ФУНКЦИОНАЛЬНОЕ ИСТОЩЕНИЕ CD4$^+$Т-КЛЕТОК У ВИЧ/ВГС-КОИНФИЦИРОВАННЫХ ПАЦИЕНТОВ, ПОЛУЧАЮЩИХ ВЫСОКОАКТИВНУЮ АНТИРЕТРОВИРУСНУЮ ТЕРАПИЮ

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Резюме. ВГС-коинфекция широко распространена среди ВИЧ-инфицированных пациентов. В России до 50% ВИЧ-позитивных больных коинфицированы ВГС. Применение высокоактивной антиретровирусной терапии (ВААРТ), в большинстве случаев, приводит к подавлению репликации ВИЧ и восстановлению иммунной системы ВИЧ-инфицированных пациентов. Однако ВГС-коинфекция препятствует эффективному восстановлению CD4$^+$Т-клеток и повышает риск заболеваемости и смерти ВИЧ-инфицированных больных, получающих ВААРТ. Известно, что скорость прогрессии ВИЧ-инфекции и эффективность восстановления иммунной системы на фоне приема ВААРТ в значительной мере зависят от уровня активации иммунной системы и степени истощения CD4$^+$Т-клеток. Целью настоящей работы было определение уровня активации и истощения, а также цитокин-продуцирующей функции CD4$^+$Т-клеток, полученных из крови получающих ВААРТ ВИЧ/ВГС-коинфицированных и ВИЧ-моноинфицированных больных. В исследование были включены ВИЧ/ВГС-коинфицированные (n = 11) и ВИЧ-моноинфицированные (n = 10) пациенты, получающие ВААРТ более двух лет. В контрольную группу вошли 10 добровольцев без признаков ВИЧ- и ВГС-инфекций. Было установлено, что у ВИЧ/ВГС-коинфицированных пациентов, в сравнении со здоровыми людьми, повышены следующие показатели: доля активированных CD38$^+$HLA-DR$^+$ CD4$^+$Т-лимфоцитов ($p < 0,05$), уровень истощения CD4$^+$Т-клеток, определенный по плотности экспрессии TIGIT на поверхности каждой клетки ($p < 0,05$), и число CD4$^+$Т-лимфоцитов, способных производить интерферон-гамма (IFNγ) после активации ($p < 0,05$). Относительное число IFNγ-продуцирующих CD4$^+$Т-лимфоцитов в крови доноров позитивно коррелировало с долей активированных CD4$^+$Т-клеток ($R = 0,514$, $p < 0,01$). Важно отметить, что, несмотря на большое ко-

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личество IFNγ-продуцирующих CD4⁺Т-лимфоцитов, средняя продукция этого цитокина в CD4⁺Т-клетках ВИЧ/ВГС-коинфицированных больных была существенно ниже, чем у здоровых субъектов ($p < 0,05$). Продукция IFNγ в CD4⁺Т-лимфоцитах не зависела от степени их активации ($p > 0,05$). Негативная корреляционная связь была установлена между содержанием IFNγ и уровнем истощения CD4⁺Т-клеток ($R = -0,400$, $p < 0,05$). Показатели истощения CD4⁺Т-лимфоцитов также обратно коррелировали с содержанием CD4⁺Т-клеток в крови ($R = -0,598$, $p < 0,01$). Полученные сведения позволяют предположить, что ВГС-коинфекция приводит к выраженному функциональному истощению CD4⁺Т-клеток и тем самым может отягощать течение ВИЧ-инфекции у пациентов, принимающих ВААРТ.

Ключевые слова: ВИЧ-инфекция, гепатит С, CD4⁺Т-лимфоциты, иммунная активация, иммунное истощение, продукция цитокинов

FUNCTIONAL EXHAUSTION OF CD4⁺T CELLS IN HIV/HCV COINFECTED HAART-TREATED PATIENTS

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Abstract. Infection with hepatitis C virus (HCV) is common among HIV-positive patients, with up to 50% of them being coinfected in Russia. While highly active antiretroviral therapy (HAART) suppresses HIV replication and restores the immune system of HIV-infected subjects, HCV coinfection interferes with CD4⁺T cell regeneration and increases the risk of patients' morbidity and mortality. During HAART, HIV-infection progression and the immune system restoration efficiency largely depend on immune activation and CD4⁺T cell exhaustion. This study determined the level of activation, exhaustion, and cytokine production in CD4⁺T cells obtained from the peripheral blood of HAART-treated HIV/HCV coinfected and HIV monoinfected subjects. The study comprised 11 HIV/HCV coinfected individuals and 10 HIV monoinfected patients receiving HAART for more than two years, with a control group of 10 volunteers without the signs of HIV or HCV infections. Compared with healthy controls, HIV/HCV coinfected patients had an increased frequency of activated CD38⁺HLA-DR⁺ CD4⁺T lymphocytes ($p < 0.05$), a higher level of CD4⁺T cell exhaustion determined according to the TIGIT expression density per cell ($p < 0.05$), and a greater proportion of interferon-gamma (IFNγ)-producing CD4⁺T lymphocytes following activation ($p < 0.05$). The frequency of IFNγ-producing CD4⁺T cells in the donors' blood positively correlated with the proportion of activated CD4⁺T cells ($R = 0.514$, $p < 0.01$). Despite having a large number of IFNγ-producing CD4⁺T lymphocytes, the HIV/HCV coinfected patients' average production of IFNγ by CD4⁺T cells was significantly lower than that in healthy controls ($p < 0.05$). The IFNγ production in CD4⁺T lymphocytes did not depend on activation ($p > 0.05$). However, a negative correlation was established between the IFNγ production and the level of CD4⁺T cell exhaustion ($R = -0.400$, $p < 0.05$). The letter was also found to inversely correlate with the CD4⁺T cell counts in the donors' peripheral blood ($R = -0.598$, $p < 0.01$). These data suggest that HCV coinfection leads to pronounced functional exhaustion of CD4⁺T cells and may aggravate the course of HIV-infection in patients receiving HAART.

Keywords: HIV-infection, hepatitis C, CD4⁺T cells, immune activation, immune exhaustion, cytokine production

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Introduction

Due to shared transmission routes, hepatitis C virus (HCV) coinfection has become prevalent among HIV-positive individuals. Worldwide, approximately 25% of HIV-infected patients are coinfected with HCV [7], while in Russia the proportion of HIV/HCV coinfected subjects goes up to 50% [15]. The majority of HIV-positive people receive highly active antiretroviral therapy (HAART), which suppresses

HIV replication and leads to the immune system regeneration defined by the increase in the peripheral blood $CD4^+$T cell counts [6]. However, in HIV/HCV coinfected people receiving HAART, hepatitis C infection interferes with $CD4^+$T cell recovery [14]. Furthermore, compared with HAART-treated HIV-monoinfected subjects, HIV/HCV coinfected patients have a higher risk of developing non-AIDS-associated diseases [10], opportunistic infections [3], and death [1]. The mechanisms behind the negative effect of hepatitis C on the course of treated HIV-infection remain poorly understood.

Immune activation and $CD4^+$T cell exhaustion are critical for the natural history of HIV-infection, affecting both the pace of the disease progression and the immune restoration efficiency during HAART [9, 11]. In treated HIV-infected individuals, HCV coinfection has been shown to significantly increase the chronic immune activation and systemic inflammation levels [12]. However, it is unclear if it affects the $CD4^+$T cells' functional state. Therefore, the purpose of this study was to determine the level of $CD4^+$T cells' activation and exhaustion, as well as the cytokine-producing function of these lymphocytes obtained from the blood of HAART-treated HIV/HCV coinfected and HIV monoinfected patients.

Materials and methods

The work plan was approved by the ethics committee of the Perm Regional Center for the Prevention and Control of AIDS and Infectious Diseases (committee registration number IRB00008964). The study included HIV-infected patients receiving HAART for more than two years (viral load < 50 copies/mL): 1) HIV/HCV coinfected subjects (n = 11); and 2) HIV-monoinfected patients (n = 10). The healthy control group (HC) comprised 10 volunteers without HIV or HCV infections.

Blood was collected from the cubital vein into Vacutainer tubes containing ethylenediaminetetraacetic acid. $CD4^+$T lymphocytes count was assessed using the commercial BD Simultest™ IMK-Lymphocyte kit ("BD Biosciences", USA) with a CytoFLEX S flow cytometer ("Beckman Coulter", USA). The HIV viral load was determined using Versant HIV-1 RNA 3.0 assay b kits by means of a Versant 440 analyzer ("Siemens", Germany).

Mononuclear cells were isolated by density centrifugation using Diacoll (1.077 g/mL, "Diaem", Russia). The samples were stored in liquid nitrogen in a medium containing 90% fetal bovine serum (FBS, "Biowest", France) and 10% dimethyl sulfoxide ("AppliChem", Germany). In a day of the study, the cells were thawed at +37 °C, washed in 10 mL of complete culture medium (10% FCS, 100 U/mL penicillin, and 100 μg/mL streptomycin ("Sigma", USA) in RPMI-1640), and then in 10 mL of Dulbecco's phosphate buffered saline (DPBS; "Gibco", USA). The cytokine-producing function of $CD4^+$T cells was assessed after 4 hours of incubation in complete culture medium containing phorbol 12-myristate-13-acetate (PMA), ionomycin, and brefeldin A ("BioLegend", USA).

Peripheral blood mononuclear cells were analyzed on CytoFLEX S flow cytometer ("Beckman Coulter", USA). Viable cells were identified by the absence of staining with the vital dye Zombie UV Fixable Viability Kit ("BioLegend", USA). Anti-CD3-BV605 and anti-CD4-PE antibodies ("BioLegend", USA) were used to identify $CD4^+$T lymphocytes. Expression of the TIGIT exhaustion marker was assessed using anti-TIGIT-AF488 antibodies ("BioLegend", USA). Anti-IFNγ-APC antibodies ("BioLegend", USA) were utilized to study the production of interferon-γ (IFNγ). Activated cells were identified using anti-CD38-PE/Fire700 ("BioLegend", USA) and anti-HLA-DR-APC-R700 ("BD Biosciences", USA) antibodies.

Statistical analysis and graph plotting were performed using the "Statistica 6" software. The data are presented as medians, interquartile ranges (25-75 percentile), and 10-90% intervals. Significance of differences between groups was established based on the Mann–Whitney U test. Correlation analysis was performed by the r-Pearson linear correlation test.

Results and discussion

All groups were similar according to age and gender (Table 1). The HIV-infection and HAART duration, HIV viral load, and $CD4^+$T cell counts did not differ between the groups comprised of HIV-infected subjects. However, $CD4^+$T cell counts in these groups were significantly reduced compared to HCs ($p < 0.05$).

In HIV/HCV coinfected patients compared with healthy individuals, the proportion of activated ($CD38^+HLA\text{-}DR^+$) $CD4^+$T lymphocytes was increased (Figure 1A; $p < 0.05$). Meanwhile, the difference between HIV monoinfected patients and healthy controls was not statistically significant ($p > 0.05$).

The level of exhaustion in $CD4^+$T cells of HIV/HCV coinfected subjects was also increased, as evidenced by the higher frequency of $TIGIT^+CD4^+$T lymphocytes ($p < 0.05$; data not shown) and the elevated expression of the inhibitory receptor TIGIT on the surface of these cells (Figure 1B; $p < 0.05$).

TABLE 1. CLINICAL CHARACTERISTICS OF HIV-INFECTED AND HEALTHY INDIVIDUALS

Characteristics	HIV/HCV coinfected patients	HIV monoinfected patients	Healthy Controls (HC)
Number of enrollments	11	10	10
Age (years)	40.0* (37.5-42.0)	43.5 (37.5-44.8)	43.0 (37.0-45.8)
Females (%)	45	50	50
HIV-infection duration (years)	16.0 (10.0-19.0)	9.5 (5.0-16.0)	–
HAART duration (years)	8.0 (3.8-13.0)	5.0 (2.5-6.2)	–
HIV viral load (copies/mL)	< 50**	< 50	–
CD4$^+$T cell counts (μL^{-1})	542 (405-663) pHC < 0.05	616 (480-763) pHC < 0.05	707 (646-880)

Note. *, the data presented as medians and interquartile ranges. **, the test-system sensitivity limit. HAART, highly active antiretroviral therapy. Significance of differences between groups was established based on the Mann–Whitney U test.

The number of CD4$^+$T cells that produced IFNγ upon activation with PMA and ionomycin was significantly higher in HIV/HCV-positive individuals as compared with healthy donors (Figure 2A; $p < 0.05$). Across all study groups, the number of IFNγ-producing CD4$^+$T lymphocytes positively correlated with the relative number of activated (CD38$^+$HLA-DR$^+$) CD4$^+$T cells (Figure 2B).

Importantly, although the number of IFNγ-producing CD4$^+$T lymphocytes in HIV/HCV coinfected individuals was increased, the average production of IFNγ in CD4$^+$T cells of these patients was significantly lower than that of healthy subjects (Figure 3A; $p < 0.05$). The IFNγ production in CD4$^+$T lymphocytes did not depend on the percent of activated cells. However, a negative correlation was established between IFNγ production and the level of CD4$^+$T cell exhaustion (Figure 3B).

Both phenotypic and functional indexes of CD4$^+$T lymphocyte exhaustion correlated with

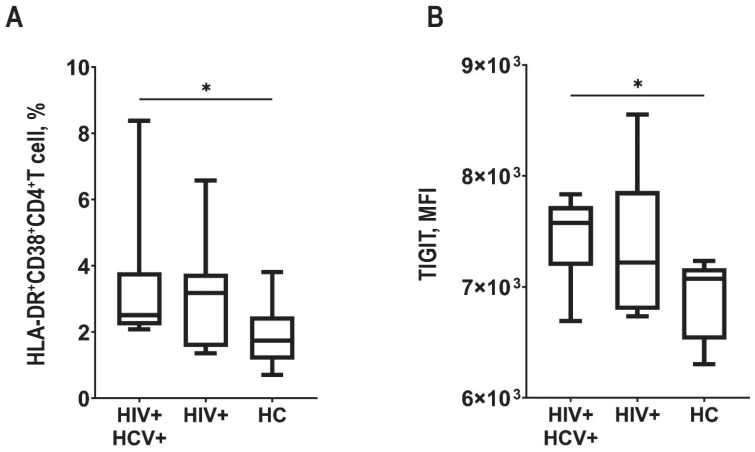

Figure 1. Level of CD4$^+$T cell activation (A) and exhaustion (B) in HIV/HCV coinfected people (HIV+HCV+), HIV monoinfected patients (HIV+) and healthy control (HC) subjects

Note. Medians (horizontal lines within rectangles), interquartile ranges (rectangles), and 10-90% intervals (vertical lines) are shown. *, $p < 0.05$ (Mann–Whitney U test). MFI, mean fluorescence intensity.

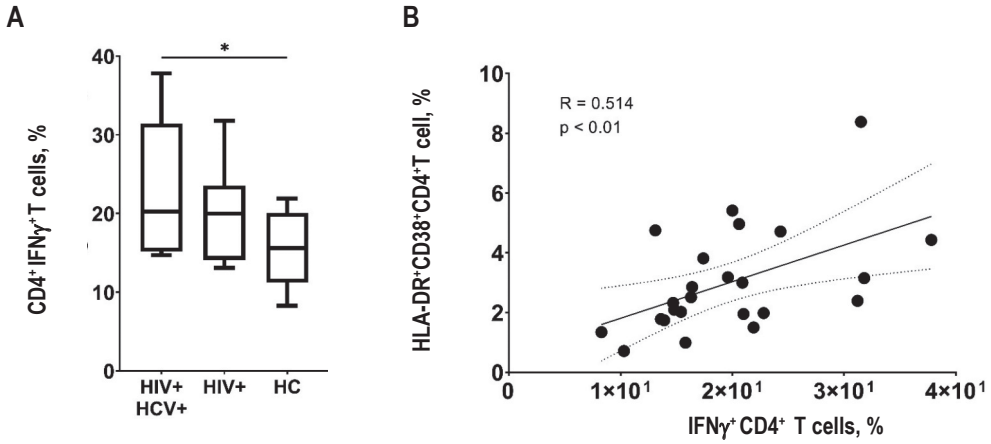

Figure 2. Frequency of IFNγ producing CD4⁺T lymphocytes (A) and its correlation with the relative number of activated CD4⁺T cells (B)

Note. (A) Medians (horizontal lines within rectangles), interquartile ranges (rectangles), and 10-90% intervals (vertical lines) are shown. *, $p < 0.05$ (Mann–Whitney U test). (B) Individual donor values, regression line and 95% confidence intervals are shown (r-Pearson correlation test). "HIV+HCV+", HIV/HCV coinfected patients; "HIV+", HIV monoinfected patients; "HC", healthy controls.

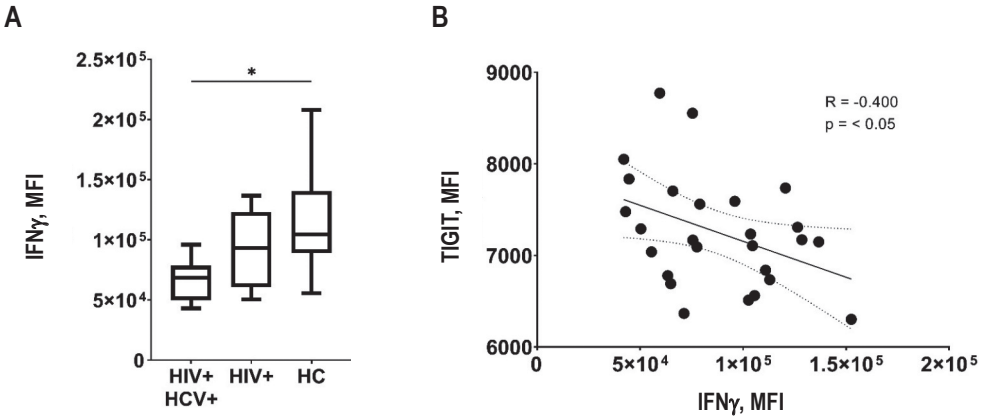

Figure 3. Level of IFNγ production (A) and its correlation with the degree of exhaustion (B) in CD4⁺T cells

Note. As for Figure 2.

CD4⁺T cell counts in donors' blood. Specifically, CD4⁺T lymphocytes count was directly related to the production of IFNγ ($R = 0.455$, $p < 0.05$) and inversely related to the proportion of exhausted CD4⁺T cells ($R = -0.598$, $p < 0.01$).

These data demonstrate that in HIV-infected patients, HCV coinfection is associated with a high level of CD4⁺T cells' activation and exhaustion. CD4⁺T lymphocytes in HIV/HCV coinfected patients show both phenotypic (expression of the inhibitory receptor – TIGIT) and functional (decrease in IFNγ production) signs of exhaustion. The frequency of exhausted CD4⁺T cells inversely correlate with the total number of CD4⁺T lymphocytes in donors' blood. These findings suggest that the negative impact of HCV on the course of HIV infection controlled by HAART is due to the functional exhaustion of CD4⁺T cells.

Previously, researchers assessed the level of CD4⁺T cell exhaustion in HIV/HCV coinfected patients by analyzing the relative number of lymphocytes expressing inhibitory receptor PD-1 [4]. The authors found that the frequency of PD1⁺CD4⁺T lymphocytes in HIV/HCV coinfected patients was higher than that in HIV monoinfected subjects or healthy individuals. A noteworthy detail is that the surface expression of inhibitory receptors alone does not allow identifying truly exhausted CD4⁺T cells, as these molecules are also expressed by CD4⁺T lymphocytes that have received an activation signal [13]. However, exhausted and activated CD4⁺T cells differ significantly in terms of the

inhibitory receptors' expression level [5]. The amount of inhibitory receptors expressed on the surface of $CD4^+$T cells in HIV/HCV coinfected patients have not been reported in the literature yet. To account for this limitation, we assessed the level of $CD4^+$T cells exhaustion by measuring the surface expression of the inhibitory receptor TIGIT, rather than by identifying $TIGIT^+CD4^+$T lymphocytes alone. Our findings show that the level of TIGIT expression on the surface of $CD4^+$T lymphocytes is significantly higher in HIV/HCV coinfected patients than in healthy individuals.

Determining the state of exhaustion in T cells requires assessing both their phenotype and function. TIGIT that was shown to be abundant on $CD4^+$T cells of HIV/HCV coinfected subjects inhibits the interaction between the costimulatory CD226 molecule and their common ligand, CD155 [8], leading to a decrease in T lymphocyte proliferation and cytokine production [5]. Previous studies have shown that in HIV-infected patients exhausted $TIGIT^+CD8^+$T cells are characterized by the reduced production of IFNγ, TNF , and IL-2 [2]. However in HIV/HCV coinfected patients, the cytokine-producing ability of the exhausted $CD4^+$T cell pool has not been evaluated. In this study, we have demonstrated for the first time that the IFNγ production is reduced in $CD4^+$T lymphocytes of HIV/HCV coinfected patients receiving HAART. These results strongly suggest a high level of $CD4^+$T cell exhaustion in patients coinfected with HIV and HCV.

Conclusion

An important finding of this study was the establishment of a link between the frequency of $CD4^+$T lymphocytes expressing TIGIT, the level of IFNγ production, and the amount of $CD4^+$T cells in the patients' blood. $CD4^+$T cell counts are a significant clinical indicator in HIV-infection as it determines the likelihood of developing non-AIDS-related diseases and death. Therefore, it can be assumed that the $CD4^+$T cell exhaustion caused by HCV coinfection may adversely impact the course of HIV-infection in patients adherent to HAART.

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