes; CRP, IL-6, and TNF; and plasma concentrations of D-Dimer, produced through the degradation of fibrin from clots. We found no statistically significant differences (Supplementary Table 2).

**DISCUSSION**

In this study, we evaluated whether PBL lymphopenia in patients with ICL is associated with either tissue depletion or entrapment and enrichment of T lymphocytes in the rectosigmoid...
mucosa. We observed the former: intestinal mucosal lymphopenia in patients with ICL with loss of CD4⁺, CD8⁺, and DN T cells yet preservation of functional Th1 and Th17 subsets. Additionally, we found infiltration of myeloid cells in the lamina propria of patients with ICL, but, in sharp contrast to HIV or SIV infections, the mucosal lymphopenia and myeloid enrichment were associated with intact enterocyte turnover and minimal systemic inflammation.

The etiology of ICL remains elusive and can include defects in production, proliferation, survival, or trafficking of lymphocytes or any combination of the above [4]. In our study, we found no evidence of lymphocyte trapping in either the inductive (lymphoid follicles) or the effector (lamina propria) sites of the colonic mucosa. In this regard, since we were able to quantify lymphocytes by flow cytometry from pooled gut biopsy specimens per individual, the lymphocytes analyzed in our study reflected the aggregate populations from both lymphoid follicles and the lamina propria [26]. In agreement with previous reports, we found CD4⁺ T cells to represent the majority of T cells found in the colonic mucosa of healthy individuals [27]. Of note, this was also preserved in the colon samples from patients with ICL, even though the CD4⁺ T cells were a minority in the PBLs of the same patients. The different proportions of CD4⁺, CD8⁺, and DN T cells between the PBLs and the colon mucosa in patients with ICL might be explained by a more restricted regulation of PBL migration to this mucosal site than to other tissues, as has been shown using both parabiotic mice [28] and colon grafts [29]. Thus, despite our findings, we cannot exclude the possibility that aberrant trafficking to other tissues, where homing is regulated differently, may still play a role in the pathogenesis of ICL, as suggested by other studies [30, 31].

Regarding the myeloid populations, the smaller proportion of CD14⁺CD16⁺ monocytes in the blood could also reflect aberrant trafficking from bone marrow to the peripheral circulation. For instance, S1PR5, a G protein–coupled receptor from the same family as S1PR1, a receptor that has been previously implicated in the pathogenesis of patients with idiopathic lymphopenias, is necessary for egress of CD14⁺CD16⁺ but not CD14⁺CD16⁻ monocytes from bone marrow into blood [32–35]; therefore, the fewer peripheral CD14⁺CD16⁺ monocytes could reflect a broader problem with this family of receptors that could affect both lymphocytes and CD14⁺CD16⁺ monocytes. In the rectosigmoid lamina propria of healthy controls, we found abundant macrophages, as has been previously shown [36], and observed even higher numbers in patients with ICL. Because the lamina propria macrophages derive from circulating monocytes [37], our data suggest that monocyte migration in the colonic tissue is probably intact in individuals with ICL.

Unlike our prior study [15], in this study, we did not observe elevated plasma levels of LPS, compared with healthy controls. The prior cohort included a smaller number of overall sicker patients with ICL than our current cohort, and it is thus possible that the higher levels reflected more acute disease states and concomitant infections. Alternatively, use of nonfasting samples (from both patients with ICL and healthy controls) that had previously undergone a freeze-thaw cycle, along with the natural variability of LPS assays, could account for this discrepancy. Despite the lack of elevated LPS levels and normal LBP levels that inversely correlated with LPS, the sCD14 level was higher in these patients with ICL than in healthy controls, consistent with our previous report [15]. Levels of LPS and sCD14 do not always correlate, and sCD14 may function best as an indicator of innate immune activation, whereby LPS is the main but not only ligand that can activate CD14⁺ monocytes to shed sCD14 [38]. However, the lack of elevation of sCD163 and neopterin levels, which are also innate immune activation markers, and the lack of systemic inflammation (based on IL-6, TNF-α, and CRP expression), would suggest that the increased sCD14 may be a more sensitive marker of lower levels of inflammation or may be representing specific alterations of monocyte responsiveness and/or maturation. Importantly, the observed sCD14 levels were significantly lower than those reported in HIV-infected patients [25].

In patients infected with HIV, depletion of CD4⁺ T cells within the GI tract is associated with loss of intestinal epithelial integrity and microbial translocation that results in systemic inflammation [9, 39]. Our results in patients with ICL contrast with findings for patients with HIV infection because, despite the presence of CD4⁺ lymphopenia in the gut, there was little evidence of enterocyte damage and systemic inflammation. Our current study agrees, however, with other studies that have observed immune activation in HIV or SIV infection to be independent of depletion of CD4⁺ T cells within the GI tract [40] and with studies in inflammatory bowel disease, in which loss of epithelial integrity and T-cell activation did not correlate with systemic inflammatory markers [41]. The preservation of enterocyte integrity, as measured by levels of I-FABP, and of intestinal Th17 and Treg CD4⁺ T cells in patients with ICL also highlights the possible roles of factors that differ between patients with ICL and patients with HIV infection in causing epithelial damage and microbial translocation. Unlike patients with ICL, patients with HIV infection have preferential depletion of Th17 CD4⁺ T cells within the GI tract, and this CD4⁺ T-cell subset has been implicated in maintenance of mucosal integrity [13, 14, 42]. Other important factors that may be affecting mucosal pathology during HIV infection include the presence of virus; the infiltration of mucosa by higher numbers of CD8⁺ T cells; the much higher infiltration of myeloid cells, compared with infiltration during ICL (J. E., unpublished observations); dysbiosis; and, in the case of treated patients with HIV infection, the use of antiretroviral drugs.

In summary, we show here that patients with ICL have lymphopenia in the rectosigmoid mucosa as they do in peripheral blood. Despite this lymphopenia, enterocyte turnover and Th17...
function are preserved and, in contrast to HIV infection, there is no significant systemic inflammation. These differences may explain, at least partially, the different CD4+ T-cell count trajectories and spectra of opportunistic infections that affect patients with ICL, compared with patients with HIV infection.

**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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