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# Impact of Tuberculosis Co-infection on Cytokine Expression in HIV-Infected Individuals

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***Abstract*—**HIV and Tuberculosis (TB) infections each speed the other's progress. HIV-infection increases the risk of TB disease. At the same time, TB infection is associated with clinical progression of HIV-infection. HIV+TB co-infected patients are also at higher risk of acquiring new opportunistic infections. An important feature of disease progression and clinical outcome is the innate and acquired immune responses. HIV and TB, however, have a spectrum of dysfunctions of the immune response. As cytokines play a crucial role in the immunopathology of both infections, it is important to study immune interactions in patients with dual infection HIV+TB. Plasma levels of proinflammatory cytokines IL-2, IFN-γ and immunoregulating cytokines IL-4, IL-10 were evaluated in 75 patients with dual infection HIV+TB, 58 patients with HIV monoinfection and 50 patients with TB monoinfection who were previously naïve for HAART. The decreased levels of IL-2, IFN-γ, IL-4 and IL-10 were observed in patients with dual infection HIV+TB in comparison with patients who had only HIV or TB which means the profound suppression of Th1 and Th2 cytokine secretion. Thus, those cytokines could possibly serve as immunological markers of progression of HIV-infection in patients with TB.

***Keywords*—**HIV, Tuberculosis, TB, HIV associated with TB, Th1/ Th2 cytokine expression.

## I. Introduction

TUBERCULOSIS and HIV infection associated with TB is one of the world's major serious public health challenges. In 2014, there were an estimated 1.2 million new HIV-associated TB cases and TB accounted for 36% of HIV-related deaths [1], [2]. There is a 32-fold increased risk of death among HIV/TB co-infected pregnant women compared to those without HIV [3]. TB is also a major cause of morbidity in HIV-infected children, with HIV-positive children having a 20-25 fold higher incidence of TB than HIV-uninfected children [3]-[5]. According to UNAIDS, Russia occupies 9th place among 15 countries with high burden of HIV-infection and 11th place among 22 countries with high burden of TB [6]. In Russia TB is a leading cause of death among people with HIV [6], [7]. Among the AIDS-related deaths, TB as a secondary opportunistic infection accounted for 60% deaths. The number of newly diagnosed HIV-associated TB cases was increased from 54.7% in 2011 year up to 68.2% in 2013 year [8]. In Russia, 62 patients with HIV/TB co-infection die daily [7], [8]. People living with HIV have 21-34 times the risk of developing TB when compared with those not infected [9]. According to the WHO experts, TB is accounting for around one in five AIDS-related deaths [10]. HIV co-infection is the most powerful known risk factor for progression of *M. tuberculosis* infection to active disease, increasing the risk of latent TB reactivation 20-fold and a major risk factor for TB recurrence [11]-[13]. Thus, HIV+TB is a deadly combination which accelerates the progression of both infections. One of the major indicators of disease progression and outcome is an immune response of the host. Both TB and HIV have profound effects on the immune system and are characterized by dysregulation in cytokine secretion which can activate virus replication and negatively regulate T-cell activation [14]-[16]. Understanding the cytokine production in patients with HIV+TB dual infection may enhance understanding the factors that determine protective immunity or susceptibility to both infections. The goal of this study was to examine the cytokine profiles in plasma of HIV+TB co-infected patients and to compare them with profiles of those with HIV monoinfection and TB monoinfection.

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## II. Methods

### A. Study Population

Seventy five patients with HIV+TB dual infection and 50 patients with TB monoinfection were enrolled in the study through the G. A. Zaharyan Moscow Tuberculosis Clinic, Department for Treatment of TB Patients with HIV. Fifty eight patients with HIV monoinfection were enrolled through Federal AIDS Centre, Central Research Institute of Epidemiology Ministry of Health. The patients were over 18 years old and previously naïve for HAART. TB diagnoses were based on clinical symptoms, sputum microscopy and radiological analyses. The patients were diagnosed as HIV seropositive by ELISA and confirmed by Western blot. The patients with HIV+TB dual infection and HIV monoinfection were divided into two groups according to CD4+ T cell count: Group 1 (CD4+< 200 cells/mm$^3$) and Group 2 (CD4+> 200 cells/mm$^3$).

*B. Sputum Microscopy and Culture*

Sputum samples were stained for acid-fast bacilli and were graded by light microscopy. Cultures were examined weekly until positive for visible colonies or for a maximum of 8 weeks.

*C. CD4+T-CELL Count*

CD4+T lymphocyte percentages were measured from freshly collected blood samples by a two color flowcytometry, using phycoerythrin-anti-CD4 (FACSort, Becton Dickinson, USA)

*D. Cytokine ELISA*

Plasma levels of IFN-γ, IL-2, IL-4 and IL-10 were measured by commercial ELISA kits (Vector-Best, sensitivity 0-5 pg/ml, RF) following the manufacturer's specifications. Each sample was run in duplicate. Quantitation was done with the help of the standard curve drawn for each run.

*E. Statistical Analyses*

Nonparametric Mann-Whitney test was performed to check for the significance differences. P value < 0.05 was considered significant.

## III. Results

We enrolled 183 patients of whom 75 had HIV+TB, 58 were HIV seropositive and 50 had TB in the study. The majority of patients with dual infection HIV+TB was men (68%). The median age among men was 36,3 years (26÷51) and among women 44,7 years (26÷52). There were no age or gender differences among group with dual infection (HIV+TB) or groups with monoinfection (HIV or TB). The clinical characteristics of patients are given in Table I.

TABLE I
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

| Characteristics (%, n) | Patient group | | |
|---|---|---|---|
| | HIV+TB (n=75) | HIV (n=58) | TB (n=50) |
| Men | 68 (n=51) | 70,6 (n=41) | 72 (n=36) |
| Age: | | | |
| Male | 36,3 (26÷51) | 33,5 (23÷52) | 32,9 (26÷50) |
| Female | 44,7 (26÷52) | 41,1 (22÷47) | 38,4 (27÷51) |
| **CD4+ cell count** | | | |
| < 200 cells/mm$^3$ | 31,5 (n=42) | 26,7 (n=46) | 0 |
| > 200 cells/mm$^3$ | 24,8 (n=33) | 6,96 (n=12) | 0 |

The secretion of IL-2 was significantly decreased in patients with dual infection HIV+TB in comparison with HIV seropositive individuals and the patients with TB (Fig. 1), ($p<0.05$; $p<0.03$; $p<0.05$; $p<0.05$, respectively). Also the decreased level of IFN-γ was observed in Group 1 (CD4+< 200 cells/mm$^3$) for HIV+TB patients.

In HIV+TB patients with CD4+> 200 cells/mm$^3$; however, the secretion of IFN-γ was elevated and in patients with HIV and TB monoinfection the expression of IFN-γ was almost the same (Fig. 2), ($p<0.02$; $p<0.03$; $p<0.03$; $p<0.03$, respectively).

The secretion of IL-4 was significantly decreased in HIV+TB patients and in HIV seropositive individuals comparing with patients who had only TB (Fig. 3), ($p<0.04$; $p<0.04$; $p<0.03$; $p<0.03$, respectively). The level of IL-4 in HIV+TB patients was decreased for both groups: for Group 1 (CD4+< 200 cells/mm$^3$) and for Group 2 (CD4+> 200 cells/mm$^3$).

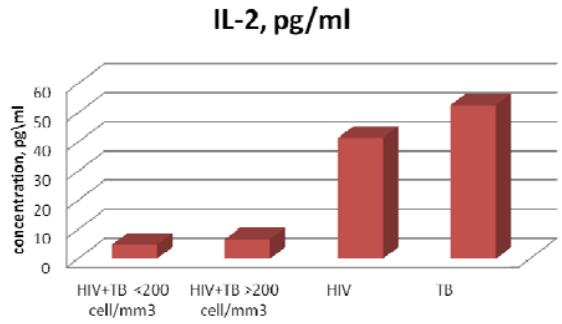


Fig. 1 Cytokine levels of IL-2 in patients with dual infection HIV+TB, HIV positive individuals and patients with TB: The levels of all studied cytokines were almost the same for Group 1 and Group 2 in patients with monoinfection HIV

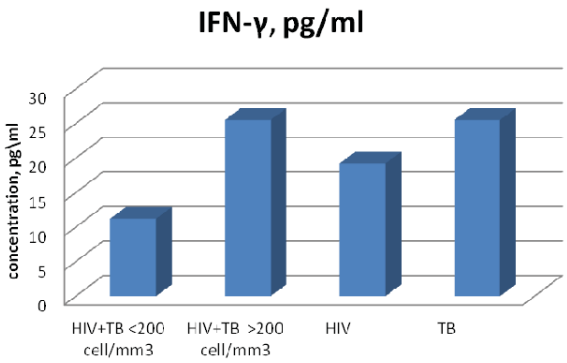


Fig. 2 Cytokine levels of IFN-γ in patients with dual infection HIV+TB, HIV positive individuals and patients with TB: The levels of all studied cytokines were almost the same for Group 1 and Group 2 in patients with monoinfection HIV

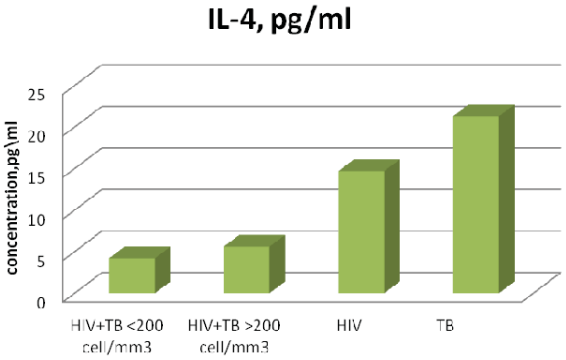


Fig. 3 Cytokine levels of IL-4 in patients with dual infection HIV+TB, HIV positive individuals and patients with TB: The levels of all studied cytokines were almost the same for Group 1 and Group 2 in patients with monoinfection HIV

Similarly, the significant decrease in IL-10 secretion was observed in HIV+TB patients for Group1 and Group 2 in comparison with patients who had only HIV or TB (Fig. 4),

(p<0.03; p<0.02; p<0.03; p<0.03, respectively).

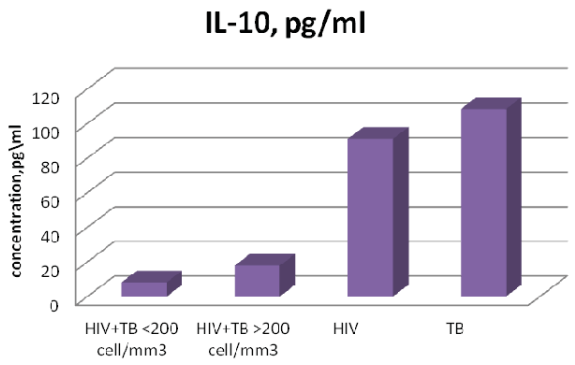


Fig. 4 Cytokine levels of IL-10 in patients with dual infection HIV+TB, HIV positive individuals and patients with TB: The levels of all studied cytokines were almost the same for Group 1 and Group 2 in patients with monoinfection HIV

## IV. Discussion

The cytokines of Th1 type enhance cell-mediated immune response. Interleukin-2 (IL-2) as well as IFN-γ plays a key role in immune response inducing activation, proliferation and differentiation of cytotoxic lymphocytes which are deterrent factor to HIV replication and *M. tuberculosis* [17]-[23]. IL-2 decreases the expression of antigen representing cells receptors, which slows down the HIV infection of cells. In the present study, the production of IL-2 was significantly decreased in HIV+TB co-infected patients for both groups, for Group 1: CD4+< 200 cells/mm$^3$ (mean:4.75 pg/ml, p<0.05) and for Group 2: CD4+> 200 cells/mm$^3$ (mean:6.7 pg/ml, p<0.03) in comparison with patients who had only HIV (mean:41.4 pg/ml, p<0.05) or TB (mean:52.7 pg/ml, p<0.05). These results are consistent with those of Benjamin et al. who suggests that high levels of IL-2 in HIV and TB patients can be a result of a compensatory reaction of the depleted CD4+cells of the host [24]. The significantly lower secretion of IL-2 in dually infected patients compared with patients who had only HIV or TB was also shown by [25]. Probably the proliferation of T cells induced by IL-2 which occurs in patients infected by *M. tuberculosis* or HIV is impaired in patients with dual infection HIV+TB. Zhang et al. also showed that IL-2 expression was significantly depressed when PMBCs were stimulated with *M. tuberculosis* in patients with dual infection [26]. However, another study demonstrated that secretion of IL-2 in HIV+TB co-infected patients with CD4+ cell count > 200 cells/mm$^3$ was higher in comparison with HIV and TB patients [27]. These differences in the results might be due to different levels of immunosuppression in patients with dual infection or possibly due to the difference in kinetics of cytokine production by different cell populations.

The decreased levels of IFN-γ in HIV+TB patients with CD4+ cell count CD4+< 200 cells/mm$^3$ (mean:11.2 pg/ml, p<0.02) observed in our study is in agreement with other investigators who got similar results [28]-[32]. Interestingly, HIV+TB patients with CD4+> 200 cells/mm$^3$ (mean:25.5 pg/ml, p<0.03) showed higher levels of IFN-γ compared with HIV (mean:19.2 pg/ml, p<0.03) and TB (mean:25.5 pg/ml, p<0.05) patients thus retaining the ability to produce IFN-γ in response to *M. tuberculosis*. Similar results were demonstrated in other several studies [33], [34]. However, the decrease in IFN-γ secretion results in reduction of cytotoxic lymphocytes differentiation and reduction of macrophage activation which leads to the increased HIV expression and progression of HIV-infection. IFN-γ as a cell mediator of macrophage activation also plays a critical role in providing host the resistance to TB infection. It was shown that impaired production of IFN-γ correlates with the progression of immunodeficiency [35], [36]. Thus, it can be suggested that the decreased secretion of IL-2 and IFN-γ in HIV+TB co-infected patients with CD4+ cell count < 200 cells/mm$^3$ enhance the progression and severity of HIV and TB as a profound suppression of Th1 cytokine response is evident.

The Th2 cytokines IL-4 and IL-10 induce humoral link of immune response. The role of IL-4 in the immunity of HIV-infection and *M. tuberculosis* is somewhat controversial. Interleukine-4 (IL-4) inhibits the expression of HIV co-receptors on the T-cell surface reducing the possibility of virus entry into cell [37], [38]. It was shown that the decreased secretion of that cytokine leads to the enhanced HIV replication. Moreover, a polymorphism in the regulatory region of IL-4 has been reported to have a protective effect against transmission of HIV through heterosexual contact [39], [40]. At the same time, the relationship was shown between increased production of IL-4 and susceptibility to TB [41]-[43]. In this work, the IL-4 levels in HIV+TB co-infected patients were significantly decreased comparing with patients who had only TB or HIV (mean: 21.3 pg/ml, p<0.03 and mean:14.7 pg/ml, p<0.03, respectively). There was no great difference in IL-4 secretion between Group 1: CD4+< 200 cells/mm$^3$ (mean:4.2 pg/ml, p<0.04) and Group 2: CD4+> 200 cells/mm$^3$ (mean:5.6 pg/ml, p<0.04). Our findings are consistent with Bal et al. who demonstrated a low production of IL-4 in mitogen stimulated PBMCs in patients with dual infection [25]. The higher levels of IL-4 in patients with TB monoinfection in comparison with HIV+TB and HIV patients show that immune system mount to a Th2 cytokine response [44].

Interleukin-10 (IL-10) as IL-4 also plays a protective role against progression of HIV-infection inhibiting the production of TNF-α and IL-6 which are known to induce HIV replication [45], [46]. It was shown that high levels of IL-10 are associated with low viral replication *in vitro* [45], [47]. A polymorphism in the IL-10 regulatory region unlike the polymorphism in IL-4 is associated with significant acceleration in the rate of HIV disease progression [48]. The recent studies showed that IL-10 secreting T-cells downregulate HIV replication in pregnant women and elderly patients [49], [50]. The role of IL-10 in TB is not yet fully studied but it is considered that it is a key cytokine in TB that regulates a balance between the inflammatory process and immunopathology [51]. In this study the levels of IL-10 in HIV and TB patients were almost the same (mean:91.2 pg/ml, p<0.03 and mean: 108.4 pg/ml, p<0.03, respectively).

However, the profound decrease in IL-10 secretion was observed in patients with dual infection HIV+TB in comparison with patients with TB or HIV alone. The similar results were shown by Bal et al. who reported significantly lower production of IL-10 in mitogen-stimulated PMBCs of HIV+TB co-infected patients [25]. The decreased IL-4 and IL-10 secretion in patients with dual infection HIV+TB demonstrates that the shift from Th1 to Th2 cytokine response did not occur as it was observed in patients with HIV or TB monoinfection.

The results of this study show that the secretion of Th1 and Th2 cytokines is suppressed in HIV+TB co-infected patients. Supposedly HIV and TB accelerate the decline of immunological functions that leads to progression of both infections. The decreased levels of proinflammatory cytokines IL-2, IFN-γ and immunoregulating cytokines IL-4, IL-10 could possibly serve as immunological markers of progression of HIV-infection in patients with TB.

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