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Assessment of the Diagnostic Value of Serum Cytokine Levels in HIV-Positive Children

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Abstract The study aimed to assess the diagnostic significance of serum cytokines (IL-4, IL-18, IFN-γ, and TNF-α) in children and adolescents with HIV infection, in relation to clinical and immunological parameters, including $CD4^+$ T-lymphocyte count, viral load, and clinical stage of the disease, as well as in comparison with healthy controls. Serum cytokine concentrations (IL-4, IL-18, IFN-γ, TNF-α) were measured by ELISA (Vector-Best, Russian Federation), and $CD4^+$ counts were determined by flow cytometry. HIV RNA viral load was quantified by PCR. Statistical analysis was performed using StatTech 4.8.11. Data were expressed as median (Me) and interquartile range (Q_1–Q_3); group differences were assessed using the Mann–Whitney U-test and Kruskal–Wallis test, with significance set at $p<0.05$. Compared with healthy controls, HIV-infected adolescents demonstrated significantly elevated serum levels of all studied cytokines ($p<0.05$). IFN-γ and TNF-α markedly exceeded both control values and reference upper limits, indicating persistent proinflammatory activation. IL-4 levels remained within the physiological range but were significantly higher than in controls ($p=0.010$), with individual elevations up to 12 pg/mL, reflecting Th2 immune imbalance. IL-18 levels were within the reference range but below the average normative value, suggesting a trend toward chronic low-grade inflammation. Among all cytokines, only IL-4 showed significant differences between clinical stages ($p=0.041$). ROC analysis confirmed its prognostic value (AUC=0.639, cut-off 1.2 pg/mL; sensitivity 69.0%, specificity 62.5%) for predicting transition to stage 4 HIV infection. These findings highlight the diagnostic and prognostic utility of cytokine profiling in comprehensive immunological monitoring of HIV-infected adolescents. Determination of IFN-γ and TNF-α may serve as indicators of systemic inflammation even with undetectable viral load, while IL-4 ≥1.2 pg/mL can predict progression to advanced clinical stages. Combined assessment of $CD4^+$ count, viral load, and cytokine profile improves risk stratification and supports personalized management of adolescents living with HIV.

Keywords HIV-infection, Cytokines, IL-4, IL-18, IFN-γ, TNF-α

1. Introduction

HIV infection is accompanied by pronounced dysregulation of the cytokine profile, which plays a key role in the pathogenesis of the disease. In patients not receiving antiretroviral therapy (ART), there is a significant increase in the levels of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6. This imbalance leads to chronic immune activation, accelerated apoptosis, and depletion of CD4+ T lymphocytes, thereby contributing to the progression of HIV infection to the AIDS stage [1,2].

Despite the effectiveness of ART, some patients experience incomplete recovery of CD4+ T cells. In such individuals, elevated expression of inflammatory cytokines persists, which hinders full immune reconstitution and is associated with a higher risk of non–AIDS-related comorbidities [6].

Increased levels of TNF-α, IL-1β, and IL-6 indicate chronic immune activation and a risk of disease progression

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[2,3]. The dynamics of cytokines make it possible to assess the likelihood of CD4+ T-cell recovery. A decrease in TNF-α and IL-6 is associated with more pronounced regeneration of immune cells, whereas their persistent elevation indicates an unfavorable prognosis [6,4].

Cytokine measurement may serve as an additional tool for monitoring ART effectiveness by identifying patients with persistent immune activation even when viral load is undetectable [7,8]. The cytokine profile provides opportunities for individualized patient management, including additional anti-inflammatory interventions to reduce the risk of complications [5].

The aim of the present study was to determine the diagnostic significance of cytokines (IL-4, IL-18, IFN-γ, TNF-α) in the serum of HIV-infected children and adolescents, in comparison with clinical and immunological parameters, including CD4+ T-lymphocyte count, viral load, and clinical stage of the disease, as well as with the indicators of a control group of healthy individuals.

2. Materials and Methods

The study included 84 children and adolescents with HIV infection who were under clinical follow-up at the Republican and City AIDS Centers and received treatment at a specialized infectious diseases hospital. The control group consisted of 24 conditionally healthy peers matched by sex and age. Participants were aged 10–18 years, with a median age of 17 years. The proportion of boys and girls was 55.6% and 44.4%, respectively. The most common clinical stage of HIV infection was stage 3 (62.5%). According to immunological classification, the majority had CD4+ counts > 500 cells/μL; severe immunodeficiency (≤200 cells/μL) was observed in 11.2% of cases. An undetectable viral load was found in 71.8% of patients, while persistent viral replication was present in 28.2%.

Immunological assessment: absolute CD4+ T-cell counts were determined by flow cytometry; serum cytokines (IL-4, IL-18, IFN-γ, TNF-α) were measured using enzyme-linked immunosorbent assay (ELISA).

Virological testing: quantitative PCR was used to detect HIV RNA in plasma.

Clinical stage, year of birth, age, duration of clinical follow-up, and number of hospital bed-days were also recorded.

Statistical analysis: data were analyzed using *StatTech 4.8.11* (LLC "Stattech", Russia; registration No. 2020615715 dated 29.05.2020). Descriptive statistics included median (Me), interquartile range (Q1–Q3), mean (M), standard deviation (SD), and 95% confidence interval (CI). Intergroup comparisons were performed using the Mann–Whitney U test, and multiple-group comparisons using the Kruskal–Wallis test. Statistical significance was set at $p<0.05$.

3. Results and Discussion

Cytokine dysregulation is an important component of the pathogenesis of HIV infection, determining the features of inflammatory activation and immune reconstitution during antiretroviral therapy (ART). To assess the nature of these alterations, serum levels of IL-4, IL-18, IFN-γ, and TNF-α were analyzed in adolescents with HIV infection in comparison with a control group of healthy children and with reference values (Table 1).

Table 1. Serum cytokine levels in HIV-infected adolescents, healthy controls, and their correspondence to reference values

Cytokine	HIV-infected, Me (Q_1–Q_3), pg/mL	Control (healthy), Me (Q_1–Q_3), pg/mL	Reference values (mean; range), pg/mL	p (HIV vs control)	Reference correspondence
IL-4	1.17 (0.94–1.78)	0.95 (0.76–1.16)	0.2; 0–4	0.010*	Within normal range; some values elevated (up to 12 pg/mL)
IL-18	250.06 (192.32–338.77)	151.31 (147.03–165.80)	370; 104–650	<0.001*	Within normal range, below the average level
IFN-γ	48.55 (23.72–86.95)	7.59 (5.79–19.25)	2; 0–15	<0.001*	Significant elevation above the upper reference limit
TNF-α	15.52 (13.56–28.45)	9.52 (8.82–12.04)	0.5; 0–6	<0.001*	Significant elevation above the upper reference limit

Note: p<0.05 – statistically significant differences (Mann–Whitney U test).

Table 2. Serum cytokine levels in adolescents with HIV-infection depending on the clinical stage

Cytokine	Stage 3 HIV, Me (Q_1–Q_3), pg/mL	Stage 4 HIV, Me (Q_1–Q_3), pg/mL	p (Mann–Whitney U test)	Reference correspondence
IL-4	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.041*	Within normal range (0–4); some individual elevations up to 12 pg/mL
IL-18	254.8 (169.6–314.3)	249.4 (207.1–399.4)	0.286	Within normal range (104–650), below the average level (370)
IFN-γ	56.0 (27.0–84.0)	43.0 (22.0–85.0)	0.504	Significant elevation above the upper reference limit (15)
TNF-α	15.0–17.0 (range)	14.0–17.0 (range)	0.733	Significant elevation above the upper reference limit (6)

Note: p<0.05 – statistically significant differences (Mann–Whitney U test).

Comparative analysis showed that HIV-infected adolescents had significantly higher levels of all studied cytokines compared with the control group of healthy peers ($p<0.05$).

When compared with reference values, IL-4 levels were within the physiological range (0–4 pg/mL) but were significantly higher than in the control group ($p=0.010$). In some patients, individual increases up to 12 pg/mL were observed, indicating an imbalance of the Th2 arm of the immune response.

IL-18 levels in HIV-infected patients (Me = 250.06 pg/mL) remained within the normal range (104–650 pg/mL) but were below the mean reference value (370 pg/mL). At the same time, they were significantly higher than in healthy children ($p<0.001$).

IFN-γ and TNF-α levels showed a marked increase not only compared with the control group but also above the upper limits of normal (15 pg/mL and 6 pg/mL, respectively; $p<0.001$), reflecting pronounced activation of the proinflammatory response and the presence of a chronic inflammatory process.

Thus, in adolescents with HIV infection receiving ART, a cytokine imbalance was identified, characterized by hyperproduction of proinflammatory mediators (IFN-γ, TNF-α), a relative increase in IL-4, and variability in IL-18 levels.

To determine the prognostic significance of cytokines, their levels were analyzed according to the clinical stage of HIV infection (stages 3 and 4) (Table 2).

The only cytokine that showed statistically significant differences between the clinical stages of the disease was IL-4 ($p=0.041$). ROC analysis confirmed its prognostic value: AUC = 0.639, with a cut-off level of 1.200 pg/mL, which allowed prediction of stage 4 progression with a sensitivity of 69.0% and specificity of 62.5%. Levels of IL-18, IFN-γ, and TNF-α did not differ significantly between the stages ($p>0.05$), remaining consistently elevated compared with normal reference values. IL-18 was within the reference range but below the mean level, whereas IFN-γ and TNF-α markedly exceeded the upper normal limits, reflecting the presence of chronic inflammatory activation regardless of disease stage.

Thus, the comparative analysis confirmed that adolescents with HIV infection receiving ART exhibit pronounced cytokine dysregulation. The most significant alterations include:

- Hyperproduction of IFN-γ and TNF-α, exceeding both the values of the control group and the upper limits of reference ranges;
- Relative elevation of IL-4, which serves not only as a marker of Th2-response imbalance but also as a significant predictor of disease progression to more advanced stages;
- Variability of IL-18, whose levels remain within the normal range but tend to reflect ongoing chronic inflammatory activation.

These findings indicate the persistence of systemic inflammation and cytokine imbalance in adolescents with HIV infection even while receiving ART, highlighting the diagnostic and prognostic value of cytokine profiling in the comprehensive assessment of immune system status.

4. Conclusions

The conducted study demonstrated that adolescents with HIV infection receiving antiretroviral therapy exhibit a pronounced dysregulation of the cytokine profile, characterized by:

1. A significant increase in IFN-γ and TNF-α levels compared with the control group and the upper limits of reference values;
2. A relative elevation of IL-4, which has prognostic value in assessing the risk of disease progression to more advanced stages;
3. Variability of IL-18, whose levels generally remain within the normal range but indicate the presence of residual inflammation.

The obtained data make it possible to formulate several practical recommendations for implementation in healthcare practice. It is advisable to use the determination of serum IFN-γ and TNF-α levels as additional markers of chronic inflammatory activation in adolescents with HIV infection. Their persistent elevation, even in the presence of an undetectable viral load, reflects ongoing systemic inflammation and may serve as an indicator of the risk for non–AIDS -related complications.

The prognostic value of IL-4 was established: a level of ≥1.2 pg/mL is associated with progression to stage 4 of HIV infection (sensitivity 69.0%, specificity 62.5%). This marker can be recommended for inclusion in the immunological monitoring algorithm for adolescents with HIV infection.

The assessment of IL-18 levels in HIV-infected adolescents allows the identification of patients with persistent inflammatory activation, even under effective viral load control. This parameter should be considered an additional criterion for evaluating immune system status and planning follow-up strategies.

The combined use of CD4+ T-lymphocyte counts, viral load, and cytokine profile data provides a more accurate stratification of patients by the risk of disease progression and complication development, thereby creating opportunities for individualized management of pediatric HIV patients.

REFERENCES

[1] Freeman ML, Shive CL, Nguyen TP, Younes SA, Panigrahi S, Lederman MM. Cytokines and T-cell homeostasis in HIV infection. *J Infect Dis*. 2016; 214 (suppl_2): S51–7.

[2] Reuter MA, Pombo C, Betts MR. Cytokine production and dysregulation in HIV pathogenesis: lessons for development of therapeutics and vaccines. *Cytokine Growth Factor Rev*. 2012; 23: 181–91.

[3] Phetsouphanh C, Xu Y, Zaunders J. CD4 T cells mediate both positive and negative regulation of the immune response to HIV infection. *Front Immunol*. 2015; 5: 681.

[4] Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014; 5: 491.

[5] Muñoz-Carrillo JL, Contreras-Cordero JF, Gutiérrez-Coronado O, Villalobos-Gutiérrez PT, Ramos-Gracia LG, Hernández-Reyes VE. Cytokine profiling plays a crucial role in activating immune system to clear infectious pathogens. In: *Immune Response Activation and Immunomodulation*. IntechOpen; 2018.

[6] Bordoni V, Sacchi A, Casetti R, et al. Impact of ART on dynamics of growth factors and cytokines in primary HIV infection. *Cytokine*. 2020; 125: 154839.

[7] Hokello J, Sharma AL, Dimri M, Tyagi M. Insights into the HIV latency and the role of cytokines. *Pathogens*. 2019; 8: 137.

[8] Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. *Open Biol*. 2020; 10: 200160.