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Decrease of Enhanced Interferon α Levels in Sera of HIV-Infected and AIDS Patients Receiving Combined Antiretroviral Therapy

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Abstract. In the advanced stages of human immunodeficiency virus (HIV) infection the defective interferon (IFN) responses have been observed. Persisting high lebels of the acid-labile interferons (al-IFNs) have been found in sera of the patients with AIDS. The combined antiretroviral therapy, that included the reverse transcriptase and viral protease inhibitors, resulted in a significant improvement of the clinical state of the majority of HIV-infected patients. In this report we describe the levels of IFNs in 41 HIV patients subjected to the combined treatment. High IFN levels (median 84, up to 576 U/ml) were found in sera of patients classified as the stage C2 or C3 of AIDS before the treatment. The combined therapy resulted in the decrease of IFN levels (median 7.5, up to 24 U/ml) that approached the levels of IFNs detected in the HIV^+, A1-A3 stage patients (median 4, up to 36 U/ml). In contrast, the unsuccessful therapy connected with the worsening of the clinical state and the decrease of $CD4^+$ cell count had no effect on the IFNs levels (median 48, up to 96 U/ml). Thus, the measurements of IFN activity in sera may be useful for monitoring the effects of the antiretroviral combined therapy. In sera of the AIDS patients, subjected to the antiviral bioassays, the mixture of the acid-labile and acid-stable form of IFN-α, with the prevailing al-IFN-α, have been detected.

Key words: interferon α; acid-labile interferon (al-IFN); al-IFN-α, AIDS, HIV-infected patients, combined antiretroviral therapy.

Introduction

Dysfunction of numerous functions of the immune system occurs in HIV-infected individuals. It was found that the peripheral blood leukocytes (PBL) of HIV^+ individuals have a decreased ability to produce virally-induced IFN-α in comparison with uninfected control subjects[15, 19, 20, 28, 37, 38, 40, 47]. The impaired production of IFN-γ was also observed in AIDS patients when their leukocytes were treated with mitogen (e.g. PHA) or LPS[3, 11, 20, 31, 32, 37, 38, 40]. During progression of HIV infection the levels of IFNs in plasma increase. In sera of AIDS patients the levels of IFNs are unusually high. The IFNs have been identified as atypical forms of the biologically active interferon, mainly acid-labile IFN-α (al-IFN-α) [7, 13-15, 20, 28, 37, 38, 44, 46]. There are several possible explanations of the biological phenomenon of the acid-lability of IFN-α. The hypotheses taken into consideration (reviewed in [35]) suggested engagement of a unique gene[27, 29], posttranslational modifications[29], binding (or other interactions) of a plasma factor(s) to the IFN molecule[29, 48, 49] or synergistic interactions be-

tween IFN-α and IFN-γ, resulting in high IFN levels determined in biological assays[6-8, 28]. Despite of the nature of al-IFN-α, that type of interferon was found to be important marker of worsening of the clinical state in the HIV infection[7, 14, 20, 37, 38, 40, 44-46].

On the other hand, a combined antiretroviral therapy resulted in the improvement of the clinical state of patients with AIDS. It coincided with the significant increase of the $CD4^+$ lymphocyte counts in blood and decrease of viremia in plasma[9, 18, 33]. The treated AIDS patients received two reverse transcriptase inhibitors and one or two viral protease inhibitors. We have concluded that the measurements of the biologically active IFNs in the sera samples of AIDS patients, subjected to the combined antiretroviral therapy, are useful to monitor results of the treatment.

Materials and Methods

Patients. Forty one HIV^+ and AIDS patients were under care of the Department of Infectious Diseases, University Medical School, Wrocław. The patients included 24 males and 17 females, age 18–54 (mean age 31), 28 of them (68%) were infected by injecting drugs, whereas 13 (32%) by sexual transmission. The $CD4^+$ lymphocyte count of every patient was determined. The patients were treated with the reverse transcriptase inhibitors (ZDV – zidovudine, 3TC – lamivudine, ddC – zalcitabine, ddI – didanosine, d4T – stavudine) and the viral protease inhibitors (SQV – saquinavir, IDV – indinavir, RTV – ritonavir) in the following combinations: ZDV + 3TC, ZDV + ddC, ZDV + 3TC + SQV, ZDV + 3TC + IDV, ZDV + ddC + SQV, d4T + 3TC + SQV, d4T + 3TC + IDV, d4T + 3TC + RTV, d4T + ddI + SQV, d4T + ddI + IDV, d4T + ddI + RTV, ZDV + ddI + RTV + SQV, d4T + ddI + RTV + SQV, d4T + 3TC + RTV + SQV.

The clinical status of the HIV^+ patients was defined according to the classification system of the Centers for Disease Control (CDC) modified in 1993[10]. The system introduced categories A, B and C accompanying with numbers 1–3. Patients classified as A have generally no symptoms (alternatively persistent generalized lymphadenopathy and acute primary retroviral disease). Patients suffered from at least one of the 28 indicator (for AIDS) diseases are classified as C. Class B is given when a patient has disease not included in A or C category. The accompanying number is dependent on the $CD4^+$ lymphocyte count: 1 for ≥ 500 cells/μl, 2 for 200–499 cells/μl and 3 for < 200 cells/μl. AIDS should be diagnozed only when an individual is classified as A3, B3, C1, C2 or C3. The patients included in this work were classified as follow: A1 – 2, A1/A2 – 2, A2 – 13, A2/A3 – 4, A3 – 9, C2/C3 – 3 and C3 – 8 patients.

The HIV-negative control group (15 males and 8 females) was heterogenous and consisted of HIV^- patients recruited at the Department of Infectious Diseases or staff of the Laboratory of Virology at Institute of Immunology and Experimental Therapy.

Blood samples were taken from ulcer vein. After centrifugation, serum samples were obtained and stored at -20^0C prior to interferon measurement.

$CD4^+$ lymphocyte count examination. Determinations of $CD4^+$ cell counts were performed by flow cytometry using FACSCount Reagents (Becton-Dickinson Facs Count System). Peripheral blood samples were stained with CD4/CD3 (Leu 4/3, Becton Dickinson) and CD8/CD3 (Leu 4/2, Becton Dickinson), conjugated monoclonal antibodies according to the manufacturer recommendations.

Interferon assay[22, 23, 36, 38]. The confluent monolayers of A549 cells (human lung adenocarcinoma, ATCC CCL 185) were prepared on the 96-well microplates in Dulbecco's-modified Eagle's minimum essential medium (DMEM) with 10% calf serum, L-glutamine and antibiotics. IFN samples diluted on separate plates were added to the cell monolayers and incubated at 37^0C for 24 h in atmosphere of 5% CO_2 in the humidified air. The cells were then washed and challenged with 100 $TCID_{50}$ of encephalomyocarditis virus (EMCV). After 48 h of incubation at 37^0C, the cytophatogenic effect was determined using a modified MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, Sigma) method[3, 17, 23], where the cell cultures were incubated with 0.5–1.0 mg/ml of MTT for 2 h at 37^0C. Then, SDS/DMF solution (13.5% (w/v) sodium dodecyl sulphate in 45% (v/v) dimethylformamide, Sigma) was added for at least 2 h and absorbances at 570 nm were measured. The end point of IFN titration (50% reduction of the cell killing) in the MTT assay was considered as the dilution of the IFN sample resulting in A_{570} value closest to the value calculated by the following formula:

$$A_{570}\,(50\%) = A_{570}\,(\mathrm{EMCV}) + \frac{A_{570}\,(\mathrm{cells}) - A_{570}\,(\mathrm{EMCV})}{4},$$

where: A_{570} (50%) – expected A_{570} value for a cell culture destroyed by the virus in 50%, A_{570} (cells) – A_{570} of the control cell culture untreated with IFN or EMCV, A_{570} (EMCV) – A_{570} of the control cell culture treated with EMCV but not with IFN. The formula had been established experimentally in our publications[21-25, 38]. Laboratory and/or international standards[34] (NIBSC

69/19 and NIAID G-023-902-527) of IFNs were included in all assays.

Interferon neutralization assay. The interferons present in sera were treated with different anti-IFN sera for 1 h at room temperature. Next, IFN level was determined and compared with the controls, containing only IFN. The polyclonal sera: sheep anti-HuIFN-α and sheep anti-HuIFN-γ were obtained from Dr. Kari Cantell (Helsinki, Finland).

Acid treatment. Serum samples were dialyzed against HCl-glycine buffer, pH 2 to inactivate bioactive IFNs (mainly IFN-γ and/or al-IFN-α) and then re-dialyzed against PBS (pH 7). To control the experiment conditions, a part of the each serum sample studied for acid sensitivity was dialyzed against pH 7 only.

Statistical analysis. The results were compared by analysis performed with the Mann-Whitney non-parametric U test. The data were considered significant when $p < 0.05$.

Results

The levels of the antiviral activity of IFNs have been determined in 78 sera of 41 asymptomatic and AIDS patients. Fifty blood samples were taken from the patients receiving combined antiretroviral therapy with two reverse transcriptase and one or two viral protease inhibitors. In 7 cases the samples were taken when the patients were treated with 2 reverse transcriptase inhibitors. The therapy was considered to be successful when the clinical improvement (increase of $CD4^+$ cell counts, receding disease symptoms or persisting absence of symptoms, improvement of mood) was observed. In other cases an unsuccessful effect was stated and administration of another set of antiviral drugs was the result of such a conclusion.

The enhanced IFN levels (above 20 U/ml) were found in 13 sera from 11 patients (Table 1). Eight of them were patients with an advanced HIV infection (CDC class C2 or C3) and three with A2 or A3. The

Table 1. Characteristics of HIV-infected patients and bioactive antiviral levels of IFNs determined in their sera

Patient				Serum no. (date)	$CD4^+$ lymphocytes (cells/μl)	CDC class[b]	Antiretroviral therapy		Interferon level in serum (U/ml)
no.	sex	age	risk group[a]				drugs (effectiveness of treatment)[c]	duration of treatment (weeks) [d]	
1	2	3	4	5	6	7	8	9	10
1	F	25	IDU	1 (26.02.98)	513	A1	ZDV + ddC (NS)	35	12
				2 (30.04.98)	601	A1	d4T + 3TC + IDV (S)	9	18
2	F	18	IDU	3 (05.03.98)	644	A1	ZDV + 3TC + IDV (s)	2	3
3	M	24	ST-He	4 (11.12.97)	450	A2	none	–	<6
				5 (15.01.98)	524	A1	ZDV + ddC + SQV (S)	5	<6
				6 (25.02.98)	436	A2	ZDV + ddC + SQV (NS)	11	6
				7 (14.05.98)	574	A1	ZDV + ddC + SQV (S)	22	6
4	F	29	IDU	8 (12.02.98)	389	A2	ZDV + ddC (NS)	52	3
				9 (26.03.98)	559	A1	d4T + 3TC + IDV (S)	6	3
				10 (07.05.98)	591	A1	d4T + 3TC + IDV (S)	12	<3
5	M	26	IDU	11 (23.06.97)	218	A2	none	–	<3
				12 (06.11.97)	214	A2	ZDV + ddC + SQV (S)	20	<6
				13 (09.02.98)	425	A2	ZDV + ddC + SQV (S)	34	<3
				14 (14.05.98)	222	A2	ZDV + ddC + SQV (NS)	48	24
6	M	31	ST-Ho	15 (19.02.98)	272	A2	d4T + 3TC + RTV (S)	32	12
				16 (09.04.98)	334	A2	d4T + 3TC + RTV (S)	39	12
7	F	20	IDU	17 (19.02.98)	360	A2	none	–	3
				18 (16.04.98)	292	A2	ZDV + ddC + SQV (NS)	8	3
8	M	25	IDU	19 (26.02.98)	471	A2	none	–	12
9	M	52	ST-He	20 (02.03.98)	280	A2	none	–	3
				21 (16.04.98)	288	A2	ZDV + ddC + SQV (S)	7	5
10	F	32	IDU	22 (05.03.98)	250	A2	ZDV + ddC + SQV (S)	52	6
11	M	34	IDU	23 (05.03.98)	279	A2	none	–	3
				24 (07.05.98)	411	A2	ZDV + ddC + SQV (S)	8	<3

1	2	3	4	5	6	7	8	9	10
12	M	27	IDU	25 (26.03.98)	392	A2	none	–	6
13	M	22	IDU	26 (26.03.98)	364	A2	none	–	3
14	M	38	IDU	27 (26.03.98)	431	A2	none	–	6
15	F	19	IDU	28 (09.04.98)	286	A2	ZDV + ddC + SQV (NS)	23	3
16	M	39	IDU	29 (09.04.98)	395	A2	ZDV + ddC + SQV (NS)	52	12
17	M	31	IDU	30 (30.04.98)	406	A2	none	–	3
18	M	20	IDU	31 (19.11.97)	182	A3	none	–	<6
				32 (19.02.98)	265	A2	ZDV + ddC + SQV (S)	12	12
19	F	28	IDU	33 (08.01.98)	199	A3	d4T + 3TC + SQV (S)	6	3
				34 (05.03.98)	211	A2	d4T + 3TC + SQV (S)	15	3
20	F	27	IDU	35 (05.03.98)	130	A3	ZDV + ddC (NS)	28	3
				36 (30.04.98)	248	A2	d4T + 3TC + RTV + SQV (S)	8	6
21	F	26	IDU	37 (19.03.98)	184	A3	none	–	6
				38 (30.04.98)	248	A2	d4T + ddI + RTV + SQV (S)	6	6
22	M	25	IDU	39 (08.12.97)	26	A3	none	–	36
				40 (05.02.98)	194	A3	ZDV + 3TC + SQV (S)	9	6
				41 (26.03.98)	166	A3	ZDV + 3TC + SQV (NS)	16	3
				42 (21.05.98)	216	A2	d4T + ddI + IDV (S)	8	3
23	F	27	IDU	43 (20.01.98)	167	A3	ZDV + ddC + SQV (NS)	33	<3
24	F	26	IDU	44 (20.02.98)	57	A3	d4T + 3TC + IDV (S)	4	6
				45 (09.04.98)	118	A3	d4T + 3TC + IDV (S)	11	12
25	F	39	ST-Ho	46 (05.03.98)	156	A3	d4T + ddI + SQV (NS)	27	3
				47 (16.04.98)	154	A3	d4T + 3TC + IDV (NS)	6	9
26	M	46	ST-Ho	48 (05.03.98)	123	A3	ZDV + 3TC (NS)	36	3
				49 (02.04.98)	175	A3	ZDV + 3TC (NS)	40	3
				50 (14.05.98)	130	A3	d4T + ddI + RTV + SQV (NS)	6	12
27	M	31	IDU	51 (19.03.98)	162	A3	d4T + ddI + RTV (S)	7	6
28	F	36	ST-He	52 (19.03.98)	146	A3	none	–	6
29	M	28	ST-Ho	53 (09.04.98)	174	A3	ZDV + ddC (NS)	52	24
30	M	45	ST-He	54 (30.04.98)	197	A3	none	–	9
31	F	32	ST-He	55 (05.03.98)	230	C2	ZDV + ddC + SQV (S)	6	12
				56 (16.04.98)	96	C3	ZDV + ddC + SQV (NS)	12	24
32	F	23	IDU	57 (05.03.98)	180	C3	ZDV + ddC + SQV (S)	15	3
				58 (26.03.98)	276	C2	ZDV + ddC + SQV (S)	18	<3
33	M	28	IDU	59 (19.03.98)	90	C3	none	–	24
				60 (30.04.98)	239	C2	ZDV + ddI + RTV + SQV (S)	6	24
34	M	32	IDU	61 (20.10.97)	82	C3	none	–	384
				62 (17.11.97)	ND	C3	none	–	576
				63 (19.02.98)	128	C3	ZDV + 3TC (S)	14	12
35	F	54	ST-He	64 (21.11.97)	42	C3	none	–	18
				65 (05.03.98)	190	C3	ZDV + ddC + SQV (S)	15	3
36	M	39	ST-Ho	66 (04.12.97)	45	C3	ZDV + ddC + SQV (NS)	34	48
				67 (08.04.98)	112	C3	d4T + ddI + IDV (S)	18	18
37	M	44	ST-He	68 (04.12.97)	4	C3	ZDV + 3TC + SQV (NS)	35	72
				69 (02.04.98)	28	C3	d4T + ddI + IDV (S)	17	9
				70 (14.05.98)	22	C3	d4T + ddI + IDV (NS)	23	6
38	M	30	IDU	71 (15.01.98)	27	C3	ZDV + 3TC + SQV (NS)	42	96
				72 (05.03.98)	187	C3	d4T + ddI + RTV (S)	7	3

1	2	3	4	5	6	7	8	9	10
39	M	33	ST-Ho	73 (12.02.98)	4	C3	none	–	144
				74 (26.03.98)	49	C3	ZDV + ddC + SQV (S)	6	3
				75 (07.05.98)	60	C3	ZDV + ddC + SQV (S)	12	6
40	M	33	IDU	76 (17.02.98)	33	C3	none	–	9
				77 (09.04.98)	166	C3	d4T + ddI + RTV (S)	8	12
41	F	24	IDU	78 (05.03.98)	70	C3	d4T + 3TC + RTV (NS)	25	48

[a] Risk group: IDU – injecting drug users, ST-He – sexually transmitted, heterosexuals, ST-Ho – homosexuals.
[b] Clinical classification according to CDC criteria, 1993 revised classification system for HIV infection[10].
[c] Antiretroviral therapy: ZDV – zidovudine, 3TC – lamivudine, ddC – zalcitabine, ddI – didanosine, d4T – stavudine, SQV – saquinavir, IDV – indinavir, RTV – ritonavir. Clinical effect of the therapy: S – successful, NS – unsuccessful.
[d] Duration of the treatment with the indicated set of drugs.

influence of successful combined antiretroviral therapy on the IFN level could be directly observed only when at least two serum samples were examined for IFN activity, and furthermore high IFN levels were found before therapy or during unsuccessful therapy. For 8 patients such observations were performed. In 7 cases (patients no. 22, 34, 35, 36, 37, 38 and 39) the decreases of IFN serum levels were observed after 6–18 weeks of successful therapy. One of the patients (no. 33), despite of 6 weeks of successful treatment, had an unchanged level of IFN in serum (Table 1).

To evaluate relationship between IFN level and clinical status of the patients, the HIV^+ patients under study were divided into grups depending on their CDC classification (reflecting HIV infection progression) and clinical effects of the antiretroviral therapy (Table 2). It was found that the successful combined therapy of patients with CDC class C2–C3 caused significant decline of the IFN levels in their sera. In contrast, unsuccessful therapy did not significantly affect high IFN levels.

The high antiviral IFN levels in HIV^+ patients were found to be neutralized by the polyclonal anti-HuIFN-α serum, but not by polyclonal anti-HuIFN-γ serum (Table 3). The IFN serum samples were also sensitive to pH 2 treatment, although not all of the antiviral IFN activity could be inactivated by acid treatment (Table 3).

Table 2. Effects of the combined antiretroviral therapy on IFNs levels in the sera of HIV^+ patients

Patients	Number of sera tested	IFN level (U/ml)			Significance[a]	
		mean±SD	median	range	P[b]	P[c]
HIV^-	23	3.91±2.97	3	<3–12	–	–
HIV^+, CDC A1-A2:						
before therapy	10	4.10±3.25	3	<3–12	NS	–
successful therapy	18	5.56±4.91	4	<3–18	NS	NS
unsuccessful therapy	7	9.00±7.75	6	3–24	NS	NS
HIV^+, CDC A3:						
before therapy	5	11.60±13.94	6	<6–36	NS	–
successful therapy	5	6.60±3.29	6	3–12	NS	NS
unsuccessful therapy	9	6.78±7.36	3	<3–24	NS	NS
HIV^+, CDC C2-C3:						
before therapy	6	192.50±236.06	84	9–576	p=0.00031	–
successful therapy	12	8.83±7.07	7.5	<3–24	p=0.03258	p=0.00761
unsuccessful therapy	6	49.00±32.29	48	6–96	p=0.00057	NS

[a] Mann-Whitney non-parametric U test was used for determination the statistical significance. In the test all experimental data lower than the sensitivity level of the IFN assay (3 U/ml) were considered as 1.0.
[b] Significant differences of IFNs levels from the group HIV^- individuals.
[c] The comparisons inside each group of HIV^+ patients were performed. Significant differences with the reference to the subgroups before therapy are shown.
NS – not significant.

Table 3. Effects of the neutralization of IFN activity of the AIDS sera by anti-IFNs animal sera and by the acid treatment at pH 2

Serum no.	IFN activity (U/ml) after treatment:				
	none	anti-IFN-α	anti-IFN-γ	dialysis at pH 2 and re-dialysis at pH 7	dialysis at pH 7
39	16	<8	16	<6	18
61	384	<8	192	48	192
62	576	8	576	72	576
64	12	<8	12	ND	ND
66	48	12	48	ND	ND
68	16	<8	16	ND	ND
71	36	<12	36	6	48
73	144	<12	144	48	144
78	48	<12	24	ND	ND

ND – not done.

Discussion

In plasma or sera of control HIV^- individuals little or none of the IFN antiviral activity can be detected. The IFN levels, not exceeded 12–20 U/ml, may be considered as physiological because they are found in normal individuals[4, 12, 26, 38, 50]. After i.v. infusion of 10^7 U/m^2 of rIFN-α2b, peak serum levels in the range of 500–600 U/ml were obtained within 15–30 min, and then IFN levels returned to baseline values by 4 h. Following i.m. or s.c. injection of that IFN, peak levels up to 100–200 U/ml persisted for 8–12 h[28, 43]. After i.v. administration of 6×10^6 U of rIFN-β, the serum levels of the IFN exceeded 300 U/ml immediately after injection and then decreased rapidly and returned to baseline in around 8 h after i.v.[41] Therefore, high levels of IFNs, persisting for months or even for years, indicate a pathological process.

The high levels of al-IFN-α in plasma have been observed in patients with autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) [39, 42, 48, 49] or AIDS, where up to 300–1000 IFN U/ml have been detected[13, 20, 29, 37, 38, 44]. The enhanced IFN levels may be due to a prolonged stimulation of the IFN-producing cells with HIV-infected cells[7, 16] or with viral proteins such as gp120[1, 6]. It is also possible that IFN is accumulated as a result of impaired binding to receptors or decrease of receptor number[30].

The enhanced serum IFN levels (above 20 U/ml) were observed in AIDS patients with advanced stage of the disease (CDC class C3 or A3, with very low $CD4^+$ lymphocyte count; Table 1). These patients were taken into consideration when observations of the effects of the antiretroviral therapy on IFN levels were performed. Because the results of the therapy were often not satisfactory, two groups of patients (representing successful and unsuccessful therapy) were analyzed (Table 2). The successful combined antiretroviral therapy resulted in the clinical improvement including the increase of the $CD4^+$ lymphocyte number and the decrease of viremia[9, 18, 33]. It was found that successful therapy led also to a significant decrease of enhanced IFN levels (Table 2). The effect was not observed in the cases of unsuccessful therapy. It suggested that one of the effects of the combined therapy was at least a partial recession of immune dysfunction. It remains to be evaluated whether this effect is permanent or transient.

In our previous works[37, 38] we described two patterns of interferon response in HIV-infected patients. The ability of peripheral blood leukocytes to produce IFN-α or IFN-γ after stimulation with NDV or PHA, and IFN level in plasma were considered. Pattern I (lack or low levels of IFN in plasma and high levels of induced IFNs) was characteristic for HIV^+ patients in good clinical state and resembling HIV^- individuals. Pattern II (high levels of IFN in plasma and low levels of induced IFNs) was connected with the progression of infection to AIDS. It was pointed out that IFN measurements were useful in monitoring progression of the disease. The results of this study indicate that measurement of the IFN level in serum may also be useful in monitoring effects of the antiretroviral therapy. Evaluation of IFN level in serum should be performed as systematically as examination of the $CD4^+$ cell count and viremia are done. These three parameters complement one another. The viremia value shows intensity of HIV replication. Analysis of the $CD4^+$ lymphocyte numbers indicates how extensive irregularities of the immune system functioning have been developed by the virus. The IFN abnormalities reflect current dysfunction of the cytokine network being an important part of the immune status.

The interferon in sera of AIDS patients was identi-

fied as IFN-α consisting of acid-labile and acid-stable forms (Table 3). The exact nature of "acid-labile IFN–α" have not been recognized yet[35]. It was shown that acid stability of IFN-α in serum of HIV-infected patients decreased in time and transition to acid lability was associated with progression to AIDS[5]. Therefore, the high al-IFN-α levels, persisting for months or years, were found to be characteristic markers of the dysregulation of the immune system.

In conclusion, the antiviral, bioactive al-IFN-α detected in plasma and/or sera is an important surrogate marker of the progression of HIV infection to AIDS. Detection of al-IFN-α may be useful for monitoring the combined antiretroviral therapy of AIDS that included reverse transcriptase and viral protease inhibitors.

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