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LETTER TO THE EDITOR

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Transient depletion of T cells during COVID-19 and seasonal influenza in people living with HIV

To the editor,

The cellular immune deficiency seen in people living with HIV (PLWH) is of potential concern as dysfunctional immune responses contribute to disease progression and dysregulated T cell responses can result in immunopathology.[1,2] Transient decrease in lymphocytes during COVID-19 is well known and a preexisting T cell depletion induced by HIV may cause deleterious clinical consequences.[3] Additionally, seasonal influenza has been compared with COVID-19 given the common features shared by these viruses, such as fever and respiratory symptoms that range from mild forms to severe pneumonia, whereas these two viruses differ in their receptors for infection and the duration and incubation period of the disease they cause. T cell responses could affect both the initial nonspecific innate immune response and the following antigen-specific adaptive immunity, which is mediated by humoral immunity and T cells including CD8+, CD4+ and regulatory T cells.[4] In this study, we investigated the changes in T cell subset composition, such as CD4+ cell count and CD8+ cell count, during seasonal influenza infection and COVID-19 among PLWH.

We conducted a retrospective analysis of the routine clinical records of PLWH at an HIV/AIDS referral hospital in Tokyo, Japan. PLWH with COVID-19 confirmed by reverse transcription polymerase chain reaction between March 2020 and September 2021 or PLWH with laboratory-confirmed seasonal Influenza between April 2010 and April 2019 were included. T cell subset were assessed at three time points: within 3 months before symptom onset, within 10 days postsymptom onset, and within 1–6 months after recovery. To examine the transient changes in the T cell count before and after infection and to exclude changes due to other factors, we included only PLWH who had been on effective antiretroviral therapy for at least 1 year and who had the results of T cell subset at all of the three time points above. We used the repeated measures analysis of variance to compare the three time points and the paired *t*-test were used to evaluate the difference between cell counts before symptom onset and during illness. Statistical significance was defined as two-sided p values < 0.05.

As shown in Table 1, there were significant changes in the transition of T cell counts in both influenza infection and COVID-19. A total of 17 COVID-19 patients was eligible; all were inpatients, and seven patients were with moderate or higher disease. Sixteen patients were male the median age was 53 years (range: 26–68). The mean CD4+ cell count was 659 cells/μl, 436 cells/μl, and 686 cells/μl (before onset, during infection and after recovery, respectively) (before onset vs. during infection: $p = 0.0001$, Figure 1A), CD8+ T cell count was 805 cells/μl, 539 cells/μl, and 831 cells/μl (before onset vs. during infection: $p = 0.0026$, Figure 1B), and CD4+/CD8+ ratio was 0.94, 0.870, and 0.96 (before onset vs. during infection: $p = 0.182$, Figure 1C). The mean lymphocyte count was 2148 cells/μl, 1505 cells/μl, and 2066 cells/μl (before onset vs. during infection: $p = 0.0003$). There was no significant change in CD4+ cell, CD8+ cell, and total lymphocyte counts between those before symptom onset and after recovery.

Next, we analyzed a total of 27 Influenza infections; there were no hospitalizations, and no patients had pneumonia or encephalopathy. All patients were male, and the median age was 39.5 years (range: 19–54). The mean CD4+ cell count was 455 cells/μl, 316 cells/μl, and 445 cells/μl (before onset vs. during infection: $p < 0.0001$, Figure 1D). CD8+ cell count was 796 cells/μl, 580 cells/μl, and 758 cells/μl (before onset vs. during infection: $p = 0.0033$, Figure 1E), and CD4+/CD8+ ratio was 0.65, 0.65, and 067 (before onset vs. during infection: $p = 0.932$, Figure 1F). The mean lymphocyte count in seasonal influenza patients was 1884 cells/μl, 1369 cells/μl, and 1825 cells/μl (before onset vs. during infection: $p = 0.0005$). There was no significant change in CD4+ cell, CD8+ cell and total lymphocyte counts between those before symptom onset and after recovery.

A transient decrease in CD4+ cell, CD8+ cell and lymphocyte counts were observed during the acute phase in both influenza infection and COVID-19 in PLWH. As a result, the CD4+/CD8+ ratio did not change in both infections. Our result indicates that the lymphocyte depletion of COVID-19 can be caused by the decrease in the total number of T cells rather than the alteration of the T cell differentiation, and it is possible that the same phenomenon occurs in the seasonal influenza infection. T cell counts are rarely tested for COVID-19 in non-HIV infected individuals. Considering that transient lymphocytopenia with COVID-19 also occurs in non-HIV-infected individuals,[5] however, transient CD4+ cell and CD8+ cell depletion in both influenza infection and COVID-19 could occur in non-HIV-infected individuals. Little has been known about the transition of T cell count in seasonal influenza virus infection, as most of them are confined to mild illness, and lymphocyte count and T cell subsets are rarely tested. Acute viral infections can cause accelerated lymphocyte consumption, decreased lymphocyte migration in the spleen or lymph nodes, or increased migration of lymphocytes to organs such as the lungs and upper respiratory tract. Transient T cell depletion can

TABLE 1 The transition of T cell count in COVID-19 and seasonal influenza virus infection

	COVID-19				seasonal influenza			
	Before onset	During infection	After recovery	*p* value[a]	Before onset	During infection	After recovery	*p* value[a]
Lymphocyte (μ/L)	2148	1505	2066	0.0003	1884	1369	1825	0.0001
CD4+(μ/L)	659	436	686	<0.0001	455	316	445	<0.0001
CD8+(μ/L)	805	539	831	0.01	796	580	758	0.002
CD4+/CD8+ ratio	0.94	0.87	0.96	0.24	0.65	0.65	0.67	0.65

Abbreviation: ANOVA, analysis of variance.

[a]*p* values were calculated using repeated measures ANOVA.

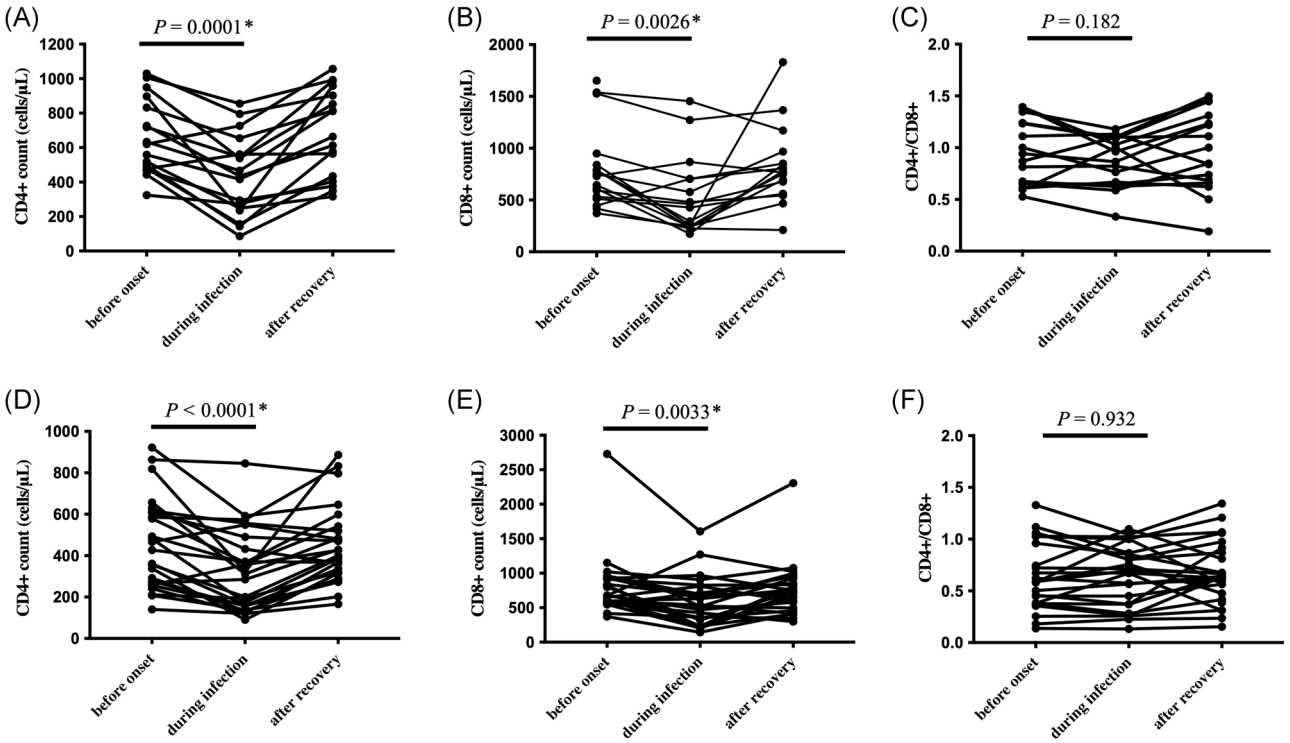

FIGURE 1 Temporal changes in the T-cell subset composition in peopele living with HIV. (A) CD4+ cell count in COVID-19, (B) CD8+ cell count in COVID-19, (C) CD4+/CD8+ ratio in COVID-19, (D) CD4+ cell count in seasonal influenza, (E) CD8+ cell count in easonal influenza, (F) CD4+/CD8+ ratio in seasonal influenza. Three time points were as follows, before onset: within 3 months before symptom onset, during infection: within 10 days postsymptom onset, after recovery: within 1–6 months after recovery. The paired *t*-test were used to evaluate the difference between cell counts before onset and during infection. *Statistical significance was defined as two-sided $p < 0.05$

also occur with other viral infections,[6] and further research is needed for assessing the clinical impact of this transient change.

AUTHOR CONTRIBUTIONS

Eisuke Adachi: carried out the project and drafted the manuscript. **Eisuke Adachi, Makoto Saito, Hiroyuki Nagai, Michiko Koga, Takeya Tsutsumi, and Hiroshi Yotsuyanagi**: were responsible for the clinical management of the patient. **Kazuhiko Ikeuchi**: contributed to data collections. **Makoto Saito and Hiroshi Yotsuyanagi**: revised the manuscript. All authors approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Ethics approval was granted by the ethics board of the Institute of Medical Science, University of Tokyo (2020-5-0420).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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