Original Article

The Effect of the Different Treatment Protocols on Virological and Immunological Responses in Patients with HIV/AIDS

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SUMMARY: This study analyzed the differences between the virological and immunological responses in patients with HIV/AIDS subjected to different treatment protocols. The cases treated with HAART were divided into groups on the basis of treatment protocols. The groups were evaluated with respect to the differences by comparing the virological and immunological responses prior to treatment and at 12 and 24 weeks of therapy. Six different treatment protocols were applied in the treated patients. As the largest clusters, the lopinavir/ritonavir-based patient group (Group 1, $n = 29$) and efavirenz-based patient group (Group 2, $n = 18$) were compared. The mean CD₄ and HIV-RNA values of Groups 1 and 2 were 184 and 243 h/μl and 422,266 and 317,684 copies/ml, respectively. At 24 weeks of treatment, the HIV-RNA levels were below detectable values in 86% and 78% of the patients in Groups 1 and 2, respectively ($p > 0.001$). The striking outcomes observed in this study demonstrated that the pretreatment HIV-RNA level, CD₄ value, gender, age, and protease inhibitor- or non-nucleoside reverse transcriptase inhibitor-based combined treatment protocols do not cause a significant difference and that patient compliance to treatment is the most important factor associated with treatment success.

INTRODUCTION

The human immunodeficiency virus (HIV), which has been first identified in 1981 in the USA, is the causative agent of acquired immune deficiency syndrome (AIDS) and is currently the leading cause of morbidity, mortality, and social burden in millions of people. The treatment process, which was started by the introduction of reverse transcriptase inhibitors in 1987, provided satisfactory outcomes by consecutive discovery of 2 new-generation medicine groups such as non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) in 1995 and allowed the use of combination treatment, which was effective against the continuously evolving virus. Following the administration of combination protocols including 2 or more medicine groups since 1996, the application of highly active antiretroviral therapy (HAART) was initiated as a milestone in the treatment of HIV infection. The life expectancy and quality increased because of the administration of the new treatment protocols. This development led to the questioning of the superiority of this treatment over others with regard to the quality of life, which depended on the side effects and treatment compliance of the patients (1,2,3,11).

The use of new medications in clinical practice requires chemoprophylaxis procedures against opportunistic infections and preparation of treatment guidelines that define the side effects and drug interactions. In ad-

dition, there is a need to update previous medication guidelines upon the introduction of new drugs and determination of new treatment protocols (1–3).

Our clinic is a large medical center that follows-up the cases with HIV/AIDS in the metropolitan Istanbul. This study aimed to determine whether different treatment protocols administered according to the updated medication guidelines led to different treatment results with regard to virological and immunological responses of 75 patients diagnosed with HIV/AIDS in our clinic between January 2002 and April 2010.

MATERIALS AND METHODS

A total of 115 patients who visited the Istanbul Training and Research Hospital, Istanbul, Turkey, for HIV/AIDS infection between January 2002 and April 2010 were retrospectively evaluated. The study was approved by the Ethics Committee of The Istanbul Education and Research Hospital. The patient data were obtained from the digital records and patient follow-up files. The classification of the cases was performed according to the criteria of Central for Disease Control and Prevention (CDC) (2,3).

HIV/AIDS was diagnosed on the basis of the results of ELISA positivity of anti-HIV antibodies and Western blot analysis. The CD₄ and CD₈ counts and HIV-RNA levels were determined using Becton Dickinson Immunocytometry Systems (San Jose, CA, USA) and the Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 test (Indianapolis, IN, USA), respectively. The demographic data of the patients such as the age and gender, administered treatment protocols and their durations, CD₄ and CD₈ counts determined before treatment and at 12 and 24 weeks after treatment initiation, and results of antibiotic resistance tests against the

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administered antiretroviral drugs were recorded in the patients' data table. The 64 treated cases were divided into groups according to the treatment durations and treatment protocols. The groups were evaluated by comparing the differences in CD₄ and CD₈ counts determined before treatment and at 12 and 24 weeks after treatment initiation as well as the virological and immunological responses. The patients who did not receive HAART treatment depending on the CD₄ value and continuous follow-ups were excluded from the study.

Statistical evaluation of the study data was performed using SPSS-13 (SPSS Inc., Chicago, IL, USA). The patient data related to CD₄ and HIV-RNA levels obtained before treatment and at 12 and 24 weeks after treatment initiation were expressed in terms of mean $\pm$ standard deviation, median (50th percentile), least-highest values, and *p* values. Age, gender, and treatment protocols were evaluated as normally distributed variables, while CD₄ and HIV-RNA levels obtained at baseline, pretreatment, and 12 and 24 weeks after treatment initiation were evaluated as non-normally distributed variables. The comparison was performed using Student's *t*-test, Bonferroni and General Linear Model for normally distributed variables, 2-way analysis, and repeated measurements. All the statistical tests were applied bidirectionally, and *p* value of <0.001 was considered statistically significant.

RESULTS

Our records revealed that a total of 115 patients were diagnosed with HIV/AIDS in our clinic between January 2002 and April 2010.

Among these, 64 patients who received treatment for at least 24 weeks were included in this study to evaluate the treatment efficacy. A total of 11 cases with treatment duration shorter than 24 weeks, cases without regular follow-ups, and followed-up cases without treatment were excluded from the study. Six different protocols were applied to the patients for whom treatment was initiated (Table 1). The lopinavir/ritonavir-based patient group was the largest cluster (Group 1, *n* = 29) and the efavirenz-based patient group was the second largest cluster (Group 2, *n* = 18). Both these groups were compared with regard to the differences in the virological and immunological responses.

In Group 1, the increased CD₄ values and reduced HIV/RNA levels detected at 12 and 24 weeks after treatment initiation were statistically significant with regard to the immunological response (*p* < 0.001) and virological response (*p* < 0.001), respectively. The HIV-RNA levels were detectable at 24 weeks after treatment initiation in 4 of the 29 patients (13.8%). However, the effect of baseline HIV-RNA levels, gender, and age at treatment initiation on virological response at 12 and 24 weeks after treatment initiation was statistically insignificant (*p* > 0.001). The virological and immunological responses of Groups 1 and 2 are presented in Table 2.

The long-term follow-ups of 4 patients from Group 1 with detectable HIV-RNA level at 24 weeks after treatment initiation revealed patient noncompliance to treatment; hence, the treatments of these patients were continued after increasing their compliance to therapy. Subsequent follow up examinations showed less than detectable HIV-RNA levels at the 24th week in 2 of those patients. The HIV-RNA test was negative after 48 weeks in 1 of the patients. Resistance development was found in 1 patient and treatment was terminated according to the result of the resistance test. The age of Group 2 patients at treatment initiation was 38.1 ± 2.1 years. The increased CD₄ values at 12 and 24 weeks after treatment initiation were statistically significant with regard to the immunological response (*p* < 0.001). The effect of pretreatment CD₄ value, age at treatment initiation, and gender on the immunological response at 12 and 24 weeks after treatment initiation was statistically insignificant. However, the reduced HIV-RNA levels at 12 and 24 weeks after treatment initiation were statistically significant (*p* < 0.001). Four patients with HIV-RNA levels over the detectable limit at 24 weeks after treatment initiation showed insufficient virological response. The effect of baseline HIV-RNA level, gender, and age at treatment initiation on the virological response at 12 and 24 weeks after treatment initiation was not significant (*p* > 0.001). Analysis of these 4 Group 2 patients with insufficient virological response demonstrated noncompliance of these patients to treatment. Hence, their treatment was continued after raising their compliance to therapy. Follow-up was terminated in 1 of the patients owing to relocation. In the other 3 patients, the HIV-RNA level tested 12 weeks later was

Table 1. The division of the treated patients for at least 24 weeks based on treatment protocols

Treatment protocol	Content	Posology (po)	Case number	Case percentage (%)
Protocol ¹⁾	LPV-RTV + 3TC-ZDV	(2 $\times$ 3) + (2 $\times$ 1)	29	45.3
Protocol ²⁾	EFV + TNF-FTC	(1 $\times$ 1) + (1 $\times$ 1)	18	28.1
Protocol ³⁾	EFC + 3TC-ZDV	(1 $\times$ 1) + (2 $\times$ 1)	8	12.5
Protocol ⁴⁾	IDV + 3TC-ZDV	(3 $\times$ 2) + (2 $\times$ 1)	5	7.8
Protocol ⁵⁾	LPV-RTV + TNF-FTC	(3 $\times$ 1) + (2 $\times$ 1)	1	1.6
Protocol ⁶⁾	NVP + 3TC-ZDV	(2 $\times$ 1) + (2 $\times$ 1)	3	4.7
Sum			64	100

¹⁾: Treatment Protocol: lopinavir 133 mg-ritonavir 33 mg + lamivudine 150 mg-zidovudine 300 mg [LPV-RTV + 3TC-ZDV].

²⁾: Treatment Protocol: efavirenz 600 mg + tenofovir 300 mg-emtricitabine 200 mg [EFV + TNF-FTC].

³⁾: Treatment Protocol: efavirenz 600 mg + lamivudine 150 mg-zidovudine 300 mg [EFC + 3TC-ZDV].

⁴⁾: Treatment Protocol: indinavir sulfate 400 mg + lamivudine 150 mg-zidovudine 300 mg [IDC + 3TC-ZDV].

⁵⁾: Treatment Protocol: lopinavir 133 mg-ritonavir 33 mg + tenofovir 300 mg-emtricitabine 200 mg [LPV-RTV + TNF-FTC].

⁶⁾: Treatment Protocol: nevirapine 200 mg + lamivudine 150 mg-zidovudine 300 mg [NVP + 3TC-ZDV].

Table 2. The median values of the immunological and virological responses in Protocol¹⁾, and Protocol²⁾

Treatment period		Protocol ¹⁾ (n = 29)	Protocol ²⁾ (n = 18)	<i>p</i>	Protocol ³⁾ (n = 8)	Protocol ⁴⁾ (n = 5)	Protocol ⁵⁾ (n = 1)	Protocol ⁶⁾ (n = 3)
		38	44	0.083	34	51	52	41
CD ₄ (h/ μ l)	0 week	183	242	0.001	265	111	183	289
	12 week	313	342	0.001	417	363	795	344
	24 week	422	427	0.001	493	381	511	543
HIV-RNA (copies/ml)	0 week	196,856	317,684	0.001	365,436	163,289	1,131,736	1,222,966
	12 week	5,485	24,838	0.001	26,381	18,234	832	59
	24 week	2,691	251,111	0.001	13,952	4,200	0	0

Table 3. The patient status based on virological response, treatment compliance, and resistance

Patient (n)		The patients with HIV-RNA < 50 (n) at 24th week	Noncompliant patients to treatment (n)	The patients with HIV- RNA < 50 (n) due to raised treatment compliance	Resistant case (n)
Protocol ¹⁾	29	25	4	3	1
Protocol ²⁾	18	14	4	4	—
Protocol ³⁾	8	4	4	2	2
Protocol ⁴⁾	5	4	1	0	1
Protocol ⁵⁾	1	1	—	—	—
Protocol ⁶⁾	3	3	—	—	—

The definitions of protocols at the Table 1, page 340.

below the detectable limit.

The pretreatment CD₄ values of the Group 1 patients (mean 186 h/ μ l) were lower than those of the Group 2 patients (mean 242 h/ μ l). This difference in the CD₄ baseline values reached 29 h/ μ l in comparison with that determined at 12 weeks after treatment initiation and completely disappeared at 24 weeks after treatment initiation. Nevertheless, this difference between the elevation slopes of the CD₄ values was not statistically significant ($p > 0.001$). Similarly, the pretreatment HIV-RNA levels of the Group 1 patients (mean 196,856 copies/ml) were lower than those of the Group 2 patients (mean 317,684 copies/ml). At 12 weeks after treatment initiation, comparison of the HIV-RNA levels of the 2 groups revealed that the mean difference in the reduced HIV-RNA levels was 1-log higher for Group 1; however, the difference disappeared at 24 weeks after treatment initiation. No statistically significant difference was found between the protocols with regard to the reduced HIV-RNA levels ($p > 0.001$).

Treatment noncompliance was observed in 4 of the 29 patients (13.8%) in Group 1 and in 4 of the 18 patients (22.2%) in Group 2. No statistically significant difference was encountered between the 2 groups with regard to patient compliance, age at treatment initiation, and gender ($p > 0.001$). The data of the patients treated with other treatment protocols in our clinic are presented in Table 2.

The patient status based on virological response, treatment compliance, and development of resistance to the administered treatment at the 24th week with respect to the treatment protocols is summarized in Table 3.

DISCUSSION

Antiretroviral therapy (ART) aims at reducing the viral burden and improving the immunological func-

tions and consequently decreasing the morbidity and mortality owing to infection for a better quality of life. The development of HAART protocols brought various medication combinations. The combination regimens for ART may be NNRTI-based (1NNRTI + 2 NRTI) or PI-based (1–2 PI + 2 NRTI) (1–4). The present study particularly evaluated the administration of PI-based combination involving Kaletra[®] (lopinavir 133 mg + ritonavir 33 mg) and Combivir[®] (lamivudine 150 mg + zidovudine 300 mg) and NNRTI-based combination involving Stocrin[®] (efavirenz 600 mg) and Truvada[®] (tenofovir 300 mg + emtricitabine 200 mg).

Based on 19% of the patients among the 115 patients diagnosed with HIV/AIDS who did not require treatment, our retrospective study demonstrated the following: the patients could recognize AIDS without observing AIDS-defining clinical symptoms; knowledge about this illness had increased; and AIDS could be detected earlier by medical screenings.

Group 1 (PI + NRTI) comprised the largest patient number (29 patients), and the protocol followed included the medications Kaletra[®] (lopinavir 133 mg + ritonavir 33 mg) and Combivir[®] (lamivudine 150 mg + zidovudine 300 mg), which were accredited in 2001 in Turkey. This PI-based regimen was found to be the first choice of treatment protocol recommended by the updated guidelines in our clinic, which comprised follow-ups of the HIV patients in 2002 (2–5).

The second treatment protocol involving a NNRTI-based combination was administered to 18 patients who formed the second largest patient group (Group 2). This protocol included the medications Stocrin[®] (efavirenz 600 mg) and Truvada[®] (tenofovir 300 mg + emtricitabine 200 mg), which were accredited in 2005 in Turkey by the Ministry of Health, although the administration of these medications was globally introduced in 2004. This 5-year-difference in the accreditation of medications

may explain the remarkable variance in the patient number between the 2 protocols (6,7).

In the present study, we evaluated the treatment efficacy in terms of virological and immunological responses and demonstrated that the CD₄ values at the 24 weeks after treatment initiation were significantly increased in comparison with the pretreatment CD₄ values and that the HIV-RNA levels were reduced below the detectable limit in most patients in both the treatment regimens (17). Furthermore, no difference was observed in these patients' responses to the treatment protocols. A review of the literature on the efficacy of the lopinavir/ritonavir-based protocol demonstrated that 25%–35% and 62%–75% of patients became HIV-RNA negative at 12 and 24 weeks after treatment initiation, respectively. In the present study, 86.2% of our patients became HIV-RNA negative at 24 weeks after treatment initiation and a greater treatment success rate was reached (14–18).

In those previous studies, treatment resistance was detected in patients who exhibited no virological response, whereas in the present study, all our unresponsive patients demonstrated treatment noncompliance. HIV-RNA negativity was achieved in 24 weeks after increasing the treatment compliance of those patients, and resistance development was detected only in 1 of the patients during follow-up examinations. Because the use of a resistance test is limited and expensive in Turkey, this investigation could not be performed for each unsuccessfully treated case. Only patients with a high HIV-RNA level in whom treatment noncompliance was found and who were re-evaluated 12 weeks after achieving treatment compliance were subjected to the resistance test.

During the weeks following viral suppression by an effective ART, an increase in the CD₄ value by 50 cells/mm³ is expected, and during each following year, the CD₄ value is known to increase by 50–100 cells/mm³ (2,4). The present study was based on the baseline CD₄ values and HIV-RNA levels, and the occurrence of AIDS-defining symptoms during the hospital visit was ignored. However, it was previously reported that the mean pretreatment CD₄ values (183 cells/mm³ for PI-based treatment and 242 cells/mm³ for NNRTI-based treatment), which significantly suppress the immune system, did not negatively affect the treatment success (6,12). Although it has been observed in various studies that NNRTIs are more effective in suppressing the viral load than PIs, the discontinuation of medication has been noted to be more common among patients taking NNRTIs owing to side effects such as hyperlipidemia and diarrhea (5). However, none of the patients in our study group discontinued therapy owing to drug side effects.

The objective of effective ART is to achieve a 1-log reduction in the HIV-RNA level in the first month of treatment and a negative or <50 copies/ml viral load in at 16–24 weeks after treatment initiation (9). In the present study, we found that the HIV-RNA quantitative test values and the detectable lower and upper limits of HIV-RNA values determined by improved PCR technology varied. The detectable HIV-RNA limit was 400–100,000 copies/ml in 2002–2004, whereas it reached 50–12,000,000,000 copies/ml in 2004–2006.

The patients under the PI-based treatment protocol exhibited a mean baseline HIV-RNA level of 196,856 copies/ml, whereas those under the NNRTI-based treatment protocol exhibited a value of 317,684 copies/ml, indicating that the mean baseline values should be considered in the evaluation of HIV-RNA levels in such retrospective studies. This difference between the 2 groups decreased at 12 weeks after treatment initiation and became equal at 24 weeks after treatment initiation as a result of regular treatment. The statistically insignificant difference could be owing to the limited number of patient, and a further study with a larger number of patients could determine the statistical difference.

Among the patients under the 3rd, 5th, and 6th NNRTI-based treatment protocols, virological unresponsiveness was found at 24 weeks after treatment initiation in 50% ($n = 4$) of the patients under the 3rd treatment protocol only. Among the patients under the PI-based treatment protocol (4th treatment protocol), resistance development was encountered in 50% ($n = 2$) of patients, whereas virological unresponsiveness was found at 24 weeks after treatment initiation in 20% ($n = 1$) of them. These patients were evaluated for resistance development at 48 weeks after treatment initiation after achieving patient compliance but were not evaluated statistically because of the limited patient number.

The CD₄ values and HIV-RNA levels of the patients at 24 weeks after treatment initiation showed that the virological and immunological responses during this period were statistically significant and equal, independent of the pretreatment CD₄ values and HIV-RNA levels that determine the clinical stage of the disease. Kocagül et al. (14) had demonstrated that patients with CD₄ < 100 cells/mm³ have a lower immunological response than those with CD₄ > 100 cells/mm³.

Various studies, which compared NNRTI- and PI-based regimens as the initial treatment regimen, have reported that the virological response of patients under NNRTI-based treatment regimen is higher (9,10,13–14). Although the main factor for treatment failure has been reported to be resistance development in Europe and the USA, in the present study, treatment noncompliance was noted to be the main reason for treatment failure (10,11).

Patient compliance is related to the patient's and physician's consensus on the administration of a treatment regimen. This signifies the regulation of the patient's life-style or creation of a new lifestyle. At the treatment initiation stage, the physician should determine the treatment course along with the patient and explain the importance of regular medication in treatment success. The lifestyle of the patient should be taken into account in regulating the medication regimen, and continuous communication with the physician regarding the side effects and regulation of the details that affect the daily life could increase both patient-physician confidentiality and treatment compliance. In the treatment protocols applied via 2 × 1 posology in practice, even skipping of 1 dose over 3 weeks could reduce the effective treatment dosage to 95% (7–9). The patient should be instructed never to skip a dose in such a limited tolerance interval. Studies on treatment compliance have demonstrated that the desire to use medication as well as

high levels of socioeconomic status and education primarily increase treatment compliance. Furthermore, treatment for alcoholism, drug addiction, and depression is suggested in patients with these problems before the administration of HAART.

Some clinical studies have found that the dose-skipping frequency increases with the increasing number of daily medicines (17–22). In such cases, treatment success depends on completely regular medication use. In the present study, the argument that the treatment failure rate increases with the increasing number of daily medicines could not be verified. The PI-based treatment group with a high number of medicines (4 + 2) demonstrated a lower rate of viral unresponsiveness than the NNRTI-based treatment group with a low number of daily medicines. This result may be attributed to the specific features of the patients under PI-based regimens, such as low CD₄ values, advanced HIV-related diseases, or opportunistic infections, which could have forced them to take their medicines regularly.

Treatment noncompliance is the major factor in the development of acquired drug resistance. However, in the present study, no resistance was encountered in the NNRTI-based treatment group with a higher rate of treatment noncompliance (22.2%), whereas resistance development was found in 1 patient in the lopinavir/ritonavir-based group with a lower rate of treatment noncompliance (13.79%).

In recent years, although many studies have evaluated the effect of gender and age on the virological and immunological responses (5), no statistically significant findings have been reported. Similarly, in the present study, gender and age at treatment initiation, as independent variables, presented no statistically significant effect on treatment compliance and treatment response at 24 weeks after treatment initiation.

In conclusion, in the present study, no significant difference was found with regard to the virological and immunological responses in patients with HIV/AIDS under different treatment protocols, and treatment compliance of patients was noted to be the most important factor for treatment success. Unlike previous reports indicating that treatment resistance is the main factor for treatment failure in Europe and the USA (23,24), in the present study, treatment noncompliance resulted in treatment unresponsiveness rather than primary resistance. However, the probability of resistance with infectious origins is rising owing to the rapidly increasing new cases, and early detection of resistance by performing tests sooner should never be ruled out because it may prevent a potential treatment failure and increase the opportunities for successful treatment.

Conflict of interest None to declare.

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