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RESEARCH ARTICLE

Preferential loss of gut-homing α4β7 CD4$^+$ T cells and their circulating functional subsets in acute HIV-1 infection

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Preferential infection and depletion of gut-homing α4β7 CD4$^+$ T cells in the blood are observed in chronic HIV/SIV infection. The dynamic change in gut-homing α4β7 CD4$^+$ T cells and their functional subsets during the acute stages of HIV-1 infection are less documented. Therefore, we conducted a cohort study to investigate whether acute HIV-1 infection induced abnormalities in gut-homing α4β7 CD4$^+$ T cells and their functional subsets. We examined the frequency, absolute number, and functionality of gut-homing α4β7 CD4$^+$ T cells in 26 acute HIV-1-infected patients compared with 20 healthy individuals. We found that circulating gut-homing α4β7 CD4$^+$ T cells were preferentially depleted during acute HIV-1 infection and were positively correlated with absolute CD4$^+$ T-cell count in blood. Notably, Th17 and Th1 cell subsets of gut-homing CD4$^+$ T cells were also decreased, which resulted in an imbalance of T helper cells (Th1):regulatory T cells (Treg) and Treg:Th17 ratios. Gut-homing Th17 and Th1 cells were also positively correlated with the absolute number of total CD4$^+$ T cells and gut-homing CD4$^+$ T cells. The gut-homing Treg:Th17 ratio was inversely correlated with the CD4$^+$ T-cell count. Taken together, the analyses of our acute HIV-1 cohort demonstrate that gut-homing α4β7 CD4$^+$ T cells and their functional subsets were profoundly depleted during acute HIV-1 infection, which may have resulted in the persistent loss of circulating CD4$^+$ T cells and an imbalance of Th1:Treg and Treg:Th17 ratios and contribute to HIV-1 disease pathogenesis.
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Keywords: gut-homing; HIV-1 disease pathogenesis; integrin α4β7; Th17 cells

INTRODUCTION

HIV/SIV predominately infects and replicates in activated memory CCR5$^+$CD4$^+$ T cells, which are enriched in gut lymph tissues.[1–3] Depletion of CD4$^+$ T cells in the effector sub-compartment of the gut mucosa occurs prior to depletion in peripheral blood and other lymphoid tissues during all stages of HIV/SIV infection.[4,5] This loss is not easily reversible despite long-term successful antiretroviral therapy (ART).[6–9] HIV/SIV infection also reduces Th17 cells and impairs gut mucosal integrity, which results in microbial translocation and high levels of immune activation and systemic inflammation in HIV/SIV-infected individuals.[10–14] Alterations in Th17:Th1 and Th17:Treg balance also contribute to disease progression in HIV/SIV infection.[15–17]

The gut-homing receptor integrin α4β7 mediates lymphocyte migration from the circulation to the intestine through interaction with MAdCAM-1 on endothelial cells of gut tissues.[18,19] The binding of integrin α4β7 and HIV-1 gp120 facilitates selective infection and replication in α4β7 CD4$^+$ T cells, which results in HIV-1 cell-to-cell spreading.[20,21] A loss of peripheral blood α4β7 CD4$^+$ T cells occurs in HIV/SIV infection.[22,23] Therefore, deficient recruitment of gut-homing α4β7 CD4$^+$ T cells from peripheral blood to gut mucosa may underlie the incomplete restoration of gut CD4$^+$ T cells in HIV-1

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patients.[24,25] Notably, most integrin α4β7-expressing Th17 cells are predominantly infected during primary SIV infection, which suggests that the loss of α4β7 Th17 cells in the periphery may compromise gut mucosal immunity.[22] Additionally, α4β7 CD4$^+$ T cells are a potential biomarker that reflects gut CD4$^+$ T-cell loss during HIV-1 and SIV infections.[26,27] Therefore, a detailed characterization of gut-homing α4β7 cells and their functional subsets is critical to reflect the dysfunction of gut mucosal immunity and HIV-1 pathogenesis.

The dynamics of gut-homing α4β7 CD4$^+$ T cells and their subsets during acute HIV-1 infection are less known. Our study investigated changes in these cell populations during acute HIV-1 infection to further understand the importance of gut-homing α4β7 CD4$^+$ T cells and their relationship to viral pathogenesis during the acute phase of HIV-1 infection.

MATERIALS AND METHODS

Study subjects

This cohort study recruited 26 acute HIV-1-infected individuals (AHIs) and 20 healthy controls (HCs) from Beijing You-An Hospital, Capital Medical University, Beijing, China. Informed consents were obtained from all participants following Internal Review Board approval. Acute HIV positivity was defined as detectable plasma HIV-1 RNA with or without one of the following criteria: positive HIV-1 p24 result or positive ELISA or Western blot, except p31 band. No patients received ART.

Immunophenotyping of T lymphocytes

Flow cytometry analyses were performed using a BD CantoII instrument (BD Biosciences, San Diego, CA, USA). The following monoclonal conjugated antibodies were used: CD3-APC-Cy7 (clone SK7), CD4-FITC (clone RPA-T4), CD8-Percp-cy5.5 (clone RPA-T8), CD25-Percp-cy5.5 (clone M-A251), CD127-PE-Cy7 (clone HIL-7R-M21), CD38-PE (clone HIT2), HLA-DR-APC (clone TU36), α4-PE (clone 9F10), β7-APC (clone FIB504) (all from BD Biosciences), and CD45RA-Pacific Blue (clone HI100) (Biolegend, San Diego, CA, USA). Data analysis was performed using FlowJo software 7.6.1 (Tree Star, Inc., Ashland, OR, USA).

Intracellular cytokine staining

Peripheral blood mononuclear cells (PBMCs) (1×10^6 cells mL^{-1}) were stimulated with PMA (50 ng mL^{-1}) and ionomycin (1 μg mL^{-1}) in the presence of brefeldin A (10 μg mL^{-1}) for 5 h at 37°C in 5% CO_2. Surfaces were stained with the appropriate conjugated antibodies, and intracellular staining was performed using anti-IL-17A-PE and IFN-γ-PE (BD Biosciences) and the BD cytofix/cytoperm fixation/permeabilization solution kit according to the manufacturer's protocols (BD Biosciences).

CD4$^+$ T-cell count and viral load measurement

CD4$^+$ T TruCount (BD Biosciences) and plasma HIV-1 viral load (Abbort, Des Plaines, IL, USA) were measured according to the manufacturer's instructions.

Statistical analysis

All statistical analyses were performed using GraphPad Prism 5 software. Data for HCs and AHIs were analyzed using the Mann–Whitney *U* test. Linear regression was performed for correlation analyses on data from HCs and AHIs with *r* and *p* values depicted. A $p < 0.05$ was considered statistically significant.

RESULTS

Analysis of study subjects

Twenty-six untreated AHIs and 20 age-matched HCs were enrolled in this study. All AHIs were men who have sex with men (MSM). Table 1 shows the characteristics of these individuals. There were no significant differences in the frequency of CD4$^+$ T cells between HCs and AHIs, but AHIs exhibited a lower mean absolute CD4$^+$ T-cell count than HCs. The mean frequency of CD8$^+$ T cells in AHIs was higher than HCs. However, mean absolute numbers of CD8$^+$ T cells were similar between these two groups. The mean HIV-1 viral load of 10 AHIs was 70 623 copies mL^{-1}. Two of these 10 AHIs were hepatitis B virus (HBV) positive. We also evaluated the degree of immune activation in HCs and AHIs. The level of immune activation was statistically higher in AHIs than HCs, as reflected by the high proportion of CD38$^+$CD8$^+$ T cells, HLA-DR$^+$CD8$^+$ T cells, and CD38$^+$HLA-DR$^+$CD8$^+$ T cells

Table 1 Characteristics of study subjects

Group	Healthy controls (HCs)	Acute HIV-1 infected patients (AHIs)	*P* value*
Cases, no	20	26	NA
Mean age, years (range)	33.5 (20–46)	35 (18–49)	0.8797
Mean HIV loads, copies mL^{-1} (range)	NA	70 623 (658–17 734 74)[§]	NA
Mean CD4 counts, cells μL^{-1} (range)	666 (379–1160)	491 (187–862)	0.0027
Mean CD4 % (range)	30 (21–44)	26 (9–44)	0.0778
Mean CD8 counts, cells μL^{-1} (range)	685 (344–1677)	1033 (298–1777)	0.1813
Mean CD8 % (range)	35 (14–53)	46 (25–71)	0.0007
HBV infection	NA	2/26	NA
HCV infection	NA	None	NA

Data are presented as the means with ranges.
* *P* values were determined using the Mann–Whitney *U* test.
[§] The viral load of 10 AHIs was documented.
NA, not applicable.

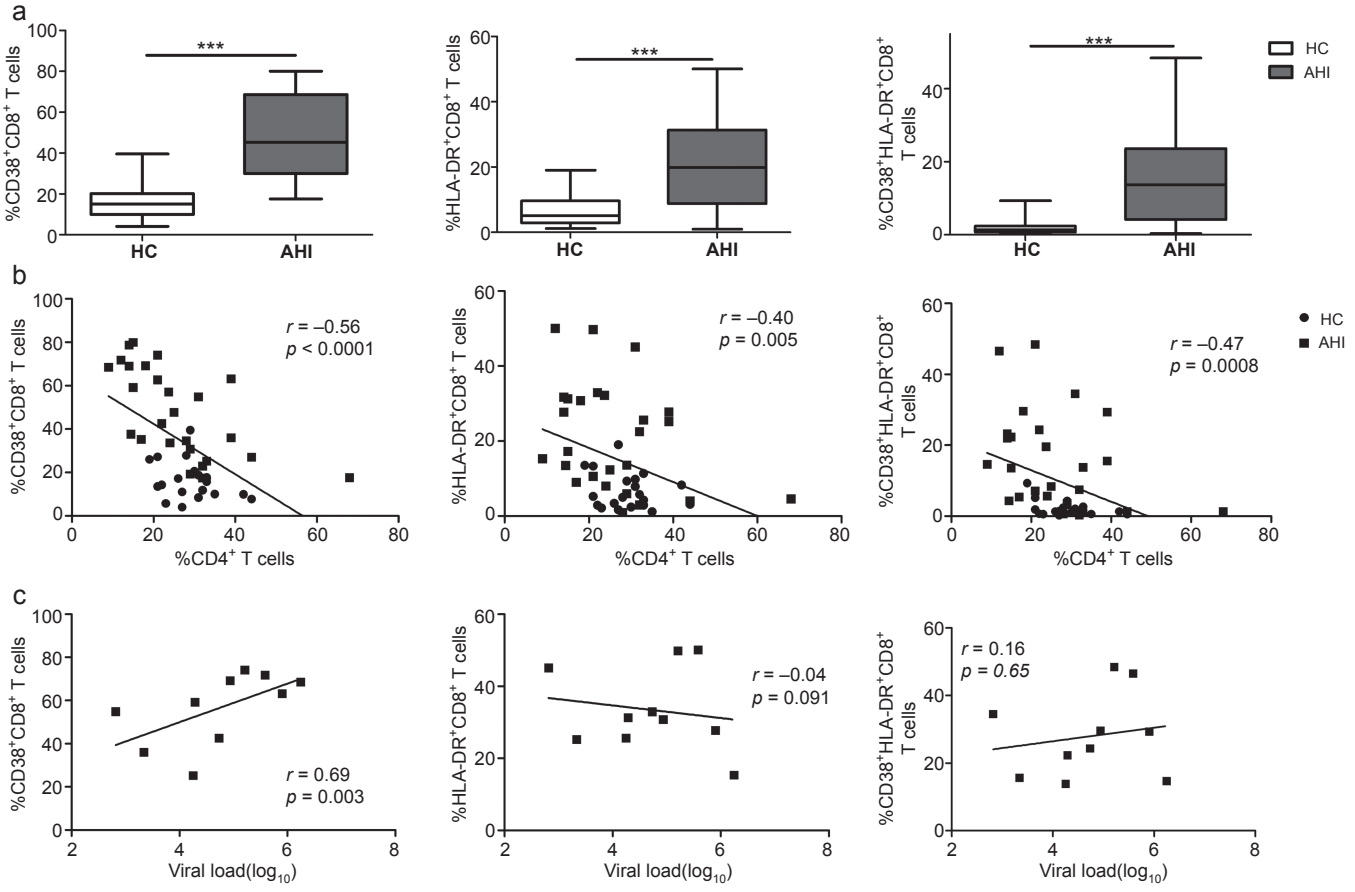

Figure 1 High levels of immune activation during acute HIV-1 infection. (**a**) Box-plot graph represents comparisons of the frequency of $CD38^+CD8^+$ T cells, $HLA\text{-}DR^+CD8^+$ T cells, and $CD38^+HLA\text{-}DR^+CD8^+$ T cells between HCs and AHIs. (**b**) Correlation between the frequency of $CD4^+$ T cells and $CD38^+CD8^+$ T cells, $HLA\text{-}DR^+CD8^+$ T cells, and $CD38^+HLA\text{-}DR^+CD8^+$ T cells in HCs and AHIs. (**c**) Correlation analyses of viral load and $CD38^+CD8^+$ T cells, $HLA\text{-}DR^+CD8^+$ T cells, and $CD38^+HLA\text{-}DR^+CD8^+$ T cells in AHIs. Each symbol represents an individual. $^{***}p < 0.001$.

(Figure 1a). We analyzed the correlation of immune activation with $CD4^+$ T cells in the AHI group. Figure 1b shows that the percentage of $CD38^+CD8^+$ T cells, $HLA\text{-}DR^+CD8^+$ T cells, and $CD38^+HLA\text{-}DR^+CD8^+$ T cells negatively correlated with the frequency of $CD4^+$ T cells. Correlations between immune activation and viral load were also analyzed in the AHI group, and a significant correlation was only observed between $CD38^+CD8^+$ T-cell levels and viral load (Figure 1c).

Preferential depletion of gut-homing $\beta7^+CD45RA^-CD4^+$ T cells occurred during acute HIV-1 infection

Figure 2a shows that four $CD4^+$ T-cell subsets were defined by β7 and CD45RA expression using flow cytometric analysis: $\beta7^+RA^-$, $\beta7^+RA^+$, $\beta7^-RA^+$, and $\beta7^-RA^-$. Gut-homing α4β7 $CD4^+$ T cells have a memory phenotype, and more than 95% of $\beta7^+CD4^+$ T cells co-express α4. Therefore, we identified $\beta7^+CD45RA^-CD4^+$ T cells as gut-homing α4β7 $CD4^+$ T cells to examine the characteristics of these cells during acute HIV-1 infection.[27] A marked decrease in the frequency and absolute number of gut-homing $\beta7^+CD45RA^-CD4^+$ T cells was found in AHIs compared to HCs (Figure 2b and 2c). No association between the frequency of gut-homing $\beta7^+CD45RA^-CD4^+$ T cells and $CD4^+$ T cells was identified (Figure 2d), but the absolute number of gut-homing $\beta7^+CD45RA^-CD4^+$ T cells positively correlated with $CD4^+$ T-cell count (Figure 2e). We also analyzed the correlation between gut-homing $\beta7^+CD45RA^-CD4^+$ T cells and viral load or immune activation level in the AHI group, but no correlation was observed (data not shown). Notably, no significant decrease in the frequency of non-gut-homing $\beta7^-CD45RA^-CD4^+$ T cells was observed after HIV-1 infection (Figure 2b). However, the absolute number of $\beta7^-CD45RA^-CD4^+$ T cells was lower during acute HIV-1 infection (Figure 2c), and the CD4 cell count was also associated with the number of $\beta7^-CD45RA^-CD4^+$ T cells (Supplementary Figure S1).

Altered profile of gut-homing Th17 cell subsets during the acute phase of HIV-1 infection

The loss of Th17 cells in gut mucosal results in inflammation in chronically HIV-1-infected individuals.[10–12] Therefore, we compared the gut-homing Th17 subpopulation between HCs and AHIs using fluorescence-activated cell sorting (FACS) analysis

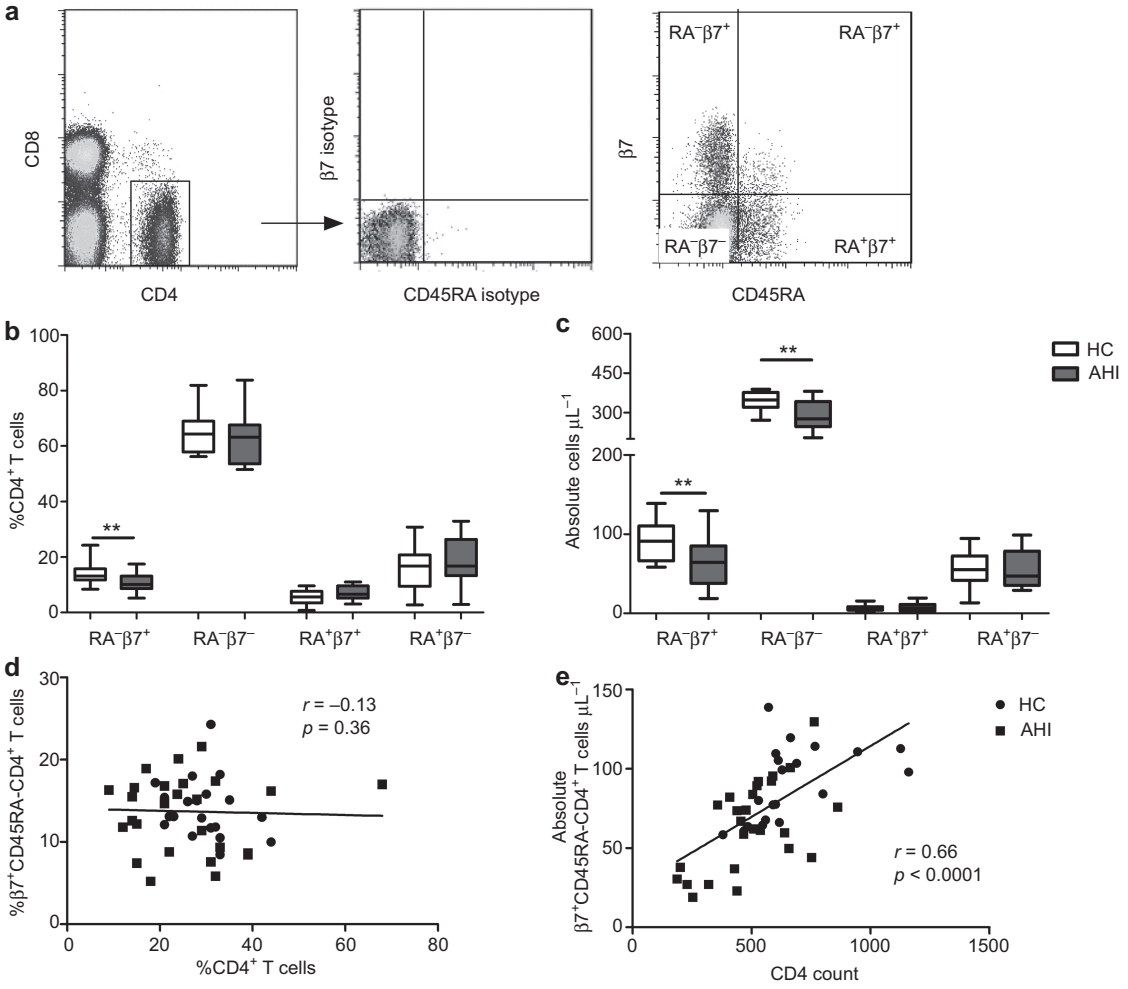

Figure 2 Peripheral gut-homing $CD4^+$ T cells are depleted in acute HIV-1 infection. (**a**) Representative flow cytometric plots of $CD4^+$ T-cell subsets in HCs. PBMCs were isolated from whole blood and stained with appropriate antibodies as described in the Materials and Methods section. The following four subsets of $CD4^+$ T cells were defined with reference to isotype control: $\beta7^+RA^-$, $\beta7^+RA^+$, $\beta7^-RA^+$, and $\beta7^-RA^-$. (**b**) Box-plot graph shows the frequency of the four subsets between the HC and AHI groups. (**c**) The absolute numbers of the four subsets are compared between the HC and AHI groups. (**d**) Correlation between the percentage of gut-homing $CD4^+$ T cells and total $CD4^+$ T cells in HCs and AHIs. (**e**) Correlation between the absolute number of gut-homing $CD4^+$ T cells and total $CD4^+$ T-cell counts in HCs and AHIs. $^{**}p < 0.01$.

(Figure 3a). The frequencies and absolute counts of Th17 cells in AHIs decreased significantly in $\beta7^+CD45RA^-CD4^+$, $\beta7^-CD45RA^-CD4^+$, and $\beta7^+CD45RA^+CD4^+$ T-cell subsets compared to HCs (Figure 3b and 3c). The reduction of gut-homing $\beta7^+CD45RA^-$ Th17 cells correlated with the decrease in $CD4^+$ T cells in absolute numbers (Figure 3d and 3e) but not viral load (data not shown). Critically, a positive correlation in the frequency and absolute cell counts was observed between gut-homing $\beta7^+CD45RA^-$ Th17 cells and gut-homing $CD4^+$ T cells (Figure 3f and 3g). A positive correlation was also observed between the non-gut-homing $\beta7^-CD45RA^-$ Th17 cell subset and CD4 count (Supplementary Figure S2a and S2b). The frequency of the $\beta7^+CD45RA^+$ Th17 cell subset negatively correlated with $CD4^+$ T cells, but a positive correlation in absolute cell number was observed (Supplementary Figure S2c and S2d).

Increased frequency of gut-homing Tregs during acute HIV-1 infection

Pathogenic HIV-1 infection is associated with an increased frequency of Tregs. Therefore, we analyzed the profile of Treg subsets during acute HIV-1 infection. We used $CD127^{low}CD25^+CD4^+$ T cells as Tregs in the present study (Figure 4a). A significant proportion of gut-homing $\beta7^+CD45RA^-$ Tregs (Figure 4b) was found in AHIs compared to HCs, but the absolute number of these Tregs was comparable between groups (Figure 4c). Acute HIV-1 infection also increased $\beta7^+CD45RA^+$ Tregs, but not non-gut-homing $CD4^+$ T cells (Figure 4b and 4c). A negative correlation between the percentage of gut-homing $\beta7^+CD45RA^-$ Tregs and $CD4^+$ T cell was found (Figure 4d), and the number of gut-homing $\beta7^+CD45RA^-$ Tregs also positively correlated with gut-homing $CD4^+$ T cells (Figure 4g).

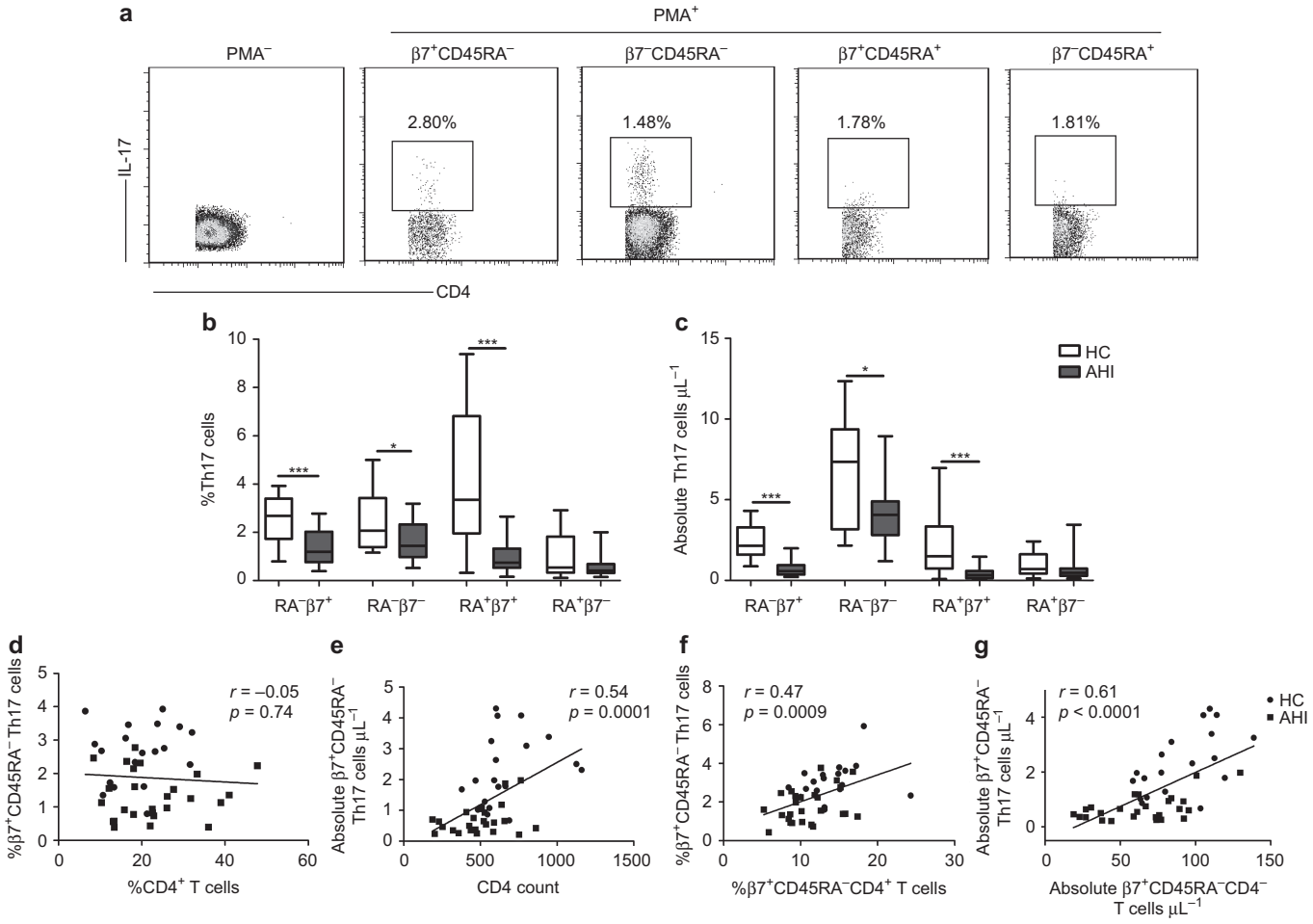

Figure 3 Decrease in the gut-homing Th17 subset in acute HIV-1 infection. (**a**) Flow cytometric analysis of Th17 cells in different $CD4^+$ T-cell subsets from a representative HC. Numbers indicate the percentage of gated cells. The frequency (**b**) and total absolute number (**c**) of Th17 cells in four subsets are compared between HCs and AHIs. Correlation between the frequency of gut-homing Th17 cells or absolute number of gut-homing Th17 cells and total $CD4^+$ T-cell count (**d**, **e**) or gut-homing $CD4^+$ T cells (**f**, **g**) in HCs and AHIs. Each symbol represents an individual. $*p < 0.05$, $***p < 0.001$.

Decreased level of gut-homing Th1 cells in HIV-1 acute infection

We further investigated the functionality of the Th1 subset via analysis of IFN-γ production in the AHI group (Figure 5a). The frequency and absolute count of IFN-γ-secreting Th1 cells in AHIs dropped significantly in the gut-homing $\beta7^+CD45RA^-CD4^+$ and non-gut-homing $\beta7^-CD45RA^-CD4^+$ T-cell subsets compared to HCs (Figure 5b and 5c). A significant correlation was observed between the number of $\beta7^+CD45RA^-CD4^+$ Th1 cells and total CD4 counts or gut-homing $CD4^+$ T cells (Figure 5d–5g), but not with viral load (data not shown). The decrease in total CD4 count was also associated with non-gut-homing $\beta7^+CD45RA^-CD4^+$ Th1 cells (Supplementary Figure S3).

Imbalance of gut-homing Th1:Treg and Treg:Th17 ratios in acute infection

The ratios of Th17:Th1 and Treg:Th17 may contribute to disease progression in HIV-1 infection.[15–17] Therefore, we determined the ratios of Th1:Treg, Treg:Th17, and Th1:Th17 of gut-homing $CD4^+$ T cells in AHIs. Acute HIV-1 infection led to a loss of gut-homing Th1:Treg compared to HCs (Figure 6b), and the Treg:Th17 ratio increased in the gut-homing $CD4^+$ T-cell subset with statistical significance (Figure 6c). No significant changes were observed in the ratio of gut-homing Th1:Th17 (Figure 6a). Correlation analyses revealed that only the ratio of gut-homing Treg:Th17 was inversely correlated with the total CD4 count (Figure 6d–6f).

DISCUSSION

This study examined the frequency and absolute number of gut-homing $CD4^+$ T cells and their functional subsets in HCs and acute HIV-1-infected individuals. Overall, the preferential depletion of gut-homing $CD4^+$ T cells occurred in the acute phase of HIV-1 infection, and alterations of gut-homing Th17, Th1, Tregs and their ratios may be responsible for the pathogenesis during acute HIV-1 infection.

The expression of integrin α4β7 on $CD4^+$ T cells may provide an alternative receptor for HIV-1.[20,21] The $CD4^+$ T cells

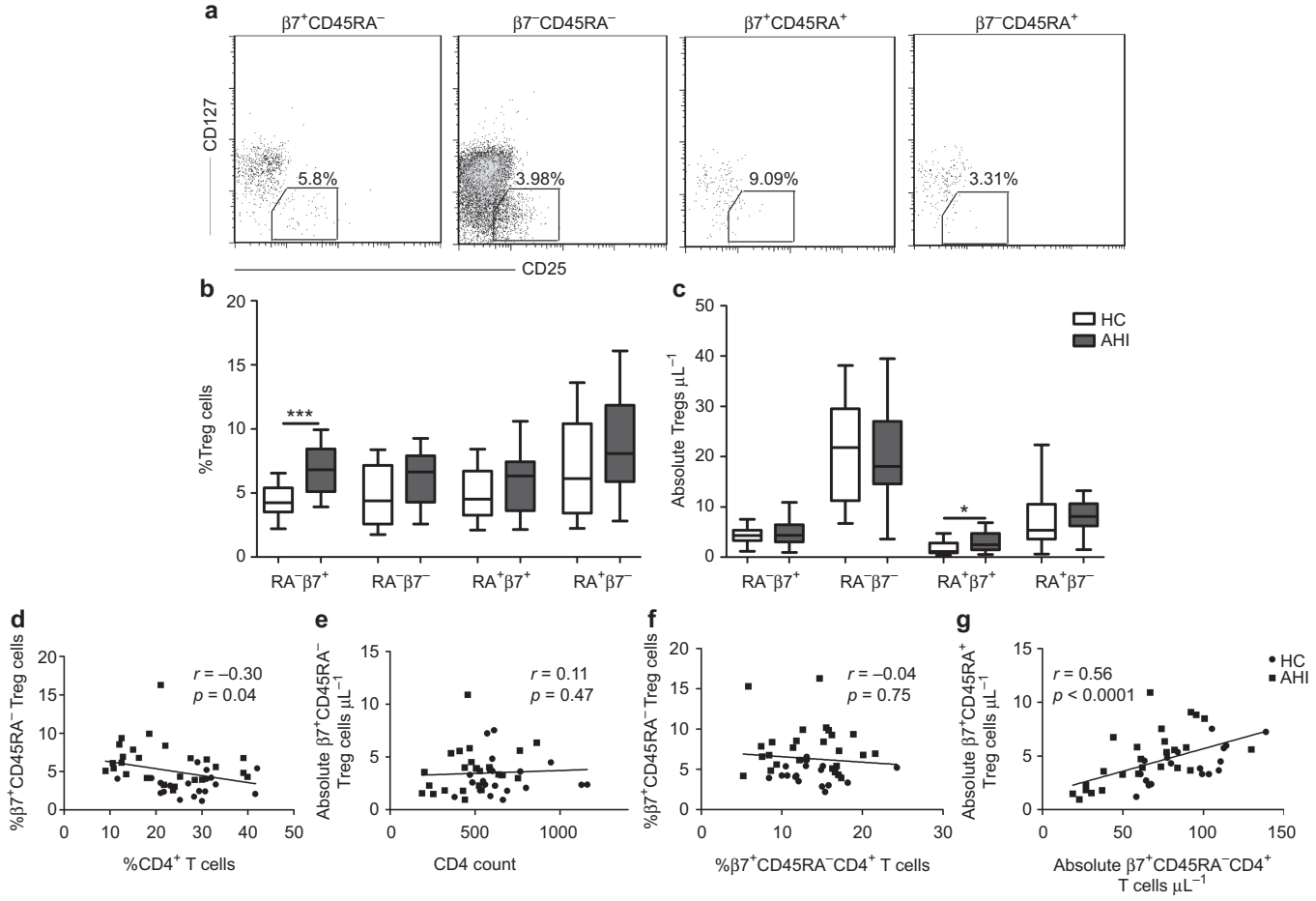

Figure 4 Increased gut-homing Tregs occurred during acute HIV-1 infection. (**a**) Flow cytometric analysis of Tregs in four $CD4^+$ T-cell subsets. Data are from a representative HC. Numbers indicate the percentage of gated cells; (**b**, **c**) Comparison of HCs and AHIs in the frequency or absolute number of Tregs in the four subsets. Correlation between the frequency or absolute number of gut-homing Tregs and $CD4^+$ T cells (**d**, **e**) or gut-homing $CD4^+$ T cells (**f**, **g**) in HCs and AHIs. Each symbol represents an individual. $*p < 0.05$, $***p < 0.001$.

that express high levels of α4β7 are memory $CD4^+$ T cells, which are preferentially depleted during acute SIV infection.[22] A lack of repopulation of gut-homing $CD4^+$ T cells from peripheral blood to gut mucosa may result in incomplete immune reconstitution despite long-term ART.[24,25] Therefore, investigation of the characteristics of gut-homing $CD4^+$ T cells during acute HIV-1 infection may be beneficial to understand HIV-1 pathogenesis. We observed that the frequency or absolute number of gut-homing $CD4^+$ T cells decreased significantly in individuals with acute HIV-1 infection compared to HCs (Figure 2b and 2c), which is consistent with a previous SIV study.[22] Gut-homing $CD4^+$ T cells positively correlated with $CD4^+$ T cells (Figure 2e), which suggests that the loss of gut-homing $CD4^+$ T cells during acute infection plays an important role in HIV-1 pathogenesis. A decreased number of non-gut-homing $\beta7^-CD45RA^-CD4^+$ T cells was observed in our analysis (Figure 2c), but acute HIV-1 infection caused the predominant depletion of the frequency and absolute cell count of gut-homing $CD4^+$ T cells, which indicates that gut-homing $CD4^+$ T cells were preferentially depleted during acute HIV-1 infection (Figure 2b and 2c). A positive correlation between gut-homing $CD4^+$ T cells and $CD4^+$ T-cell count was observed, which suggests a critical role of these cells in AIDS pathogenesis.

HIV-1 infection was accompanied with the dissemination of microbial products from the lumen of the intestinal mucosa to the peripheral circulation, which resulted in chronic immune activation in HIV-1 infection.[28,29] Numerous studies demonstrated that the loss of gut Th17 cells likely played an important role in microbial translocation during HIV/SIV infection.[11,14] Macal *et al.* demonstrated that the effective recovery of gut $CD4^+$ T cells paralleled the high level of Th17 cells.[12] However, to our knowledge, few studies investigated gut-homing Th17 cells during acute HIV-1 infection. Our results demonstrated that the frequency and absolute number of gut-homing Th17 cells were reduced in AHIs (Figure 3b and 3c). A correlation between gut-homing Th17 cells and total $CD4^+$ T cells or gut-homing $CD4^+$ T cells was also displayed (Figure 3d–3g). Our observation of decreased gut-homing Th17 cells in AHIs may reflect the low-level trafficking of Th17 cells from blood to gut, which accelerates the depletion of gut Th17 cells during acute HIV-1 infection.

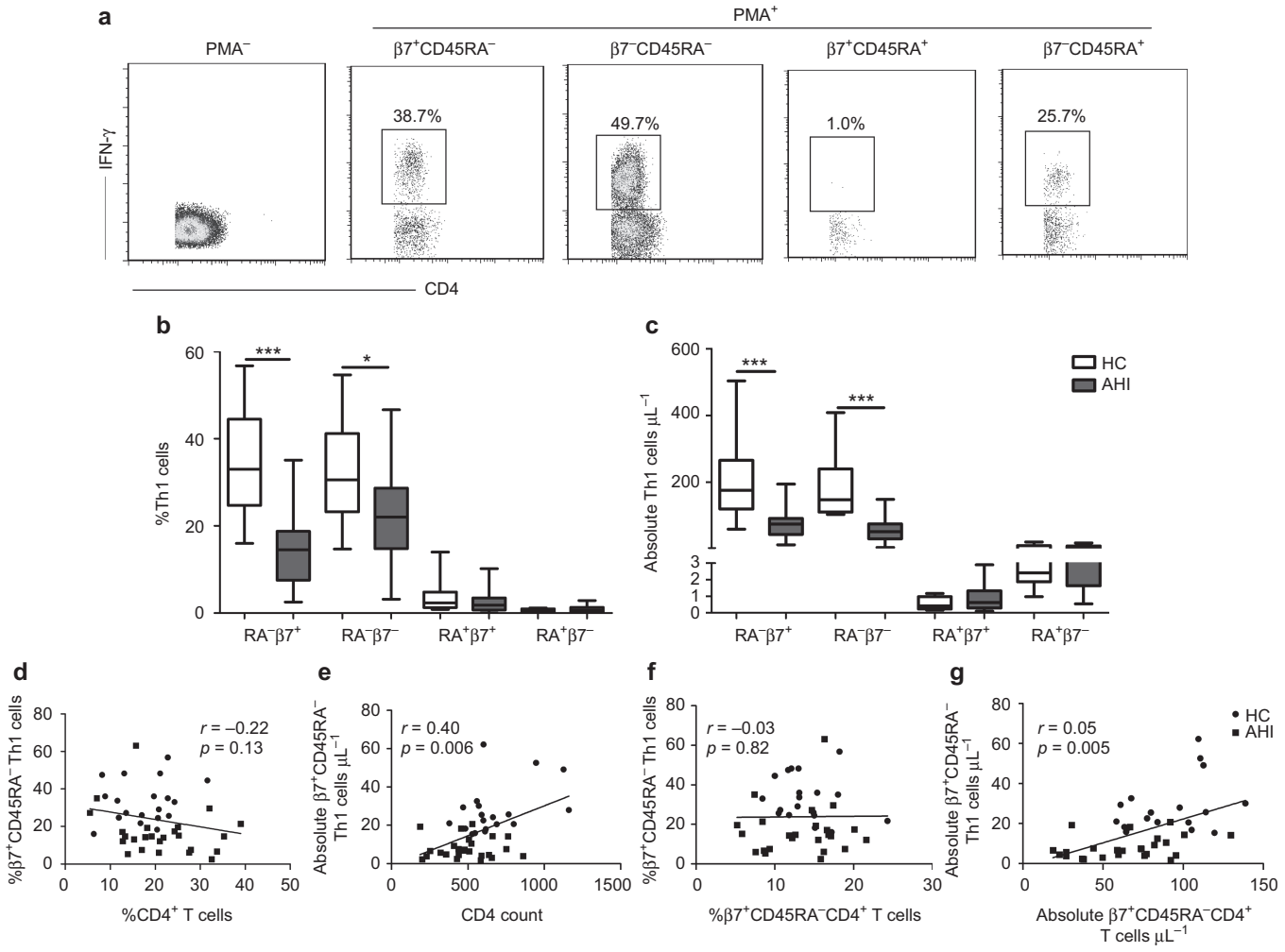

Figure 5 Depletion of gut-homing Th1 cells during acute HIV-1 infection. (**a**) Flow cytometric analysis of Th1 cells in four CD4$^+$ T-cell subsets. Data are from a representative HC. Numbers indicate the percentage of gated cells; (**b**, **c**) Comparison of HCs and AHIs in the frequency or absolute number of Th1 cells in the four subsets. Correlation between the frequency or absolute number of gut-homing Th1 and CD4$^+$ T cells (**d**, **e**) or gut-homing CD4$^+$ T cells (**f**, **g**) in HCs and AHIs. Each symbol represents an individual. *$p < 0.05$, ***$p < 0.001$.

Th1 cells are the dominant subset in the gut mucosa during chronic infection, and the loss of Th1 cells in HIV/SIV infection impairs their responses to bacterial pathogens in gut mucosal tissues.[16,30] The decline of gut-homing Th1 cells during acute infection in our data (Figure 5b and 5c) indicates that a lack of Th1 cell recruitment from blood to the gut mucosa may occur during persistent HIV-1 infection and contribute to AIDS progression.

The frequency of gut-homing Tregs was increased in our analysis (Figure 4a). However, no significant difference in the absolute number of gut-homing Tregs was observed in AHIs compared to HCs (Figure 4c) because of the loss of total CD4$^+$ T cells in AHIs. Severe depletion of gut Tregs occurs during acute SIV infection, which may result in immune hyperactivation in gut tissues.[31,32] We did not confirm this phenomenon in HIV-1 primary infection using gut biopsies, but our results of an increased percentage of gut-homing Tregs in peripheral blood and high levels of immune activation in AHIs suggest that gut Tregs are reduced after HIV-1 infection, and more Tregs in blood are required to home to the gut mucosa and supplement the loss of Tregs in gut tissues.

An imbalance of Treg:Th17 and Th1:Th17 ratios are also involved in the pathogenesis of acute HIV/SIV infection.[16,33,34] Altered gut-homing Treg:Th17 and Th1:Treg ratios were documented during chronic HIV-1 infection despite ART.[25] Abnormal ratios of Th1:Treg and Treg:Th17 were also demonstrated in AHIs (Figure 6b and 6c). However, changes in the Th1:Th17 ratio were not observed in our analysis (Figure 6a). Possible explanations for these results include the decline of gut-homing Th1 cells similar to that of Th17 cells, as well as the small sample size of our analysis.

Early treatment at Fiebig stage I/II may prevent the loss of Th17 cells and immune activation that contribute to the dysfunction of the gut mucosal barrier.[35] Long-term HIV-1 non-progressors (LTNPs) exhibit intact CD4$^+$ T-cell populations in

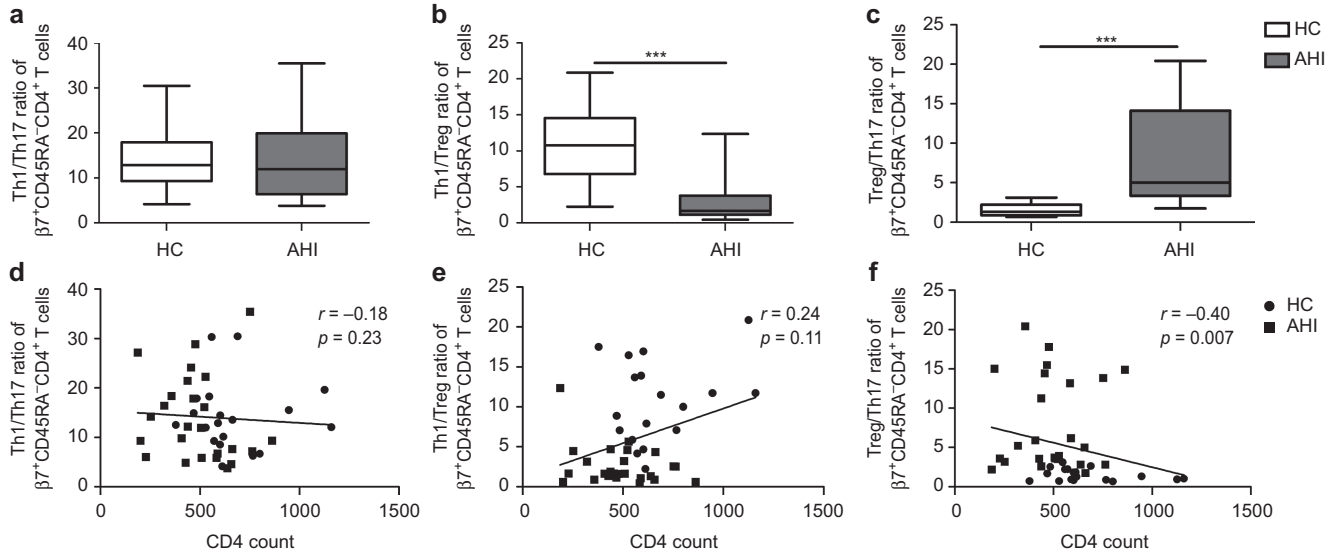

Figure 6 Imbalance of gut-homing Th1:Treg and Th17:Treg ratios during acute HIV-1 infection. The patient-matched ratios of Th1/Th17 (**a**), Th1/Treg (**b**), and Treg/Th17 (**c**) of gut-homing $CD4^+$ T cells are compared between HC and AHI study subjects. Correlation between gut-homing Th1/Th17 (**d**), gut-homing Th1/Treg (**e**), or gut-homing Treg/Th17 (**f**) and total $CD4^+$ T-cell counts. Each symbol represents an individual. $***p < 0.001$.

the gut mucosa and a preserved balance of $CD4^+$ T-cell subsets in blood and mucosal sites.[36] Therefore, the protection mechanism of LTNPs may be similar to the effect of early treatment during acute HIV-1 infection, and gut-homing α4β7 $CD4^+$ T cells may be beneficial in the maintenance of normal $CD4^+$ T-cell levels in LTNPs and the reconstitution of gut $CD4^+$ T cells during the early initiation of ART in HIV-1-infected individuals. The effect of early treatment on gut-homing α4β7 $CD4^+$ T cells should be examined in the future. Our research also has limitations because we were unable to obtain gut biopsies to confirm the relevant dynamic changes between gut-homing $CD4^+$ T cells and mucosal $CD4^+$ T cells, which hindered our further understanding of the critical role of gut-homing $CD4^+$ T cells in HIV-1 pathogenesis.

In conclusion, this study found that gut-homing α4β7 $CD4^+$ T cells were preferentially depleted during acute HIV-1 infection and that the functional subsets Th1 and Th17 were also decreased. These changes could result in the persistent loss of gut $CD4^+$ T cells and the imbalance of gut-homing Th1:Treg and Treg:Th17 ratios, thereby contributing to disease pathogenesis.

COMPETING INTERESTS

The authors have no funding or conflicts of interest to disclose.

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Supplementary information of this article can be found on *Cellular & Molecular Immunology* website: http://www.nature.com/cmi.

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