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Comparison of Three Different Anti-retroviral Regimens in Terms of Immunological and Virological Response

Üç Farklı Anti-retroviral Tedavi Rejiminin İmmünolojik ve Virolojik Açıdan Karşılaştırılması

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Abstract

Introduction: After introduction of highly active anti-retroviral treatment (HAART), the mortality and morbidity rates among HIV/AIDS patients have been reduced. CD4+ T cell and HIV RNA measurement is important in the follow-up during the treatment. The aim of this study was to evaluate three different ART regimens in terms of immunological and virological response.
Materials and Methods: The study was designed as a retrospective cohort study. Treatment-naive adult HIV/AIDS patients who applied to our outpatient clinic between 2011 and 2017 were included in this study. Treatment regimens included two nucleoside reverse transcriptase inhibitors (NRTI) with either one of a non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) or protease inhibitor (PI). CD4+ T cell counts and HIV RNA levels were analysed at 1st month, 3rd month, 6th month and 12th month.
Results: Sixty-three patients (87% were male) aged 43±13 (min 19, max 66) years were included in this study. Fourteen (22.2%) received NRTI and INI treatment (INI group), 18 (28.6%) received NRTI and PI (PI group) and 31 (49.2%) received NRTI and NNRTI (NNRTI group). Immunologically, the PI group was the most successful while NNRTI group was the least successful. INI group had significantly higher immunological response rate than NNRTI group in the first three months. The treatment was more successful in INI group in terms of virological response than in PI and NNRTI groups in the first three months. However, at the end of 6 and 12 months, no statistically significant difference was observed between the groups, neither immunologically nor virologically.
Conclusion: Our results have shown that all regimens were effective at the end of 12 months. Among the combinations available, the most appropriate one should be selected individually.
Keywords: CD4, virological, immunological, anti-retroviral treatment, dolutegravir

Öz

Giriş: Yüksek etkili anti-retroviral tedavi [highly active anti-retroviral treatment (HAART)] sayesinde HIV/AIDS hastalarının morbidite ve mortalite oranları azalmıştır. Tedavinin takibinde CD4+ T hücre and HIV RNA ölçümleri önemlidir. Bu çalışmanın amacı üç farklı anti-retroviral tedavi (ART) rejimini immünolojik ve virolojik yanıt açısından değerlendirmektir.
Gereç ve Yöntem: Çalışma retrospektif kohort çalışması olarak planlandı. 2011-2017 yılları arasında polikliniğimize başvuran tedavi naiv yetişkin HIV/AIDS olguları çalışmaya dahil edilmiştir. Tedavi rejimleri; iki nükleozid revers transkriptaz inhibitörü (NRTİ) ile birlikte bir non-nükleozid revers transkriptaz inhibitörü (NNRTİ) ya da integraz inhibitörü (İNİ) ya da proteaz inhibitörü (Pİ) içermekteydi. Hastaların CD4+ T hücre sayıları ve HIV RNA seviyeleri birinci ay, üçüncü ay, altıncı ay ve 12. ayda analiz edilmiştir.
Bulgular: Yaşları 19-66 arasında değişen ve %87'si erkek olan toplam 63 hasta çalışmaya dahil edilmiştir. Hastaların on dördü (%22,2) NRTİ ve İNİ tedavisi (İNİ grubu), 18'i (%28,6) NRTİ ve Pİ tedavisi (Pİ grubu), 31'i (%49,2) NRTİ ve NNRTİ tedavisi (NNRTİ grubu) almaktaydı. İmmünolojik olarak Pİ grubu en başarılı, NNRTİ grubu ise en başarısız grup olarak bulundu. İNİ grubunda ilk üç ayda NNRTİ grubuna göre daha yüksek immünolojik yanıt oranı saptandı. İNİ grubunun ilk üç ayın sonunda Pİ ve NNRTİ gruplarına göre virolojik olarak daha başarılı olduğu bulundu. Bununla birlikte, 12. ayın sonunda, immünolojik veya virolojik olarak gruplar arasında anlamlı istatistiksel fark gözlenmedi.
Sonuç: Sonuçlarımız tüm tedavi rejimlerinin 12 ayın sonunda etkili olduğunu göstermiştir. Mevcut kombinasyonlar arasında kişiye en uygun olanı seçilmelidir.
Anahtar Kelimeler: CD4, virolojik, immünolojik, anti-retroviral tedavi, dolutegravir

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Introduction

Human immunodeficiency virus (HIV) infection is an important infectious disease caused by HIV[1]. Acquired immune deficiency syndrome (AIDS) is a condition where opportunistic infections may occur due to immune system defects predominantly in CD4+ T cells. Although the prevalence of HIV is low (<1%) in Turkey, the increase in the number of newly diagnosed cases through years is remarkable[2].

In 1987, first-generation anti-retroviral agents (ART) were introduced and by 1996, new generation anti-HIV drugs with different mechanism of actions -namely highly active ART (HAART) consisting of at least three drugs in combination- were introduced. Highly active ART provides a significant decrease in viral load and increase in CD4+ T cell counts, thus, AIDS-related mortality decreases and life quality of patients improves[3,4].

Currently, there are more than 25 anti-HIV drugs that are grouped in six majorclasses[5]. Most of these drugs are used in combinations to achieve maximum efficiency. Various studies have shown that if one of a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitors (PI) or integrase inhibitors (INI) is combined with two potent nucleoside reverse transcriptase inhibitors (NRTI), the treatment success is quite high in treatment-naive cases[5]. Factors such as co-morbidities, viral load, baseline antiviral drug sensitivity of the virus, adverse events, dose intervals, drug-drug interactions, patient compliance, and drug accessibility should be taken into account when deciding on the most appropriate drug choice[6].

Viral load and CD4+ T cell count are the two important markers of ART response and HIV disease progression. Both have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression[7].

HIV infects CD4+ T cells and CD4+ T cell count drops gradually, resulting in weakened immune system. Therefore, it is important to monitor CD4+ T cell count and percentage in HIV/AIDS cases during follow-up[3].

In terms of treatment follow-up, viral load and CD4+ T cell counts should be monitored in all HIV-positive cases. Since HIV drug options are limited in Turkey and studies comparing drug regimens in Turkish patients are inadequate, we aimed to compare immunological and virological responses between three different anti-retroviral regimens by using NNRTI, PI or INI in combination with NRTI.

Materials and Methods

Patient Group

Treatment-naïve HIV/AIDS patients over 18 years of age were included in this study. Pregnant women, treatment-experienced patients, patients without compliance and/or who left follow-up were excluded.

Data of all HIV/AIDS patients who were treated with different ART regimens between 2011 and 2017 were analyzed, retrospectively. All patients were treated with NRTI+NNRTI (NNRTI group) or NRTI+PI (PI group) or NRTI+INI (INI group) regimens at least for one year. Anti-retroviral agents combinations included; zidovudin/lamivudine or tenofovir disoproxil fumarate/emtricitabine and abacavir/lamivudine in NRTI class, nevirapine or efavirenz in NNRTI class, lopinavir/ritonavir or darunavir/ritonavir in PI class, raltegravir, dolutegravir or elvitegravir/cobicistat in INI class[5].

Ethics Committee approval had been received at the Tepecik Training and Research Hospital on 02.05.2016 (2016-1). Patients' data were analysed at 1st month, 3rd month, 6th month and 12th month including CD4+ T cell counts and HIVRNA levels. An adequate immunological response was defined as an increase of 50-150 cells/mm^3 in CD4+ T cell counts per year[5,8]. In addition, a stable HIV RNA level of <200 copies/mL was defined as virological response[5].

Laboratory Measurements

HIV RNA was measured as copies/mL by real time polymerase chain reaction performed using Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 device (Roche Molecular Systems, Branchburg, USA). The minimum detection limit for this device was 20 copies/mL. CD4 cell count (mm^3/mL) was measured by Becton-Dickinson FACSCalibur Flow Cytometer device (San Jose, USA).

Statistical Analysis

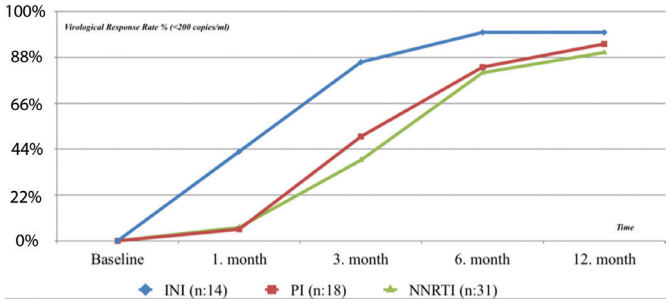
SPSS 18.0 (IBM Corporation, Armonk, New York, United States) software was used for data analysis. Quantitative data were shown as mean±standard deviation and median (maximum-minimum), while categorical data were presented as n (number) and percentage (%). The distribution of qualitative variables were presented as frequency and percentages in cross tables. For comparison of independent categorical data with each other, the Pearson chi-square test and Fisher's exact test were used. For all tests, the margin of error was determined as α=0.05 and tested bidirectionally. The confidence level of 95% was selected and a p value of less than 0.05 was considered statistically significant.

Results

Of 63 naïve HIV/AIDS patients, eight were women (13%) and 55 were men (87%). Seventy-two patients who did not fulfill the inclusion criteria were excluded from the study. The mean age of patients was 43±13 (19-66) years. The mean follow-up time was 4 (1-14) years. Totally, 14 patients were treated with NRTI+INI (22.2%), 18 with NRTI+PI (28.6%) and 31 with NRTI+NNRTI (49.2%). Backbone NRTI were as follows: tenofovir disoproxil fumarate/emtricitabine (88.9%), zidovudin/lamivudine (9.5%) and abacavir/lamivudine (1.6%).

Baseline median CD4+ T cell count was 370±391 (4-2469) cells/mm^3, and the median HIV RNA level was 100.000 (743-10.000.000) copies/mL. Age, median CD4+ T cell counts and HIV RNA levels of the patients for each group are presented in Table 1.

When all the three groups were compared in terms of immunological response (>50 cell/mm^3 increase in CD4+ T cell counts in consecutive measurements), at the end of 12 months, PI group was the most and NNRTI group was the least successful group. Despite the high CD4+ T cell counts at the beginning of the treatment, INI group had a significantly higher increase especially at the end of three months. Immunological response in INI group was significantly higher in NNRTI group in this period (p=0.046). However, there was no other statistically significant difference between the three treatment groups at the end of 12 months and consecutive measurements. Immunological response rate was 82.5% at the end of 12 months among the overall cohort. Immunological responses are presented in Table 2 and Table 3.



Graphic 1. Virological response in three regimens

When the patients were evaluated in terms of virological response, the patients in INI group had a significant advantage over the other groups in the first three months. Overall 86% of patients in the INI group achieved virological response at the 3rd month of treatment, while this was 50% in the PI group (PI vs. INI, p=0.039) and only 39% in the NNRTI group (NNRTI vs. INI, p=0.009). Superiority of the INI group continued at the end of the 6th and 12th months of treatment. While all patients had virological response in INI group, this rate reached over 80% at 6th month and over 90% at 12th month in both other treatment groups (p>0.05). The patients in PI and NNRTI treatment groups had similar virological response rates and no significant difference was found at any evaluated treatment time points. Total virological response in all patients receiving any ART was found to be 85.7% at the 6th month and 93.7% at the 12th month of ART. Virological responses in three treatment groups are presented in Table 4, Table 5 and Graphic 1.

Table 1. Baseline characteristics of the patients

Treatment group	Patient number	Mean age (years)	Median CD4+ T cell count (cells/mm^3)	Median HIV RNA levels (copies/mL)
PI	18	41	262	164.133
NNRTI	31	42	418	100.000
INI	14	46	578	231.000
Total	63	43	370	100.000

PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INI: Integrase inhibitor

Table 2. Immunological response rates (>50 cells/mm^3 increase in CD4+ T cell counts on consecutive measurements)

Time	INI		PI		NNRTI		Total	
	n=14	%	n=18	%	n=31	%	n=63	%
0 - 1. months	10	71.4%	14	77.8%	14	45.2%	38	60.3%
0 - 3. months	13	92.9%	14	77.8%	20	64.5%	47	74.6%
1 - 3. months	9	64.3%	10	55.6%	17	54.8%	36	57.1%
3 - 6. months	6	42.9%	7	38.9%	19	61.3%	32	50.8%
6 - 12. months	7	50.0%	7	38.9%	16	51.6%	30	47.6%
0 - 12. months	12	85.7%	17	94.4%	23	74.2%	52	82.5%

PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INI: Integrase inhibitor

Table 3. Comparison of treatment groups in terms of immunological response

p values			
Time	**INI vs PI**	**INI vs NNRTI**	**PI vs NNRTI**
0 - 1. months	0.496	0.189	0.054
0 - 3. months	0.255	**0.046**	0.516
1 - 3. months	0.892	0.789	0.961
3 - 6. months	0.821	0.408	0.223
6 - 12. months	0.788	0.920	0.573
0 - 12. months	0.404	0.327	0.079

PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INI: Integrase inhibitor

Table 5. Comparison of the regimens in terms of virological response

p values			
Time	**INI vs PI**	**INI vs NNRTI**	**PI vs NNRTI**
1. month	**0.017**	**0.007**	0.698
3. month	**0.039**	**0.009**	0.638
6. month	0.165	0.090	0.567
12. month	a	a	0.530

a: No statistics are computed, PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INI: Integrase inhibitor

Table 4. Virological response (<200 copies/mL)

Time	INI		PI		NNRTI		Total	
	n=14	%	n=18	%	n=31	%	n=63	%
1. month	6	42.9%	1	5.6%	2	6.5%	9	14.3%
3. month	12	85.7%	9	50.0%	12	38.7%	33	52.4%
6. month	14	100.0%	15	83.3%	25	80.6%	54	85.7%
12. month	14	100.0%	17	94.4%	28	90.3%	59	93.7%

PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, INI: Integrase inhibitor

Discussion

In this retrospective study, three different ART groups were compared in terms of immunological and virological response. INI group had significant advantage over NNRTI group at the end of 3 months. However, the efficacy of all the three drug regimens in terms of immunological response was found to be similar at the end of 12 months of ART. Virological response rates were also similar between all the groups at the 6th month and 12th month of therapy, but INI group was superior to other groups in the first three months.

Currently, some of the drugs in our study are considered to be alternative therapy options in recent guidelines with the introduction of single tablet combinations and potent new agents[9]. These alternative agents are still used in developing countries such as Turkey, where there is limited access to all drugs. These data suggest that treatment success still can be achieved by ensuring treatment compliance and proper management of side effects.

When our study was evaluated in terms of immunological response; it was determined that PI group was the most successful and NNRTI group was the least successful group. However, there was no significant difference among all the groups at the end of 12 months. In a study of 1397 naive patients, there was no significant difference in immunological response and clinical outcomes, between patients receiving PI and those receiving NNRTI after five years of follow-up[10]. In another study, the factors that rapidly increase the number of CD4+ T cells above 500 cell mm^3 were found to be younger age, higher baseline CD4+ T cell counts, and initiation of a PI-based regimen instead of NNRTI-based regimen[11]. In our study, PI group was also found to have highest immunological response rate. This may also be due to the baseline lower CD4+ T cell counts in PI-based regimen group compared to other groups. Protease inhibitors are potent, but due to pill burden and availability of drugs with fewer side effects, some of them are recommended as alternative drugs[9].

INI group was relatively new in Turkey during the study period and according to the HIV guidelines; treatment was started regardless of the number of CD4+ T cell counts in the light of two major studies[12,13]. This may be the reason for lower patient number and the median baseline CD4+ T cell counts. Although, the highest baseline median CD4+ T cell counts were in the INI group, the highest immunological response rate was also in this group at the end of the first three months (p=0.046 when compared with NNRTI group).

In our study, INI group was found to be associated with faster virological response, however, at the end of the six and 12 months, there was no significant difference between the groups. In a study comparing raltegravir with efavirenz combined with tenofovir and lamivudine, virological suppression was found to be significantly faster in raltegravir group, but no difference was observed in antiviral efficacy in the raltegravir and efavirenz arms at weeks 24 and 48, in concordance with our results[14].

INI group was also found to be associated with more rapid virological response in another study[15].

We did not find any difference in virological response rates between NNRTI and PI groups at the end of 12 months. In a major clinical trial, 1857 treatment-naive patients were treated with ritonavir-boosted atazanavir or efavirenz either with abacavir-lamivudine or tenofovir-emtricitabine[16]. At the end of 96 weeks, there was no significant difference in virological response between the groups, irrespective of the NRTI group.

In our study, there were three options as backbone; zidovudine/lamivudine, tenofovir/emtricitabine and abacavir/lamivudine. However, the efficacy of these drugs was not compared separately. This can be described as a limitation, but in the study above-mentioned, it was shown that virological success was achieved in 80% of patients irrespective of the used backbone NRTI[16]. Approximately 90% of the backbone regimen in our study was tenofovir/emtricitabine, thus, it was considered that NRTI groups would not affect the outcome of treatment. In our study, total virological response in all groups was found to be 85.7% at six months and 93.7% at 12 months of treatment.

In a study conducted in Turkey with 1306 naive patients, HIV-transmitted drug resistance mutations were investigated and resistance to NRTI, NNRTI and PI were found to be 8.1%, 3.3% and 2.3%, respectively[17]. Recent data have shown that INI resistance mutations were not found in naive HIV-1-infected patients in Turkey. However, treatment-experienced patients had major resistance mutations associated with raltegravir and elvitegravir[18]. These data show that it is a rational approach to select an agent with high genetic resistance barrier such as PI or dolutegravir to obtain treatment success and prevent resistance development in patients with low CD4+ T cell counts until resistance test results are obtained or where resistance testing is not available. In our study, lowest baseline median CD4+ T cell counts were in the PI group. This may be due the above mentioned reason.

Our study has several limitations: it was conducted with a small number of patients in a single center with retrospective design. Baseline CD4+ T cell count and viral load levels were not similar. The agents were evaluated as a group and drug resistance was not specified, in addition, impact of NRTI class was not evaluated.

Conclusion

Our results have shown that all regimens were effective at the end of 12 months. Among the combinations available, the most appropriate one should be selected individually. We also conclude that alternative agents could still be used in developing countries where single tablet regimens are not widely available. For this reason, selection of the appropriate drug for each patient is extremely important and drug compliance must be ensured.

While the number of HIV-positive patients in Turkey is increasing, there are only a very few studies exist analysing the efficacy of ART in Turkish patients. We believe that our findings may be useful for further treatment strategies and researches that will be conducted in our country.

Ethics

Ethics Committee Approval: Ethics Committee Approval had been received at the University of High Sciences, İzmir Tepecik Training and Research Hospital (2016-1).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.S., S.A., H.A., M.T., Ş.K., Concept: U.S., S.A., H.A., M.T., Ş.K., Design: U.S., S.A., H.A., M.T., Ş.K., Data Collection or Processing: U.S., S.A., H.A., M.T., Ş.K., Analysis or Interpretation: U.S., S.A., H.A., M.T., Ş.K., Literature Search: U.S., S.A., H.A., M.T., Ş.K., Writing: U.S., S.A., H.A., M.T., Ş.K.

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