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Original Article

Study on the application of CD4+ T lymphocyte rapid detection method in treating AIDS

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Abstract: Objective: This study aimed to investigate CD4+ T lymphocyte rapid detection method in treating AIDS. Methods: 98 AIDS patients admitted to our hospital from February 2018 to December 2019 were selected as the research group (RG), and 95 healthy patients as the control group (CG). The contents of CD4+ T lymphocytes and total lymphocytes in the peripheral blood of the two groups were detected by flow cytometry, the diagnostic value of CD4+ T lymphocytes in AIDS patients was analyzed by ROC curve, and the contents of IL-10 and TGF-β1 in the two groups were detected by ELISA. The changes of CD4+ T lymphocyte content in AIDS patients 1 month, 3 months and 6 months after intervention were detected by flow cytometry. Pearson correlation coefficient was applied to test the correlation of CD4+ T lymphocytes with total lymphocytes, IL-10 and TGF-β1, respectively. Multivariate logistic regression analysis was applied to test the risk factors affecting poor prognosis of AIDS patients. Results: CD4+ T lymphocytes and total lymphocytes in the RG were evidently lower than those in the CG, while IL-10 and TGF-β1 were higher than those in the CG. AUC of CD4+ T lymphocytes in AIDS diagnosis was 0.806. CD4+ T lymphocyte was positively correlated with the total lymphocytes and negatively correlated with IL-10 and TGF-β1. CD4+ T lymphocytes were enhanced, and IL-10 and TGF-β1 were reduced in AIDS patients after HAART treatment. Age, clinical stage, CD4+ T lymphocyte count, IL-10 and TGF-β1 were independent risk factors for poor prognosis of AIDS patients. Conclusion: CD4+ T lymphocyte detection can be used for early diagnosis of AIDS. It is an indicator of the therapeutic effect of HAART and immune function reconstruction in patients with AIDS and acts on the adverse prognosis of AIDS patients.

Keywords: CD4+ T lymphocyte, rapid detection method, AIDS

Introduction

Acquired immune deficiency syndrome (AIDS) is an extremely harmful infectious disease, and has become an important global public health problem endangering people's health [1]. AIDS is induced by human immunodeficiency virus (HIV) infection [2]. HIV is a retrovirus that causes defects in immune system [3]. After entering the body, HIV can attack the immune system of human body. It takes the most important CD4+ T lymphocytes as the main target, and destroys the CD4+ T lymphocytes in a large number, and then makes the body lose the immune function [4]. HIV transmission is mainly by AIDS patients and HIV carriers as the source of infection, through blood transmission, sexual transmission, mother to child transmission and other transmission channels [5]. Epidemiological investigations show that more than 37 million people worldwide are infected with HIV virus and more than 12 million people have died of the diseases caused by HIV infection [6]. At present, clinical diagnosis of AIDS mainly relies on laboratory tests, including virus detection, antibody detection, T cell subpopulation immune function detection and other auxiliary tests [7]. There is still no cure for AIDS clinically worldwide, and the most commonly used and effective method is highly active antiretroviral therapy (HAART) [8]. Since the incubation period of HIV in the body is relatively long, with an average of 8-9 years, the main clinical stages of HIV infection are acute HIV infection, asymptomatic HIV infection and AIDS [9]. Patients in AIDS stage have low immune function and are accompanied by various complications of infection, which eventually

Table 1. Comparison of general data [n (%), (x ± sd)]

Group	CG (n = 95)	RG (n = 98)	t/χ^2 value	*P* value
Gender				
Male	48 (50.53)	52 (53.06)	0.124	0.725
Female	47 (49.47)	46 (46.94)		
Age (years)	44.31±4.96	44.52±5.26	0.285	0.775
BMI (kg/m^2)	23.12±2.15	22.91±2.09	0.688	0.492
Nationality			0.092	0.761
Han	63 (66.32)	67 (68.37)		
Minorities	32 (33.68)	31 (31.63)		
Smoking history			0.001	0.969
Yes	40 (42.11)	41 (41.84)		
No	55 (57.89)	57 (58.16)		
Residence			0.383	0.535
Urban	54 (56.84)	60 (61.22)		
Rural	41 (43.16)	38 (38.78)		
Education level			0.173	0.678
High school or higher	59 (62.11)	58 (59.18)		
< high school	36 (37.89)	40 (40.82)		
Eating habits			0.137	0.711
Light	51 (53.68)	50 (51.02)		
Spicy	44 (46.32)	48 (48.98)		
Drinking			0.216	0.622
Yes	37 (38.95)	35 (35. 71)		
No	58 (61.05)	63 (64.29)		
Marital status			0.111	0.739
Married	53 (55.79)	57 (58.16)		
Unmarried	42 (44.21)	41 (41.84)		

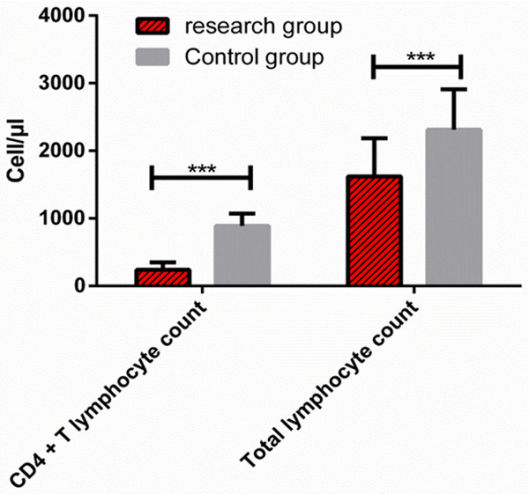

Figure 1. Comparison of CD4+ T lymphocyte count and total lymphocyte count in peripheral blood between the RG and the CG. The CD4+ T lymphocyte count and peripheral blood total lymphocyte count in the RG were evidently lower than those in the CG. Note: ***indicates P < 0.001.

lead to death and have extremely high mortality [10]. Therefore, it is urgent to explore a safe and effective detection method and diagnostic markers for the diagnosis, treatment and prognosis of AIDS.

CD4+ T lymphocyte is a kind of T cell, which expresses CD4 molecule, the main cell receptor of HIV [11]. CD4+ T cells in AIDS patients will be greatly reduced after HIV infection. When the number of CD4+ T cells is less than 500 cells/mm^3, the incidence of opportunistic infections and malignant tumors is greatly increased, and the human immune system may have serious defects [12]. CD4+ T lymphocyte can not only reflect the disease development of AIDS patients, but also is a key laboratory test index for the evaluation of antiviral treatment effect. Accurate detection of CD4+ T level of patients is conducive to guiding medical workers to make adjustments to the treatment plan of patients [13]. According to the AIDS-related treatment standards formulated by the World Health Organization (WHO), antiretroviral therapy is recommended when the CD4+ T cell count less than 500 cells/mm^3 [14]. CD4+ T cells in patients treated with HAART will gradually increase and can effectively control the development of viremia [15]. At present, CD4+ T lymphocyte counting methods mainly include microscopic imaging counting, flow cytometer counting, ELISA detection platform counting, POCT platform counting and microfluidic platform counting [16]. Flow cytometer is a device for counting cells based on fluorescence signals and fluid mechanics. It has the advantages of high accuracy, fast detection and good accuracy, and is currently recognized as the gold standard for CD4+ T cell counting [17].

This study mainly examined the effect of CD4+ T cell count on the treatment of AIDS patients by detecting CD4+ T cell count in AIDS patients,

Table 2. Diagnostic efficacy of CD4+ T lymphocyte count in AIDS

Group	AUC	95% CI	Standard error	Cut-off value	Sensitivity (%)	Specificity (%)
CD4+ T lymphocyte count	0.806	0.745-0.868	0.031	354/μl	70.41	82.65

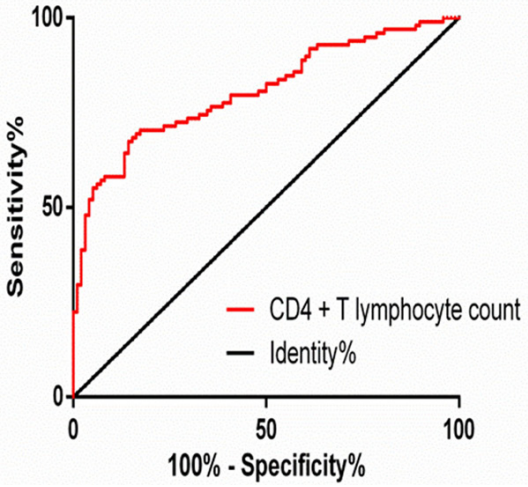

Figure 2. ROC curve for AIDS diagnosis. The sensitivity and specificity of CD4+ T lymphocyte count in diagnosing AIDS were 70.41% and 82.65%, respectively.

aiming to provide new basis for early diagnosis, treatment and prognosis of AIDS.

Materials and methods

General data

Ninety-eight AIDS patients admitted to our hospital from February 2018 to December 2019 were obtained as the research group (RG), and 95 health people as the control group (CG). The RG consisted of 52 men and 46 women, aged 19-61 years with an average age of 44.52±5.26 years. The CG consisted of 48 men and 47 women, aged 18-60 years with an average age of 44.31±4.96 years.

Inclusion and exclusion criteria

Inclusion criteria: Patients aged > 18 years; both anti-HIV antibody tests showed positive results; patients met the diagnostic criteria for AIDS [18].

This study was approved by the ethics committee. The subjects and their families were informed and signed a fully informed consent form.

Exclusion criteria: Patients had systemic immune system diseases; patients have used immunosuppressants or hormone drugs for a long time; serious opportunistic infection and previous acute exacerbation of chronic diseases were not controlled; patients with mental diseases; patients had severe cognitive dysfunction and could not cooperate with treatment; the clinical data were incomplete and the patients lost to follow.

HAART therapy

All patients in the RG were given HAART standard treatment regimen: efavirenz (Shanghai Desano Biopharmaceutical Co., Ltd., Shanghai, China, H20163464), 600 mg once per day; lamivudine (Hunan Qianjin Xiangjiang Pharmaceutical Co., Ltd., Zhuzhou, China, H20103481), 300 mg once per day; tenofovirdisoproxil (Chengdu Brilliant Pharmaceutical Co., Ltd., Chengdu, China, H20163436), 300 mg once per day, with a treatment course of 6 months.

Detection method

CD4+ T cell count and peripheral blood lymphocyte count: EDTA-K2 anticoagulation vacuum blood collection vessel was used to collect 5 ml of fasting peripheral venous blood, and the following operations were carried out (all at room temperature); two sample detection tubes were taken and the following monoclonal antibody combinations were added respectively (Immunotech, USA): (1) FITC-/PE-/PE-Cy5- (negative control); (2) CD4-FITC/CD8-PE/CD3-PE-Cy5 (CD4+ and CD8+ T cell subpopulations) and 100 μl of anticoagulated blood were added, shaken and mixed well, incubated in the dark for 15 min, added with 500 μl of human hemolysin, and hemolyzed for 15 min. A 2 ml phosphate buffer (PBS) was added, centrifugated at 1500 r/min for 5 min, and washed twice. Cells were resuspended with 1 ml PBS and detected by EPICS-XL flow cytometer (Beckman Coulter, USA). Peripheral blood lymphocyte was detected by clinical routine automatic blood cell counter.

Outcome measures

CD4+ T lymphocyte count and peripheral blood total lymphocyte count: 5 ml fasting venous

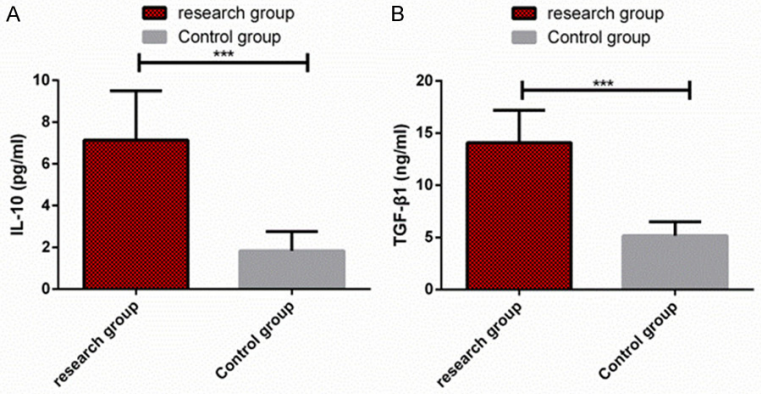

Figure 3. Comparison of cytokines between the RG and the CG. The levels of IL-10 and TGF-β1 in the RG were evidently higher than those in the CG. Note: ***indicates P < 0.001.

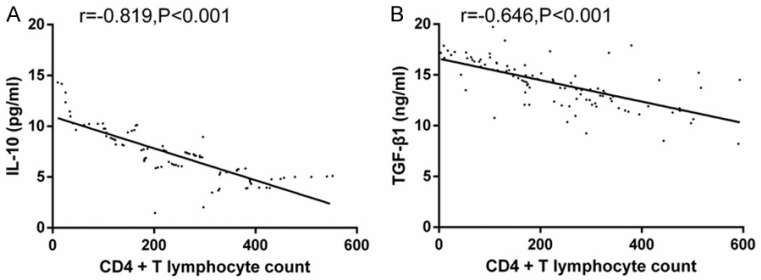

Figure 4. CD4+ T lymphocyte count in AIDS patients was negatively correlated with cytokine IL-10 (A) and TGF-β1 (B).

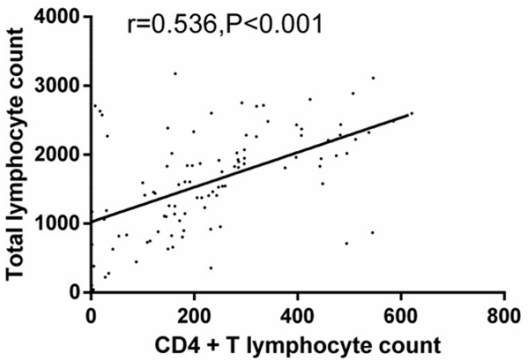

Figure 5. CD4+ T lymphocyte count in AIDS patients was positively correlated with total lymphocyte count in peripheral blood.

blood was collected from the RG before treatment and 1 month, 3 months and 6 months after intervention and collected from the CG at admission for detection.

Contents of cytokines IL-10 and TGF-β1: 5 ml fasting venous blood was collected form the RG before and at the end of treatment and collected from the CG at admission, centrifuged at 2000 r/min for 10 min at room temperature, and the upper plasma was separated. The contents of IL-10 and TGF-β1 were tested by ELISA. The steps were performed in strict accordance with the instructions of IL-10 ELISA and TGF-β1 ELISA kits (Shanghai Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-(a)-0032, JK-(a)-14-47).

Determination of therapeutic effect: All patients were evaluated for therapeutic effect and prognosis 12 months after antiviral therapy. Effective and good prognosis: within 12 months after intervention, CD4+ T lymphocyte count increased by more than 100/μl, no new diseases occurred, and the disease status was effectively controlled. Ineffective and poor prognosis: within 12 months after intervention, CD4+ T lymphocyte count increased by less than 100/μl or dropped to the pre-treatment level, resulting in new diseases or aggravation of the disease; progressed to stage 3 or 4 severe AIDS; or the patient died.

Statistical analysis

SPSS20.0 (IBM Corp., Armonk, NY, USA) was applied for data analysis, and Graphpad Prism 6 (Graphpad Software, San Diego, USA) for visualizing the data. Measurement data were represented by mean ± standard deviation (x ± sd) and analyzed by independent sample t test, and the comparison before and after intervention was conducted by paired t test. The data of multiple time points in the group were analyzed by one-way ANOVA, and the SNK-q test was applied for pair-wise comparison of different time points in the group. Counting data were expressed by the number of cases/percentage [n (%)], and analyzed by chi-square test. ROC was applied to test the diagnostic value of CD4+ T lymphocytes in AIDS patients. Pearson correlation coefficient was used to ex-

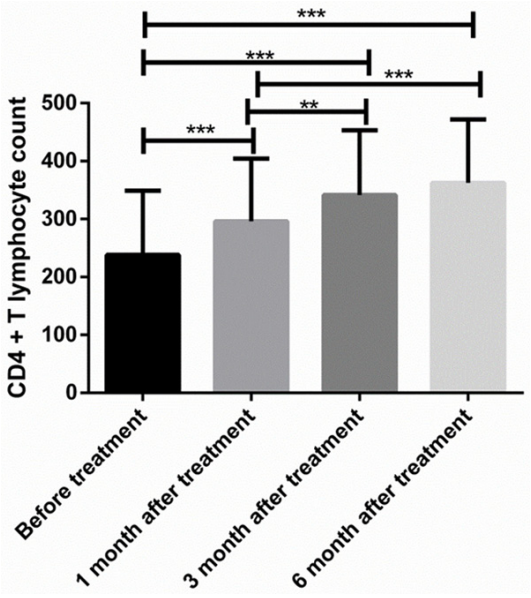

Figure 6. Comparison of CD4+ T lymphocyte changes in AIDS treatment. CD4+ T lymphocyte counts at 1 month, 3 months and 6 months after intervention were evidently higher than those before treatment ($P < 0.05$). Compared with 1 month after intervention, the counts at 3 months and 6 months after intervention were evidently increased ($P < 0.05$). Compared with 3 months after intervention, there was no evident difference at 6 months after intervention. Note: **indicates $P < 0.01$, ***indicates $P < 0.001$.

plore the correlation, and multivariate logistic regression analysis was used to analyze the risk factors affecting poor prognosis. $P < 0.05$ indicated statistically significant difference.

Result

General data

There was no evident difference between the RG and the CG in general data such as gender, age, body mass index (BMI), nationality, smoking, residence, educational level, eating habits, drinking, and marital status ($P > 0.05$) (**Table 1**).

Comparison of CD4+ T lymphocyte count and peripheral blood total lymphocyte count between the RG and the CG

The CD4+ T lymphocyte count and total peripheral blood lymphocyte count in the RG were 238.32±110.53 cells/μl and 1621.67±563.34 cells/μl respectively, which were evidently lower than those in the CG (889.03±182.58 cells/μl and 2312.62±598.45 cells/μl, respectively) ($P < 0.05$) (**Figure 1**).

Diagnostic efficacy of CD4+ T lymphocyte count in AIDS

The ROC curve of CD4+ T lymphocyte count for AIDS diagnosis was visualized. The AUC of CD4+ T lymphocyte count for AIDS diagnosis was 0.806 (95% CI: 0.745-0.868), the cut-off value was 354 cells/μl, the diagnostic sensitivity was 70.41%, and the specificity was 82.65% (**Table 2** and **Figure 2**).

Comparison of cytokines between the RG and the CG

The contents of IL-10 and TGF-β1 in the RG were 7.14±2.36 pg/ml and 14.07±3.12 ng/ml respectively, evidently higher than those in the CG (1.84±0.92 pg/ml and 5.17±1.32 ng/ml) ($P < 0.05$) (**Figure 3**).

Correlation between CD4+ T lymphocyte count and cytokines

We analyzed the correlation of CD4+ T lymphocyte count with cytokines IL-10 and TGF-β1 in AIDS patients by Pearson correlation coefficient. The results showed that CD4+ T lymphocyte count had a negative correlation with cytokine IL-10 and TGF-β1 levels ($r = -0.819$, $r = -0.646$, $P < 0.001$) (**Figure 4**).

Correlation between CD4+ T lymphocyte count and peripheral blood total lymphocyte count

We analyzed the correlation between CD4+ T lymphocyte count and total peripheral blood lymphocyte count in AIDS patients by Pearson correlation coefficient. The results showed that CD4+ T lymphocyte count had a positive correlation with total peripheral blood lymphocyte count ($r = 0.536$, $P < 0.001$) (**Figure 5**).

Comparison of CD4+ T lymphocytes changes in AIDS treatment

The CD4+ T lymphocyte count of patients at 1 month, 3 months and 6 months after intervention was evidently higher than that before intervention ($P < 0.05$). Compared with 1 month after intervention, the counts at 3 months and 6 months after intervention were evidently increased ($P < 0.05$). Compared with 3 months

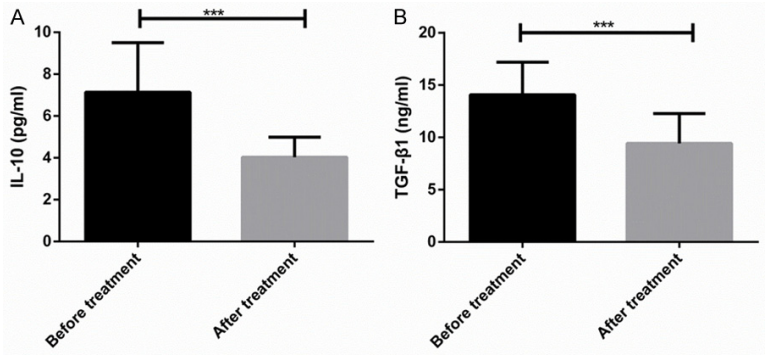

Figure 7. Comparison of cytokines of AIDS patients before and after intervention. Six months after intervention, IL-10 (A) and TGF-β1 (B) were evidently lower than those before treatment. Note: ***indicates P < 0.001.

after intervention, there was no evident difference at 6 months after intervention, and the improvement was most obvious at 1 month after intervention (**Figure 6**).

Comparison of cytokines in AIDS patients before and after intervention

Six months after intervention, IL-10 and TGF-β1 in AIDS patients were evidently lower than those before treatment (P < 0.05) (**Figure 7**).

Univariate analysis of poor prognosis of AIDS patients

After single factor analysis of patients with good prognosis and patients with poor prognosis, we found that there were no evident differences in gender, body mass index (BMI), nationality, smoking history, residence, educational level, eating habits, drinking, marital status, and transmission route between the RG and the CG (P > 0.05), but there were evident differences in age, clinical stage, CD4+ T lymphocyte count, IL-10, and TGF-β1 (P < 0.05) (**Table 3**).

Multivariate analysis of poor prognosis of AIDS patients

We included age, clinical stage, CD4+ T lymphocyte count, IL-10, TGF-β1 into the analysis, and listed them as independent variables for evaluation. Whether there is a poor prognosis was taken as dependent variable. Logistic regression model was used for multivariate analysis. The results showed that age, clinical stage, CD4+ T lymphocyte count, IL-10, TGF-β1 were independent risk factors for poor prognosis of AIDS patients (**Tables 4**, **5**).

Discussion

AIDS is a chronic infectious disease with long incubation period and high mortality rate [19]. Although no cure has been found in clinic, many studies have shown that it is possible to reduce the mortality by blocking the replication of virus in vivo, improving the immune function of patients, resisting other virus infections, and delaying the development of the disease [20]. At present, the most effective treatment clinically is HAART, which acts in the progress of AIDS by rebuilding the immune system function of patients and inhibiting the proliferation of HIV [21]. Therefore, it is of great significance to find a safe and effective method to monitor the therapeutic effect clinically.

CD4+ T lymphocyte count is a common indicator for observing curative effect and is also the best indicator to reflect the immune state of the body. In the study by Hu et al. [22], the content of CD4+ T lymphocytes in AIDS patients decreased evidently, and the degree of down-regulation increased with the increase of clinical stages, suggesting that CD4+ T lymphocytes are markers for diagnosing AIDS patients. In this study, we detected the CD4+ T lymphocyte content of AIDS patients and healthy subjects, and found that the content of AIDS patients was evidently lower than that of healthy subjects. Furthermore, we visualized the ROC curve of CD4+ T lymphocyte in the diagnosis of AIDS patients. The results showed that the AUC of CD4+ T lymphocyte in the diagnosis of AIDS patients alone was 0.806, suggesting that CD4+ T lymphocyte may be used as a marker for the diagnosis of AIDS. In the study of Gedle et al. [23], among the long-term change trend of CD4+ T lymphocytes in AIDS patients receiving HAART treatment, it is suggested that CD4+ T lymphocytes increase fastest within three months after treatment, and the growth trend becomes slower in the later stage. In addition, in the study of Adland et al. [24], it is necessary to restore the number and activity of CD4+ T lymphocytes and control viremia, so as to rebuild immune function and reduce the infection of pediatric patients. In

Table 3. Univariate analysis of poor prognosis of AIDS patients [n (%), x ± sd]

Factor	n	Good prognosis group (n = 76)	Poor prognosis group (n = 22)	t/χ^2 value	*P* value
Gender				0.025	0.874
Male	52	40 (52.63)	12 (54.55)		
Female	46	36 (47.37)	10 (45.45)		
Age (years)				25.680	< 0.001
≥ 60	32	15 (19.74)	17 (77.27)		
< 60	66	61 (80.26)	5 (22.73)		
BMI (kg/m^2)		23.67±2.04	23.97±2.19	0.598	0.551
Nation				0.001	0.983
Han	67	52 (68.42)	15 (68.18)		
Minorities	31	24 (31.58)	7 (31.82)		
Smoking history				0.010	0.920
Yes	41	32 (42.11)	9 (40.91)		
No	57	44 (57.89)	13 (59.09)		
Residence				0.533	0.465
Urban	60	48 (63.16)	12 (54.55)		
Rural	38	28 (36.84)	10 (45.45)		
Education level				2.154	0.142
High school or higher	58	42 (55.26)	16 (72.73)		
< high school	40	34 (44.74)	6 (27.27)		
Eating habits				0.141	0.707
Light	50	38 (50.00)	12 (54.55)		
Spicy	48	38 (50.00)	10 (45.45)		
Drinking				0.005	0.942
Yes	35	27 (35.53)	8 (36.36)		
No	63	49 (64.47)	14 (63.64)		
Marital status				0.349	0.554
Married	57	43 (56.58)	14 (63.64)		
Unmarried	41	33 (43.42)	8 (36.36)		
Transmission route				0.051	0.821
Sexually Transmitted	86	67 (88.16)	19 (86.36)		
Blood transfusion or drug abuse	12	9 (11.84)	3 (13.64)		
Clinical staging				42.950	< 0.001
1	41	40 (52.63)	1 (4.55)		
2	31	27 (35.53)	4 (18.18)		
3	17	8 (10.52)	9 (40.91)		
4	9	1 (1.32)	8 (36.36)		
CD4+ T lymphocyte count (cells/μl)	98	398.82±114.92	252.26±106.72	5.349	< 0.001
IL-10 (pg/ml)	98	2.63±0.89	6.11±1.13	15.170	< 0.001
TGF-β1 (ng/ml)	98	8.33±3.42	13.41±3.86	5.959	< 0.001

this study, we detected the change trend of CD4+ T lymphocytes after intervention. The results showed that the growth rate was the largest in the first month after intervention, and there were obvious differences compared with the later three months. There was no evident difference between the later stage and the earlier stage, indicating that CD4+ T lymphocytes recovered best in the first three months after intervention during HAART treatment, and recovered slowly or remained unchanged in the later stage, which finding was similar to the

Table 4. Logistic multivariate regression analysis assignment

Factor	Variable	Assignment
Age	X1	< 60 = 0, ≥ 60 = 1.
Clinical staging	X2	Clinical stage < 3 = 0, clinical stage ≥ 3 = 1.
CD4+ T lymphocyte count	X3	The data belong to continuous variables and are analyzed with original data.
IL-10	X4	The data belong to continuous variables and are analyzed with original data.
TGF-β1	X5	The data belong to continuous variables and are analyzed with original data.

Table 5. Multivariate analysis of poor prognosis of AIDS patients

factor	β	S.E	Wald	P	OR	95% CI
Age	0.863	0.354	5.921	0.015	0.420	0.209-0.841
Clinical staging ≥ 3	3.056	0.512	35.604	< 0.001	6.937	3.315-14.682
CD4+ T lymphocyte count	3.402	0.531	41.069	< 0.001	9.264	4.216-20.034
IL-10	7.834	1.212	29.068	< 0.001	20.387	10.251-84.732
TGF-β1	8.012	1.352	30.120	< 0.001	19.231	12.052-67.921

results of Gedle and Adland. In addition, we also detected the levels of IL-10 and TGF-β1 in the serum of the two groups, and found that both cytokines in AIDS patients were evidently increased. After receiving HAART treatment, the levels were evidently decreased. It showed that the immune function was inhibited after the body was infected with HIV. After intervention, the immune function of the patient was recovered to a certain extent. Luo et al. [25] found that after intervention, the immune function and CD4+ T lymphocytes of AIDS patients were rebuilt and the immune system recovered, which may be related to the damage and destruction of the immune system after HIV infection. In addition, we also analyzed the correlation between CD4+ T lymphocytes and the total lymphocyte count in peripheral blood. The results showed that CD4+ T lymphocytes were positively correlated with the total lymphocyte count in peripheral blood. Obirikorang et al. [26] found that the total number of lymphocytes and CD4+ T lymphocytes in AIDS patients could reflect the infection process of patients. This indicated that the total lymphocyte count in peripheral blood was also expected to become an indirect method for detecting CD4+ T lymphocytes. In this study, we also found that CD4+ T lymphocyte count was negatively correlated with cytokines IL-10 and TGF-β1, suggesting that CD4+ T lymphocyte count was an indicator of immune function recovery and may be related to nonspecific immune activation of the body. Finally, we analyzed the risk factors for poor prognosis of AIDS patients, and found that AIDS patients over 60 years old, clinical stages in stage 3 and 4, low levels of CD4+ T lymphocytes, high levels of IL-10 and TGF-β1 had a correlation with the high risk of poor prognosis. Franzetti et al. [27] showed that when patients aged over 60 years and CD4+ T lymphocytes were less than 100 cells/μl, their immune function dropped sharply, the probability of opportunistic infection increased, and the mortality rate increased, which is similar to our results.

This study has confirmed the role of CD4+ T lymphocyte detection in the early diagnosis and prognosis evaluation of AIDS, but there is still room for improvement. For example, we can study the treatment compliance of AIDS patients and explore the regulatory mechanism of CD4+ T lymphocytes in the treatment process of AIDS patients. In the future, we will further improve the research from the above direction.

In conclusion, the detection of CD4+ T lymphocytes can be used for early diagnosis of AIDS, which is an index reflecting the therapeutic effect of HAART and immune function reconstruction, and has a certain evaluation effect on the adverse prognosis of AIDS patients.

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Disclosure of conflict of interest

None.

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