Eur J Med Res (2011) 16: 473-479

Study of T Cell Subsets and IL-7 Protein Expression in HIV-1-infected Patients after 7 Years HAART

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Abstract
Objective: To study the changes in T cell subsets and IL-7 in HIV-1-infected patients after seven years of highly active antiretroviral therapy (HAART).
Methods: Seventy-five individuals were included in this study (25 with effective HAART, 18 with ineffective HAART, 17 untreated HIV+ patients, and 15 volunteers in the HIV negative control group). The counts of $CD4^+$, $CD8^+$, $CD8/CD38^+$, and $CD8/HLADR^+$ T cells as well as the IL-7 protein expression was measured at 5 time points during a period of seven years in patients starting HAART (baseline) and in the HIV negative control group. The expression of CD127 on $CD3^+$ T cells was measured by flow cytometry at a single time point (after 7 years) in patients with HAART and was compared with untreated HIV+ patients and the HIV negative control group.
Results: At baseline $CD4^+$ T cell counts of HIV-1-infected patients were lower than that in the control group ($p < 0.01$), whereas the $CD8^+$, $CD8/HLADR^+$ and $CD8/CD38^+$ T cell counts were higher than those in the control group ($p < 0.01$). After seven years of effective HAART, the $CD4^+$ T cell counts had increased and the $CD8^+$ T cell count had decreased, although not to the normal levels ($p < 0.05$). Both the $CD8/HLADR^+$ and $CD8/CD38^+$ T cell counts had gradually approached those of the control group ($p > 0.05$). In the ineffective HAART group, the $CD8/CD38^+$ T cell count had not decreased significantly, and $CD8/HLADR^+$ T cell count gradually decreased. Before treatment, IL-7 serum levels of patients were significantly higher than that in the control group ($p < 0.01$). After seven years of effective HAART, IL-7 levels had gradually decreased, but were still higher than in the control group ($p < 0.01$). The CD127 expression on $CD3^+$ $CD8^+$ T cells in effective HAART patients was higher than in untreated HIV+ patients ($p < 0.05$), but was lower than that in the control group ($p < 0.05$). CD127 expression on $CD3^+$ $CD4^+$ T cells was not significantly different among the control group, untreated HIV+ patients and effective HAART group.
Conclusion: After seven years of effective HAART, the quantity and capacity of T cell subsets and IL-7 in HIV-1-infected patients had been partially restored, and the abnormal immune activation has significantly diminished.
Key words: HIV-1, highly active antiretroviral therapy (HAART), T cell subsets, IL-7

Introduction

Human immunodeficiency virus-1 (HIV-1) mainly attacks $CD4^+$ T cells of the immune system, which leads to a serious impairment of immune function. The pathological changes associated with HIV-1 infection include changes in both the population and function of $CD4^+$ T cells, as well as abnormal activation of the immune system [1]. Highly active antiretroviral therapy (HAART) can inhibit virus replication in vivo, and thereby inhibit the progression of AIDS [2]. It has been reported that HAART can partially restore immune function in HIV-1-infected patients; however, how long the recovery period is and how long the inhibition of abnormal immune activation would last remain unknown. Moreover, there is still a lack of studies on the function of long-term HAART on immune restauration in HIV-1-infected patients.

IL-7, which plays a crucial role in T cell homeostasis, also regulates peripheral naive T cell survival and rhIL-7 was found to simultaneously increase $CD4^+$ and $CD8^+$ T cell counts, particularly memory T cells. Furthermore, the expression level and regulatory mechanism of the IL-7Rα chain (CD127) is positively correlated with the lifetime of T cells in peripheral blood. The expression of CD127, which is a specific surface marker of T cells, can be lowered by HIV-1-specific lymphocytes, thereby impairing its regulatory function. Low CD127 levels on $CD8^+$ T cells lead to a proliferation of HIV (see also discussion).

In this study, the changes in T lymphocyte subsets and peripheral blood IL-7 protein expression was investigated during a period of seven years in patients starting HAART (baseline) and in the HIV negative

control group. In addition, the expression of CD127 on $CD3^+$ T cells were measured by flow cytometry in patients with HAART and was compared with untreated HIV+ patients and the HIV negative control group. By analysing differences among those groups, we aimed to investigate the immune restauration achieved by seven years of HAART in HIV-1-infected patients.

Materials and Methods

Study Groups

The HIV-1-infected adults were retrospectively reviewed between 1998 and 2009 at the St. Josef Hospital, Ruhr-University Bochum, Germany and Qing Chun Hospital, Zhejiang Province, China. All the patients infected by HIV-1 had no severe opportunistic infections. Patients receiving more than seven years of HAART were divided into two groups: Effective group (group A): plasma HIV-RNA lower than the level of detection (50 copies/mL) after 1 year of HAART. Ineffective group (group B): plasma HIV-RNA higher than the level of detection (50 copies/mL) after 1 year of HAART. The cause of ineffective therapy (e.g. resistance or lack of compliance) was not investigated. The plasma HIV-RNA level of the patients was documented annually. If the plasma HIV-RNA level was repeatedly above detection level antretroviral therapy was changed within one year, but was still not stable after 7 years. Some analyses were compared with an untreated group (group C): HIV-1 infected individuals who didn't receive antiretroviral therapy. As a control group served HIV negative volunteers with no history of acute or chronic illnesses, especially immunologic diseases and tumours, no infections during the previous two months and no abnormal findings in physical examinations.

Sample Collection and Processing

Peripheral blood (7 mL) was taken from each of the subjects, and the samples were drawn into tubes with EDTA. Half of the sample was measured by flow cytometry (Becton, Dickinson and Company). Plasma extracted from the other half of the sample was used to measure the viral load and IL-7 protein expression. The blood samples of the patients who received long-term HAART were taken annually.

Detection of Plasma HIV-RNA

An HIV-1 Monitor 1.5 commercial kit (Roche) and COBAS AmpliSensor-PCR were used for quantitative analysis of HIV-RNA in the plasma samples. The measurements were performed according to the manufacturers' instructions.

Flow Cytometry

Three different combinations of fluorescent antibodies ($CD8^+$ $CD127^+$ T, $CD8^+$ $CD45RO^+$ $CD127^+$ T and $CD8^+$ $CD45RA^+$ $CD127^+$ T) were separately drawn into three tubes of 50 μL EDTA blood from each sample. Flow cytometry (Becton, Dickinson and Company) and System U software were used to analyse the results. The same method was applied to detect $CD4^+$, $CD8^+$, $CD8/CD38^+$, and $CD8/HLADR^+$ T cells in the peripheral blood. The fluorescent antibodies used were as follows: CD3 FITC, CD4 PerCP 5.5, CD8 APC-H7, CD45RO PECy7, CD45RA PECy7, CD127 PE, CD4 FITC, CD8 FITC, CD38 PE, and anti-HLA-DR APC.

Table 1. Baseline characteristics of study population.

	Effective Group	Ineffective Group	Untreated Group	Control Group
Number of Subjects	25	18	17	15
Sex				
Male	19(76%)	13(72.2%)	13(76.5%)	9(60%)
Female	6(24%)	5(27.8%)	4(23.5%)	6(40%)
Age	47.6±9.1	45.7±10.4	39.7±11.3	40.5±9.7
	(35〜71)	(31〜60)	(36〜63)	(33〜57)
Transmission				
Sexual	21(84%)	16(88.8%)	16(94.1%)	—
Blood	3(12%)	1(5.6%)	1(5.9%)	—
Other	1(4%)	1(5.6%)	0	—
$CD4^+$ T (cells/μL) *	187	175	341	736
	(22~367)	(56~341)	(78~400)	(452~1038)
＜200	13(52%)	10(55.6%)	2(11.8%)	0
≥200~＜350	11(44%)	8(44.4%)	5(29.4%)	0
≥350	1(4%)	0	10(58.8%)	15(100%)
Therapy				
2NRTIs+NNRTI	13(52%)	11(61.1%)	—	—
2NRTIs+PI	12(48%)	7(38.9%)	—	—

*: baseline $CD4^+$ T cell counts are shown by medians with ranges. NRTI: Nucleoside Reverse Transcriptase Inhibitor, NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor, PI: Protease Inhibitor.

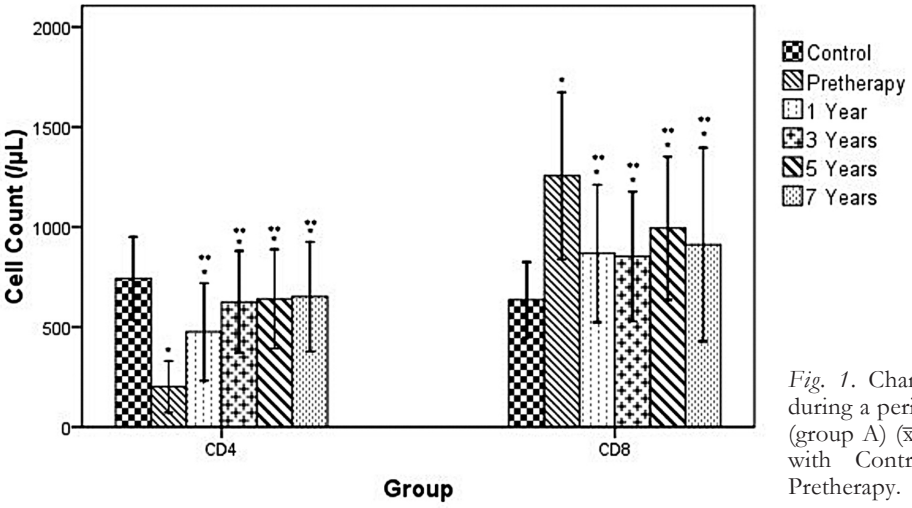


Fig. 1. Changes of CD4+ T and CD8+ T cells during a period of seven years effective HAART (group A) ($\bar{x} \pm$ SD, n=25). *: P<0.05 compared with Control, **: P<0.05 compared with Pretherapy.

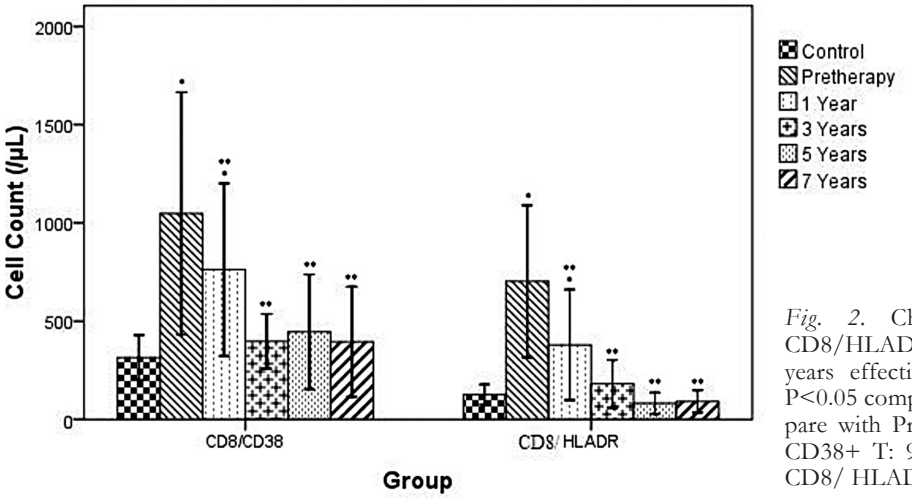


Fig. 2. Changes of CD8/CD38+ T and CD8/HLADR+ T cell during a period of seven years effective HAART ($\bar{x} \pm$ SD, n=25). *: P<0.05 compared with Control, **: P<0.05 compare with Pretherapy. Reference level of CD8/ CD38+ T: 90-600 cells/μL, Reference level of CD8/ HLADR+ T: 30-200 cells/μL.

IL-7 Quantitative Determination

ELISA was used to determine the concentration of IL-7 (μg/L). The absorbance at 450 nm was measured using an ELISA Reader. The reagent was purchased from R & D Company, US. The measurements were performed according to the manufacturer's instructions.

Statistical Analysis

All data was denoted by mean and standard deviation ($\bar{x} \pm$ SD). To compare the T cell subsets during the long-term effective HAART, matching Student's t-test was used. Mann-Whitney U-test was used for analysis of the other continuous data. All data were entered and analyzed using SPSS version 16 packages, and p value of less than 0.05 was considered statistically significant.

Results

The Clinical Characteristics of the Study Population

According to the included criteria, seventy-five individuals were enrolled in this study. Of the seventy-five individuals, sixty were HIV-1-infected patients (25 with effective HAART, 18 with ineffective HAART, 17 untreated HIV+ patients), and fifteen were HIV negative volunteers (control group). The viral loads of effective HAART therapy patients were lower than the level of detection (50 copies/mL), and the viral loads of ineffective HAART therapy patients fluctuated between 56 copies/mL to 185000 copies/mL (data not shown). Futher epidemiological and clinical baseline characteristics of the 4 different groups are shown in Table 1.

Changes in CD4+ and CD8+ T Cells after Seven Years of Effective HAART

Before treatment, the CD4+ T cell counts of group A patients were significantly lower than that in the control group (201 vs 751 cells/μL, $p < 0.01$) as shown in Figure 1. After seven years of effective HAART, CD4+ T cell counts had increased significantly (652 vs 201 cells/μL, $p < 0.05$). However, although the counts had reached a stable level after the third year of the treatment, it was still less than that in the control group after seven years effective HAART (652 vs 751 cells/μL, $p < 0.05$). The mean CD4+ T recovery in pa-

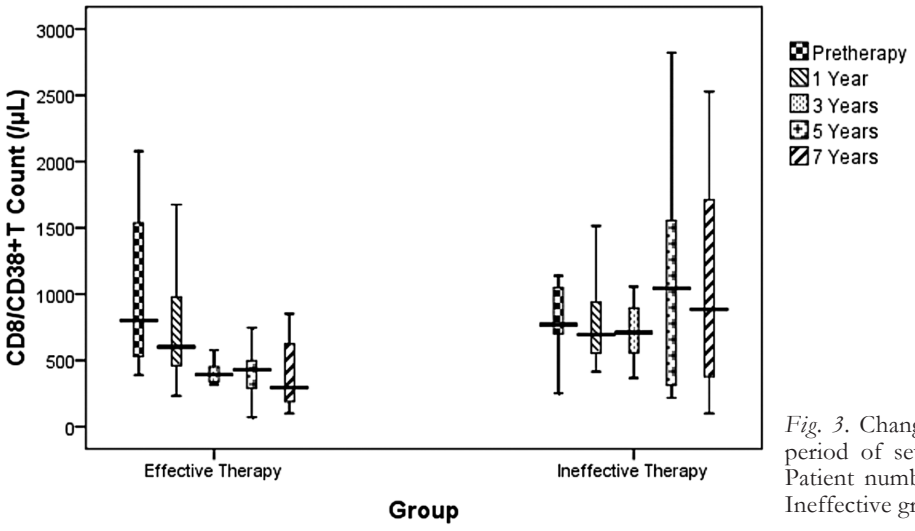


Fig. 3. Changes of CD8/CD38+ T cells during a period of seven years HAART ($\bar{x} \pm$ SD,/µL). Patient numbers: Effective group (A) (n = 25), Ineffective group (B) (n = 18).

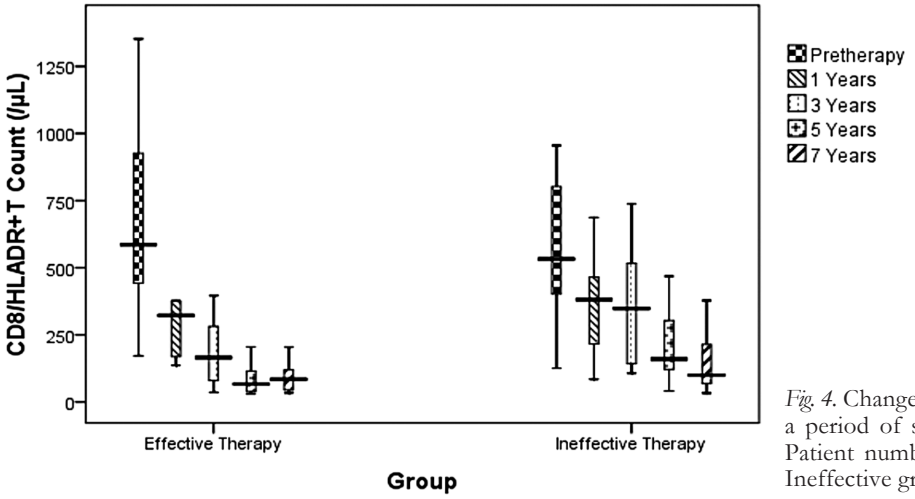
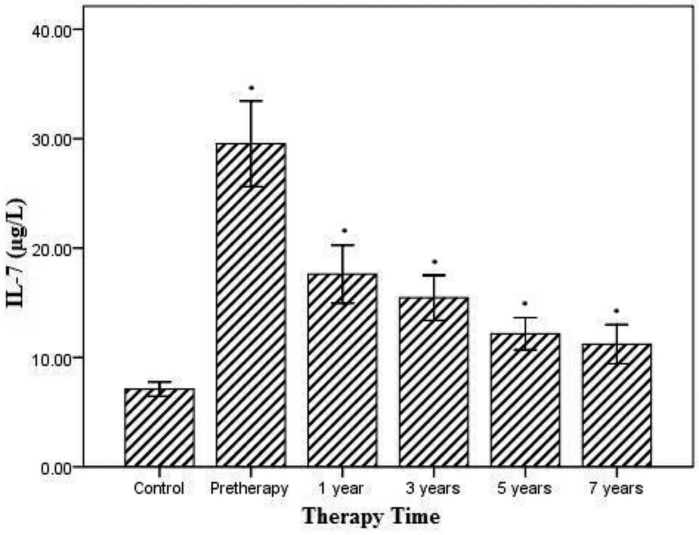


Fig. 4. Changes of CD8/HLADR+ T cells during a period of seven years HAART ($\bar{x} \pm$ SD,/µL). Patient numbers: Effective group (A) (n = 25), Ineffective group (B) (n = 18).



F*ig. 5*. Changes of IL-7 serum concentration during a period of seven years effective HAART (group A) ($\bar{x} \pm$ SD, n=25). *: P<0.05 compared with Control.

tients with 200-350/µL CD4+ T at baseline was higher than in patients starting with less than 200/µL CD4+ T. After 1, 3, 5 and 7 years of treatment the mean CD4+ T cell count in the 200-350/µL group increased to 605/µL, 775/µL, 801/µL and 838/µL respectively. In the same time frame the mean CD4+ T cell count in the <200/µL group increased to 328/µL, 476/µL, 485/µL and 498/µL respectively (Table 2).

In addition, before treatment, the CD8+ T cell counts in the above patients were significantly higher than that in the control group (1255 vs 593 cells/µL, $p < 0.01$). After seven years of effective HAART, the CD8+ T cell counts had decreased significantly, but were still higher than that in the control group (911 vs 593 cells/µL, $p < 0.05$) (Fig. 1).

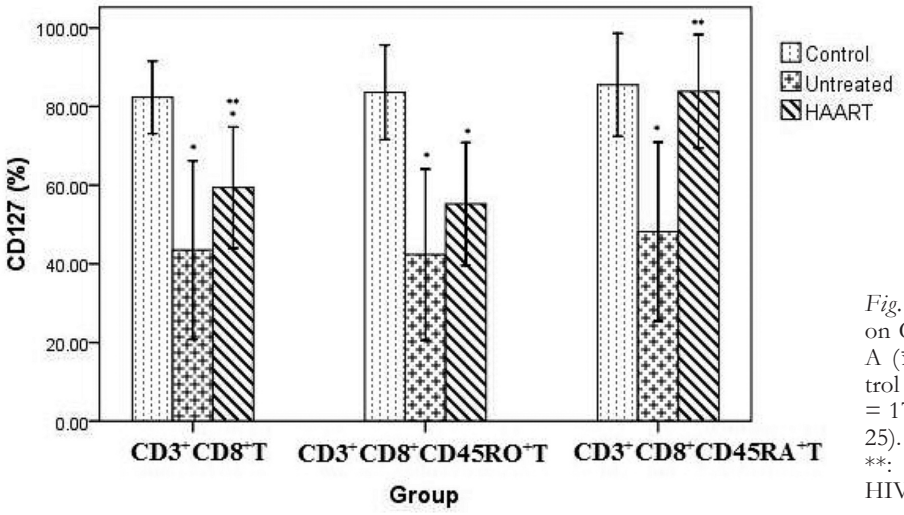


Fig. 6. Difference of CD127 expression on CD3+ CD8+ T cell subsets in group A ($\bar{x} \pm$ SD, %). Patient numbers: Control group (n = 15), Untreated group (n = 17), Effective HAART group (A) (n = 25). *: P<0.05 compared with Control, **: P<0.05 compared with untreated HIV+ patients.

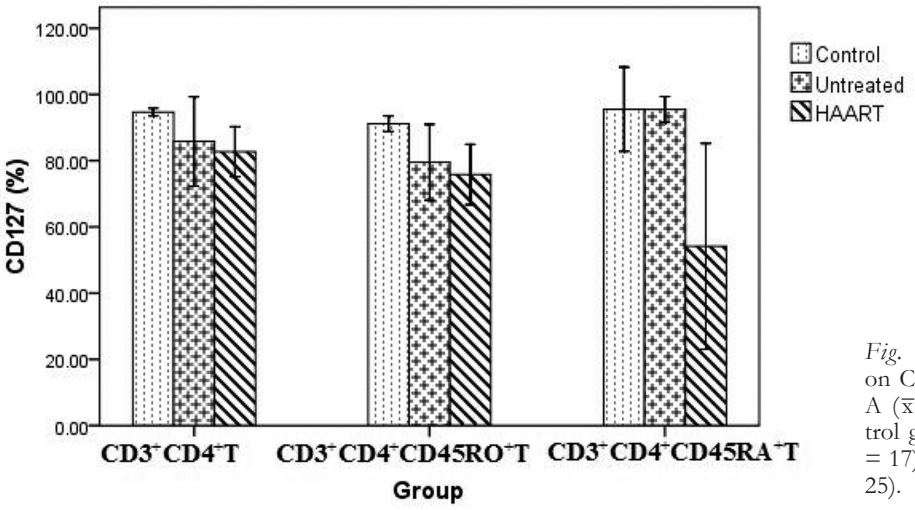


Fig. 7. Difference of CD127 expression on CD3+ CD4+ T cell subsets in group A ($\bar{x} \pm$ SD, %). Patient numbers: Control group (n = 15), Untreated group (n = 17), Effective HAART group (A) (n = 25).

Table 2. The mean CD4+ T cell count (cells/μL) during HAART.

Baseline CD4 (cells/μL)	1 year	3 years	5 years	7 years
<200	328	476	485	498
200~350	605	775	801	838

Analysis of CD8/CD38+ and CD8/HLADR+ T Cells after Seven Years HAART

Before therapy, both the CD8/CD38+ T cell count and the CD8/HLADR+ T cell count of group A patients were found to be significantly higher than in the control group (1048 vs 314 cells/μL, 703 vs 125 cells/μL, $p < 0.01$). After seven years of effective HAART, both CD8/CD38+ and CD8/HLADR+ T cell counts had returned close to normal levels (394 vs 314 cells/μL, 90 vs 125 cells/μL, $p > 0.05$) as shown in Figure 2.

Furthermore, the CD8/CD38+ T cell counts in the ineffective HAART group (B) did not decrease significantly (Fig. 3), and were higher than that of the control group after seven years of HAART (1079 vs 324 cells/μL, $p < 0.05$). However, CD8/HLADR+ T cell counts of the ineffective HAART group gradually decreased (Fig. 4).

Analysis of IL-7 Protein Expression after Seven Years of Effective HAART

Before treatment, the peripheral blood IL-7 levels in HIV-1-infected patients were significantly higher than in controls (29.5 vs 7.1 pg/mL, $p < 0.01$). Over the seven years of effective HAART, there was a gradual decrease in the levels of IL-7 (Fig. 5). In the first year of HAART, the IL-7 level showed the largest decrease; however, by the seventh year of HAART, the IL-7 level was still higher than that in the controls (11.2 vs 7.1 pg/mL, $p < 0.05$).

Changes in CD127 Expression on CD3+ T Cells after Seven Years of Effective HAART

CD127 expression on the surface of CD3+ CD8+ T cells in untreated HIV-1-infected patients (group C) was lower than in the control group (43.5% vs 82.3%, $p < 0.05$). The CD127 expression in group A patients with effective HAART was higher than that in group

C (59.4% vs 43.5%, $p < 0.05$), but still lower than that in the control group (59.4% vs 82.3%, $p < 0.05$). After seven years in group A, the expression level of CD127 on the surface of virgin ($CD45RA^+$) $CD3^+$ $CD8^+$ T cells had returned close to that in the control group (83.8% vs 85.5%, $p > 0.05$). Although CD127 expression on memory ($CD45RO^+$) $CD3^+$ $CD8^+$ T cells increased, it was still lower than that in the control group (55.2% vs 83.6%, $p < 0.05$) (Fig. 6).

However, expression of CD127 on the surface of $CD3^+$ $CD4^+$ T cells was not significantly different between the seven years of effective HAART, untreated and control group (Fig. 7).

Discussion

HIV-1 can, by infecting $CD4^+$ T cells, induce a progressive decline of lymphocytes, a deficiency in immune function and a variety of opportunistic infections. $CD8^+$ T cells are activated in the initial stage of infection as the main defensive barrier, and the cytolytic T lymphocyte response is soon induced to inhibit viral replication. Some transmembrane molecules are highly expressed during the activation period, indicating the activated state of cells [3, 4], for example, HLA-DR and CD38 molecules are indicators of T cell activation. Normally, these two molecules are seldom expressed simultaneously on $CD4^+$ and $CD8^+$ T cells. After infection, the CD38 expression levels of T cells are three to five times higher than normal, and they correlate to disease progression [5].

In the present study, the changes in $CD4^+$ and $CD8^+$ T cell counts were investigated during seven years of HAART. The study duration was partly chosen because of external factors (exchange of staff between Germany and China). During this course of therapy, $CD4^+$ T cells increased and $CD8^+$ T cells decreased significantly (Fig. 1). After the third year of HAART, $CD4^+$ and $CD8^+$ T cell counts were maintained at stable levels, although those were still far from the levels of the control group. This is in accordance with observational cohort studies where a plateau is reached after 2-8 years depending on the baseline count [6]. It has been demonstrated that baseline CD4 count is a significant prognostic indicator for HAART therapy. Some studies showed that patients with the higher baseline CD4 count at HAART initiation have better chance to restore to normal CD4 count [7-9]. In our study, we have done the correlate analysis between baseline CD4 and the recovery CD4 counts after 1, 3, 5 and 7 years. The mean CD4 recovery was higher with high baseline CD4 count, however, the related coefficient analysis was not very satisfactory ($P > 0.05$). It may be caused by the small sample size.

Meanwhile, the fact that $CD8/CD38^+$ and $CD8/HLADR^+$ T cell counts in peripheral blood decreased and, finally, fell to within the normal range, demonstrated the decrease of abnormal immune activation. However, no statistically significant reduction in $CD8/CD38^+$ T cell counts was observed in the ineffective HAART patients (Fig.3). Although $CD8/HLADR^+$ T cell counts gradually decreased, the decrease was less than in the effective HAART group (Fig. 4). Thus, we conclude that long-term (at least 7 years) effective HAART could have an effect on immune restauration in HIV-1-infected patients, and that continued detection of $CD8/CD38^+$ T cells is an optimal way to quantify and explicate the immune activation levels in HIV-1-infected patients undergoing HAART.

IL-7 plays a crucial role in T cell homeostasis. This cytokine is implicated in thymopoiesis, sustaining thymocyte proliferation and survival. It also regulates peripheral naive T cell survival by inducing the production of the anti-apoptotic molecule Bcl-2 [10]. In a recent study, subcutaneous injection of rhIL-7 was found to simultaneously increase $CD4^+$ and $CD8^+$ T cell counts, particularly memory T cells [11]. IL-7 concentration in the peripheral blood of HIV-1-infected patients was proven to be higher than that in healthy people, and it was considered to accompany a decrease in $CD4^+$T cells when the IL-7 production was induced [10, 12]. On the basis of seven years investigation of patients with effective HAART, the IL-7 in peripheral blood decreased during antiretroviral therapy, but was finally maintained at a stable level far above normal levels. We speculate that HAART can inhibit HIV-1 reproduction, restore T cell subsets and IL-7 receptor protein expression, and lower the negative feedback of IL-7 to $CD4^+$ T as described by Chomont et al. [13]. The abnormal levels of IL-7 may be due to an incomplete recovery of the IL-7/CD127 regulation mechanisms after seven years of HAART. Chomont et al. have also demonstrated that HAART can only partially downregulate the HIV reservoir [13], whereas IL-7-induced mitosis of transitional memory T cells can lead to the persistence of the HIV reservoir [14].

The expression level and regulatory mechanism of the IL-7Rα chain (CD127) is positively correlated with the lifetime of T cells in peripheral blood [15]. CD127, as a specific surface marker of T cells, can be used to clarify two mechanisms: the transformation of effector T cells to memory T cells and the maintenance of memory T cells [16]. The expression levels of CD127 can be lowered by HIV-1-specific lymphocytes, thereby impairing its regulatory function. MacPherson et al. have found that downregulating the expression level of CD127 on $CD8^+$ T cells leads to a proliferation of HIV [14]. However, the CD127 expression in HIV-1-infected patients could be partially recovered after antiviral therapy. Furthermore, patients with high expression levels of CD127 enhanced IL-7 signals, stimulating the expression of Bcl-2, and regulating the survival and proliferation of T cells [17].

This study indicated that the expression of CD127 on the surface of $CD3^+$ $CD8^+$ T cells in untreated HIV-1-infected patients was lower than that in the controls. After seven years of HAART, the CD127 on $CD3^+$ $CD8^+$ $CD45RA^+$ T cells had increased to normal levels (Fig. 6). We speculate that effector $CD4^+$ and $CD8^+$ T cells were activated due to the residual viral replication. The low CD127 expression on $CD8^+$ T cells could favour the apoptosis of effector $CD8^+$ T cells, which abrogates the transformation of effector $CD8^+$ T cells to memory T cells. Therefore, HIV-1-specific $CD8^+$ T cells could not survive longer. However, long-term HAART can inhibit the replication of

HIV-1 and enhanced CD127 expression on the surface of T cells, which could restore the quantity and capacity of T cell subsets. There were no statistically significant differences among the CD127 expressions on the surface of $CD3^+$ $CD4^+$ T cells in the effective HAART group, the untreated group and the control group. Although similar results have already been reported [13, 18], the specific mechanisms are not clear and need further study.

In conclusion, after seven years of effective HAART, the quantity and capacity of T cell subsets and IL-7 of HIV-1-infected patients were partially restored, and the abnormal immune activation was significantly reduced. However, seven years of HAART could not achieve complete immune reconstitution. Continued investigation of $CD8/CD38^+$ T cells may help to monitor immune activation in HIV-1-infected patients during long-term HAART.

Acknowledgements: This work was supported in part by the National Eleventh Five-year Plan Key Program of Major Infectious Diseases of China (Grant No.2008ZX10001-006, No.2008ZX10001-006).

References

1 McCune JM. The dynamics of $CD4^+$T cell depletion in HIV disease. Nature. 2001; 410:974-979.
2. Louie M, Hogan C, Di Mascio M, et al. Determining the relative efficacy of highly active antiretroviral therapy. J Infect Dis. 2003; 187(6):896-900.
3. Bouscart F, Levacher-Clergeot M, Dazza MC, et al. Correlation of CD8 lymphocyte activation with cellular viremia and plasma HIV RNA levels in asymptomatic patients infected by human immunodeficiency virus type 1. AIDS Res Hum Retroviruses. 1996; 12: 17-24.
4. Burgisser P, Hammann C, Kaufmann D, et al. Expression of CD28 and CD38 by $CD8^+$ T lymphocytes in HIV-1 infection correlates with markers of disease severity and changes towads normalization under treatment. Clin Exp Immunol. 1999; 115: 458-463.
5. Koning FA, Otto SA, Hazenberg MD, et al. Low-level $CD4^+$ T cell activation is associated with low susceptibility to HIV-1 infection. J Immunol. 2005; 175(9):6117-6122.
6. Hughes R, Sterne J, Walsh J et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. HIV Med. 2011 May 16.
7. Byakwaga H, Murray JM, Petoumenos K et al. Evolution of $CD4^+$ T cell count in HIV-1-infected adults receiving antiretroviral therapy with sustained long-term virological suppression. AIDS Res. Hum Retroviruses. 2009; 25(6):756-776.
8. Robbins GK, Spritzler JG, Chan ES et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group protocol 384. Clin. Infect. Dis. 2009; 48(3):350-361.
9. Florence E, Lundgren J, Dreezen C et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med. 2003; 4(3):255-262.
10. Beq S, Nugeyre MT, Ho Tsong Fang R, et al. IL-7 Induces Immunological Improvement in SIV-Infected Rhesus Macaques under Antiviral Therapy. J Immunol. 2006; 176:914-922.
11. Sereti I, Dunham RM, Spritzler J, et al. IL-7 administration drives T cell-cycle entry and expansion in HIV-1 infection. Blood. 2009; 113:6304-6314.
12. Hellerstein MK, Hoh RA, Hanley MB, et al. Subpopulations of long-lived and short-lived T cells in advanced HIV-1 infection. J. Clin. Invest. 2003; 112:956-966.
13. Chomont N, El-Far M, Ancuta P, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med. 2009; 15:893-900.
14. MacPherson PA, Fex C, Sanchez-Dardon J, et al. Interleukin-7 receptor expression on $CD8^+$ T cells is reduced in HIV infection and partially restored with effective antiretroviral therapy. J. Acquir Immune Defic Syndr. 2001; 28:454.
15. Paiardini M, Cervasi B, Albrecht H et al. Loss of CD127 expression defines an expansion of effector $CD8^+$ T Cells in HIV-infected individuals. J Immunol. 2005; 174:2900-2909.
16. Nemes E, Lugli E, Nasi M, et al. Immunophenotype of HIV+ patients during CD4 cell-monitored treatment interruption: role of the IL-7/IL-7 receptor system. AIDS. 2006; 20:2021-2032.
17. Benito JM, López M, Lozano S, González-Lahoz J, Soriano V. Down-regulation of interleukin-7 receptor (CD127) in HIV infection is associated with T cell activation and is a main factor influencing restoration of CD4(+) cells after antiretroviral therapy. J Infect Dis. 2008;11; 198(10):1466-1473.
18. Colle JH, Moreau JL, Fontanet A, Lambotte O, Delfraissy JF, Thèze J. The correlation between levels of IL-7Ralpha expression and responsiveness to IL-7 is lost in CD4 lymphocytes from HIV-infected patients. AIDS. 2007; 21(1):101-103.

Received: December 21, 2010 / Accepted: May 23, 2011

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