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Evaluation of CD4/CD8 ratio in treatment follow-up of patients with HIV diagnois in an infection clinic

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Abstract

Aim: Antiretroviral therapy (ART) regimens used in the treatment of HIV are assumed to suppress the virus in plasma indefinitely and restore CD4 lymphocyte count. There is increasing evidence that a reversed CD4/CD8 ratio is associated with immune dysfunction, even in patients who have achieved virological suppression with ART and have elevated CD4 lymphocytes. The CD4/CD8 ratio has emerged as a guiding marker as an indicator of immunoactivation in HIV-infected patients. It was aimed to evaluate the CD4/CD8 ratio of HIV-diagnosed patients at baseline and at follow-up after ART regimen.

Materials and Methods: A total of 150 patients were included in the study by retrospectively scanning the CD4/CD8 ratio at the initial and 24th week of follow-up in patients who were diagnosed with HIV and started treatment in the Infectious Diseases and Clinical Microbiology Clinic of the Hospital of the Medical Faculty between 2011-2021. ART treatment regimens were divided into three groups as nucleoside reverse transcriptase inhibitor (NRTI)+protease inhibitor (PI), NRTI+non-nucleoside reverse transcriptase inhibitor (NNRTI) or NRTI+ integrase strand transfer inhibitor (INSTI).

Results: A total of 150 patients were included in the study. While the initial CD4/CD8 ratio of the patients was 0.36, it increased to 0.61 at the 24th week of treatment. Among the 144 patients whose baseline values were CD4/CD8$<$1, the rate of the ones who achieved CD4/CD8$\geq$1 value at week 24 after ART regimens was found as 13.2% (19/144). It was observed that the CD4/CD8 ratio in the group receiving INSTI was higher (15.1%) than those of the other groups. The undetectable HIV RNA level after treatment was significantly mostly observed in the group, receiving the integrase-based regimen, with 77.1%. With effective ART, CD4/CD8 normalization is higher in individuals with high CD4 T cell counts before treatment. There was a significant increase in the CD4/CD8 ratio in all three ART regimen groups. However, most of the patients who achieved a CD4/CD8 ratio $\geq$1 were in the INSTI-based ART group.

Conclusion: The CD4/CD8 ratio may contribute to clinical evaluation in long-term follow-up as a marker of immunological response in individuals treated with a diagnosis of HIV.

Introduction

HIV infected individuals have secondary immunodeficiency, and a decrease in CD4 lymphocyte count is inevitable when untreated. It is assumed that ART suppresses the virus in plasma and restores the CD4 T lymphocyte count. The absolute CD4 count and HIV viral load may not accurately reflect the risks that the patients confront. It is shown that immune dysfunction persists despite the viral suppression and normalization of CD4 count, and sustained immune activation leads to a higher rate of non-HIV events such as cardiovascular disease, kidney disease, liver disease, neurocognitive disorders and non-AIDS malignancies in the long term [1, 2]. A low CD4/CD8 ratio is an immune risk phenotype and is associated with altered immune function, immune aging, and chronic inflammation in both HIV-infected and uninfected populations [3]. There is increasing evidence that a reversed CD4/CD8 ratio is associated with persistent immune dysfunction, even in patients who have achieved virological suppression with ART and have elevated CD4 lymphocytes [4]. The CD4/CD8 ratio has emerged as a new marker as an indicator of all-cause mortality in HIV-infected patients [5, 6]. Early initiation of ART provides a higher rate of improvement in the CD4/CD8 ratio [7].

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We aimed to evaluate the effects of INSTI, PI or NNRTI group third ART regimens on recovery of CD4/CD8 ratio in individuals.

Materials and Methods

The CD4/CD8 ratio at the beginning and 24th week follow-up was retrospectively scanned from the hospital automation system in patients who were diagnosed with HIV and started treatment in Inonu University Hospital of Medical Faculty Infectious Diseases and Clinical Microbiology Clinic between 2011 and 2021. A total of 150 patients were included in the study by excluding the patients whose initial treatment was not given by our clinic and who did not have control at the 24th week. CD4 percentage, CD8 percentage and total lymphocyte count were recorded at the time of the patient's first HIV diagnosis and at the 24th week of the patients who were followed up after HIV was diagnosed and ART was started. While the absolute CD4 lymphocyte/CD8 lymphocyte count was found, the CD4/CD8 percentage was calculated by multiplying the total lymphocyte count. Patients were divided into three groups as NRTI+PI, NRTI+NNRTI or NRTI+INSTI according to the ART treatment regimens initiated. Data were recorded in SPSS v.26.00 program and Wilcoxon signed-rank test was used for non-parametric dependent quantitative data. Chi-square test was applied for categorical variables. The statistical significance value was accepted as $p<0.05$. The study was approved by the İnönü University Ethical Community (The number of decisions: 2021/ 2683).

Results

Of the patients, 140 (93.3%) were male and 10 (6.7%) were female. When the ages of the cases at the time of diagnosis were evaluated, the mean age was 36.8±12.5 years (min:17, max:74). The most used regimen was the integrase-based regimen with a rate of 78.67%. While the initial CD4/CD8 ratio of the patients was 0.36, it increased to 0.61 at the 24th week of treatment. Comparison of CD4/CD8 ratios according to ART regimens is given in (Table 1). Among the 144 patients whose baseline values were CD4/CD8<1, the rate of the ones who achieved CD4/CD8≥1 value at week 24 after ART was found as 13.2% (19/144). 17 of 19 patients were using an integrase-based ART regimen. It was observed that 15.1% of the patients in the INSTI group, 5.9% in the PI group, and 7.1% in the NNRTI group had reached CD4/CD8 ratio of ≥1, but no statistically significant difference was observed (p:0.454). Of the 114 patients with a baseline CD4/CD8 ratio of <0.5, 41.2% achieved a value of ≥0.5 at week 24 with ART. When evaluated according to ART groups, although it was higher in INSTI-based regimens, it did not reach a significant difference (p:0.613). The undetectable HIV RNA level after treatment was significantly mostly observed in the group, receiving the integrase-based regimen, with 77.1% (p:0.000). The distribution of HIV RNA results by ART regimen is given in (Table 2). The list grouped by the third ART treatment regimen is presented in (Table 3).

Discussion

The primary goal of antiretroviral therapy is to prevent HIV-related morbidity and mortality and to maintain a life period close to those of non-HIV. With continuous viral suppression, immune function and general quality of life are improved [8]. In order to reduce morbidity and mortality and to prevent the transmission of HIV to others, ART is recommended for all people with HIV as soon as possible regardless of CD4 count [9]. The CD4/CD8 ratio has been associated with the risk of death in individuals with HIV diagnosis, and it has been shown to predict serious non-AIDS events even if the CD4 count is ≥500 in individuals treated with ART [5]. In a study in Denmark, an increase in the number of CD8 T cells was shown to predict non-AIDS mortality [10]. However, despite virological suppression by ART in HIV-infected individuals, normal values cannot be achieved for CD4 T-cell counts in 10-40% of them. To date, the mechanism underlying the incomplete immune reconstitution in HIV-infected patients has not been fully elucidated [11]. It has been reported that the CD4/CD8 ratio, which is seen in healthy individuals, cannot be achieved even in patients with suppressed viral load and taking long-term effective ART [12]. Although the clinical and prognostic implications of the CD4/CD8 ratio are still controversial, the higher ratio is accepted as the better. It may be useful to apply the CD4/CD8 ratio as a new tool to identify and monitor patients who maintain a persistent dysregulation despite having high CD4 counts [13,14]. In a study, the CD4/CD8 ratio at the start of ART was 0.39, and it was reported that 14% of the patients reached CD4/CD8≥1 level in the follow-up. The estimated normalization rate was calculated as 4.4% in one year, 11.5% in two years, and 29.4% in five years. When the group with a CD4/CD8 ratio of less than 0.30 compared with the group with a CD4/CD8 ratio higher than 0.45, incidence of events not identified with AIDS was independently associated with non-AIDS-related events or an increased risk of death [13]. In an observational cohort study, although the evidence that CD4/CD8 ratio is prognostic for non-AIDS death in virologically suppressed HIV patients is low, it has been reported that both low CD4/CD8 ratio and high CD8 count are associated with AIDS death rate [15]. In a study examining patients who received ART for 15 years, a decrease in CD8 counts and an increase in CD4/CD8 ratio were observed, and only the group with baseline CD4 count≥200 reached a CD4/CD8≥1 value. It was found that patients with high CD4 count at the beginning of treatment were associated with normalization of the CD4/CD8 ratio in a shorter time [16]. In a study conducted in Canada, it was reported that CD4/CD8 ratio returned to normal in the 28% of the cases during a median 2.6-year follow-up, and patients with a higher baseline CD4+ T-cell count were more likely to achieve normalization [4]. In another study, after two years of ART in HIV-diagnosed patients, who were divided into three groups with CD4 count <200, 200-500 and ≥500 according to immune response, it was shown that the CD4/CD8 ratio increased significantly in the first three years. The increase in CD4/CD8 ratio in the group with CD4 count ≥500 was found to be higher than the other two groups [17]. In a study conducted in Madrid, while the mean CD4/CD8 value was 0.32 and in 28% of the cases it was <0.2, 44% of the patients achieved a CD4/CD8≥1 ratio within 1.5 years. In the study, it was

Table 1. Comparison of baseline and 24th week CD4/CD8 ratios according to ART regimens.

Antiretroviral treatment regimens	Patient Number n (%)	Baseline CD4/CD8 ratio (mean)	24th week CD4/CD8 ratio (mean)	p value
NRTI+INSTI	118 (78.7)	0.38	0.64	0.000
NRTI+PI	17 (11.3)	0.29	0.53	0.001
NRTI+NNRTI	15 (10)	0.26	0.44	0.023
Total	150 (100)	0.36	0.61	0.000

*NRTI: Nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INSTI: Integrase strand transfer inhibitor.

Table 2. HIV RNA results at the 24th week according to ART regimens.

Antiretroviral treatment regimens	HIV RNA negative n (%)	HIV RNA positive n (%)	Total n (%)	p value
NRTI+INSTI	91 (77.1)	27 (22.9)	118 (100)	
NRTI+PI	8 (47.1)	9 (52.9)	17 (100)	0,000
NRTI+NNRTI	5 (33.3)	10 (66.7)	15 (100)	
Total	104 (69.3)	46 (30.7)	150 (100)	

*NRTI: Nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INSTI: Integrase strand transfer inhibitor.

shown that a higher CD4/CD8 T-cell ratio before ART was associated with normalization rates of ≥1 after treatment, and it was stated that the risk of AIDS and non-AIDS events could be predicted by the changing ratio after treatment, not by the initial CD4/CD8 ratio [18]. According to the data in our study, a statistically significant increase in CD4/CD8 ratio was found in all ART regimen groups, and individuals who reached CD4/CD8≥1 were almost all of whom had a baseline CD4 count ≥200. Individuals with high CD4 T cell counts before treatment have better CD4/CD8 normalization with effective ART. In a prospective cohort study, a higher CD4/CD8 ratio was found in patients given NNRTI group regimens compared to PI group regimens, when the cut-off for CD4/CD8 ratio was taken as ≥1.0 [19]. In a post hoc analysis of the SINGLE study; when the CD4/CD8 ratio at the 48th and 96th weeks of efavirenz and dolutegravir treatment as the third ART regimen was compared, the patients with CD4/CD8 ratio ≥1.0 at the 96th week were found to be higher, while no significant difference was observed in case the cut-off value was taken as ≥0.5 [20]. A posthoc analysis of the STARTMRK trial showed faster normalization for CD4/CD8 ratio in the group of patients receiving raltegravir, when raltegravir was compared to efavirenz [21]. Raltegravir was associated with higher CD4/CD8 normalization rates when the cut-off point was chosen as ≥0.4. In a randomized double-blind clinical trial comparing dolutegravir and raltegravir as third ART agents, no statistically significant differences were observed in the ratio of patients who achieved CD4/CD8 ratio ≥0.5 and ≥1 at the 48th and 96th weeks [22]. In a multicenter prospective study, 41.5% of individuals with HIV were receiving an ART regimen including NNRTI, 23.1% including PI, and 35.4% including INSTI. It has been reported that INSTI-based ART regimen is associated with higher CD4/CD8 gain during this period [23]. In a study, where the effect of ART regimens on the normalization of CD4/CD8 ratio in HIV cases was investigated, it was reported that ART regimens containing NNRTI were given in 47.3%, PI in 45.5%, and INSTI in 7.2% of the cases. The baseline mean CD4/CD8 ratio was calculated as 0.37 in the NNRTI group, 0.32 in the PI group, and 0.47 in the INSTI group. NNRTI and INSTI-based ART were associated with more normalization compared to a PI-based regimen, when the CD4/CD8 normalization ratio was taken as 1.0. It was indicated that the comparison between the INSTI and NNRTI groups did not reach the threshold of statistical significance. When the CD4/CD8 ratio gain in the NNRTI-containing group was examined, a further decrease especially in CD8 counts was observed [24]. In another study examining the effect of ART regimens on the normalization of the CD4/CD8 ratio; when a cut-off value of CD4/CD8≥1.0 was used, as a result of the comparison

Table 3. List grouped by third ART treatment regimen.

		n	%
NNRTI			
	Efavirenz	14	9.3
	Nevirapin	1	0.7
PI			
	Darunavir	17	11.3
INSTI			
	Elvitegravir	59	39.3
	Dolutegravir	40	26.7
	Raltegravir	2	1.4
	Biktegravir	17	11.3
Total		150	100

*NRTI: Nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INSTI: Integrase strand transfer inhibitor.

of the normalization of the CD4/CD8 ratio regarding the INSTI-containing regimen and non-INSTI-containing regimen, normalization was reported to be more significant in the INSTI-containing group [25]. As a matter of fact, while some studies have reported that ART regimens containing NNRTI group have a better increase in CD4/CD8 ratio than the regimens containing INSTI, many studies have reported that ART regimens containing INSTI group have a greater contribution to the increase of CD4/CD8 ratio compared to other ART regimens. In our study, the mean CD4/CD8 ratio of HIV-diagnosed individuals according to ART regimens was calculated as 0.38 in patients receiving INSTI, 0.29 in ones receiving PI, and 0.26 in the ones receiving NNRTI Although the proportion of patients who achieved a CD4/CD8 ratio of ≥1 was higher in those receiving INSTI-based ART compared to other groups, it was not statistically significant. In addition, when those who reached a CD4/CD8 ratio of ≥0.5 were analyzed, no significant difference was found between the groups, but the ratio of the patients who achieved this value was found to be higher in the INSTI group than the others We think that the retrospective data of the study and the inadequacy of the number of patients in some drug regimens are the limitations of the study.

Conclusion

The efficacy of ART regimens has been demonstrated in increasing the CD4/CD8 ratio and reducing HIV RNA to a non-detectable level. HIV RNA levels became significantly undetectable at the 24th week with ART, especially with integrase-based regimens. An increase in the CD4/CD8 ratio occurred in all treatment regimens. However, most of the patients who achieved a CD4/CD8 ratio ≥1 were in the group receiving INSTI-based ART. The CD4/CD8 ratio may contribute to clinical evaluation in long-term follow-up as a marker of immunological response in individuals treated with a diagnosis of HIV. Further research in long-term cohorts is needed to elucidate the mechanisms that lead to a consistently low rate of immunological response despite viral suppression.

Ethics approval

The study was approved by the Inonu University Ethical Community (The number of decisions: 2021/ 2683)

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