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Examination of the Reasons for Change in Treatment in Patients Infected with Human Immunodeficiency Virus

İnsan İmmünyetmezlik Virüsü ile Enfekte Hastalarda Tedavi Değişiklik Nedenlerinin İrdelenmesi

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Abstract

Introduction: Highly active antiretroviral therapy (HAART) has significantly reduced morbidity and mortality in patients infected with Human immunodeficiency virus (HIV). Despite this success, the sustainability of the initial treatment regimen has become difficult as patients continue the treatment for life. Highly active antiretroviral therapy regimen change may often be necessary due to intolerance/toxicity, pregnancy, comorbidities, difficulty in patient compliance and failure to achieve virological suppression. In this study, it was aimed to examine the reasons for HAART change in patients followed up for HIV/AIDS in Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine Hospital.
Materials and Methods: In this retrospective, cross-sectional, single-center study, 151 patients followed up at Hatay Mustafa Kemal University, Tayfur Ata Sökmen Medical Faculty Hospital for HIV between January 2018 and December 2020 were included in the study.
Results: One hundred-seventeen (77.5%) of the cases were male and 34 (22.5%) were female. The mean age was 39.08±14.2 years (20-83). Treatment changes were made in 35 (23.2%) of the cases. The most common reason for treatment change was intolerance/toxicity (19) in 12.6% of cases. Other reasons for change; pregnancy was six (4%), treatment non-compliance was four (2.6%), patient request was three (2%), and physician decision was three (2%). No drug changes were detected in the cases due to virological failure.
Conclusion: There is generally little data available in Turkey on the reasons for regime change in HIV patients using HAART. Therefore, the data we will obtain in this study can help draw a long-term plan for HAART drug management.
Keywords: HIV, highly active antiretroviral therapy, change in therapy

Öz

Giriş: Yüksek aktiviteli antiretroviral tedavi (HAART), İnsan immünyetmezlik virüsü (HIV) ile enfekte hastalarda morbidite ve mortaliteyi önemli ölçüde azaltmıştır. Bu başarıya rağmen hastalar tedaviye ömür boyu devam ettikleri için başlangıç tedavi rejiminin sürdürülebilirliği zor bir hale gelmiştir. Yüksek aktiviteli antiretroviral tedavi rejim değişikliği; intolerans/toksisite, gebelik, komorbiditeler, hasta uyum zorluğu ve virolojik baskılanmanın sağlanamaması gibi nedenlerle sıklıkla gerekli olabilmektedir. Bu çalışmada Hatay Mustafa Kemal Üniversitesi Tayfur Ata Sökmen Tıp Fakültesi Hastanesi'nde HIV/AIDS nedeniyle takip edilen hastalarda HAART değişiklik nedenlerinin irdelenmesi amaçlandı.
Gereç ve Yöntem: Bu retrospektif, kesitsel, tek merkezli çalışma HIV nedeniyle Ocak 2018-Aralık 2020 yılları arasında Hatay Mustafa Kemal Üniversitesi Tayfur Ata Sökmen Tıp Fakültesi Hastanesi'nde takip edilen 151 olgu çalışmaya dahil edildi.
Bulgular: İnsan immünyetmezlik virüsü ile yaşayan bireylerin %77,5'i (117) erkek, %22,5'i (34) kadındı. Yaş ortalaması 39,08±14,2 yıl (20-83) idi. İnsan immünyetmezlik virüsü ile yaşayan bireylerin %23,2'sinde (35) de tedavi değişikliği yapılmıştı. En sık tedavi değişiklik nedeni intolerans/toksisite %12,6 (19) birey idi. Diğer değişiklik nedenleri; gebelik %4 (6), tedavi uyumsuzluğu %2,6 (4), hasta isteği %2 (3), hekim kararı %2 (3) idi. İnsan immünyetmezlik sendromu ile yaşayan bireylerde virolojik yanıtsızlık nedeniyle ilaç değişikliği tespit edilmedi.
Sonuç: Yüksek aktiviteli antiretroviral tedavi kullanan HIV hastalarında rejim değişikliği nedenlerine dair Türkiye'de genel olarak çok az veri mevcuttur. Bu nedenle, bu çalışmada elde edeceğimiz veriler HAART ilaç yönetimi için uzun vadeli bir plan çizmeye yardımcı olabilir.
Anahtar Kelimler: HIV, yüksek aktiviteli antiretroviral tedavi, tedavi değişikliği

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Introduction

Acquired immunodeficiency syndrome (AIDS) was clinically defined in 1981 and the virus causing the disease was first identified in 1983[1]. According to the United Nations human immunodeficiency virus (HIV)/AIDS Program data, 37.7 million people were living with HIV worldwide in 2020, 680,000 people died from HIV-related diseases and 27.5 million people received antiretroviral treatment[2]. In our country, there were 29,284 HIV (+) persons and 2052 patients with AIDS diagnosed from 1985 to November 15, 2021[3]. The life expectancy of people living with HIV (PLHIV) has increased with the use of current highly active antiretroviral therapy (HAART) regimens. With the use of HAART since 1996, there has been a marked and sustained reduction in AIDS-related mortality and morbidity[4-6]. With the increase in life expectancy, comorbidities are more common and drug interactions may occur. For these reasons, problems may occur in continuing the initial HAART regimen. In this study, it was aimed to evaluate the treatment regimens and treatment changes applied in PLHIV followed in our clinic.

Materials and Methods

This retrospective, cross-sectional, single-center study included 151 PLHIV followed up at Hatay Mustafa Kemal University, Tayfur Ata Sökmen Medical Faculty Hospital between January 2018 and December 2020 for HIV/AIDS. People living with HIV older than 18 years of age, using HAART, whose diagnosis of HIV/AIDS was confirmed by ELISA and Western Blot were included in the study. Age, gender, reason for investigating HIV infection, transmission routes, clinical characteristics, laboratory results, initial HAART, reasons for changing HAART, and subsequent HAART regimen and patient follow-up files were searched and recorded from the hospital automation system. For viral load determination of PLHIV, HIV-RNA levels were studied by real-time polymerase chain reaction (Bosphore HIV-1 Quantification Kit, Anatolia geneworks, Turkey). CD4+ T lymphocyte counts were studied by flow cytometry method. Failure to stop virus replication within six months in patients using antiretroviral therapy was defined as treatment failure. Virological unresponsiveness was defined as failure to decrease or maintain viral replication to <50 copies/mL[7]. Reasons for HAART change were classified as follows: Simplification of treatment, virological unresponsiveness; the occurrence of comorbidities, and drug tolerability/toxicity issues[8].

The study was approved by the Hatay Mustafa Kemal University, Tayfur Ata Sökmen Medical Faculty Retrospective Ethics Committee (reference no: 06, date: 22.04.2021).

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences version 21 program.

Results

Of the 151 PLHIV included in the study, 77.5% (n=117) were male and 22.5% (n=34) were female. The mean age of PLHIV was 39.8±14.2 (20-83). The transmission route in PLHIV was heterosexual contact in 74.8% (n=113), men having sex with men (MSM) in 21.9% (n=33), and bisexual contact in 2% (n=3). The mode of transmission was unknown in 1.3% (n=2) of PLHIV. There was no contamination with blood and blood products and no intravenous drug-substance use. The Human immunodeficiency virus transmission routes in PLHIV are given in Table 1. Examining the marital status of the PLHIV, 47.7% (n=72) were single, 46.4% (n=70) were married, 3.3% (n=5) were widowed, and 2.6% of them (n=4) were divorced.

The average CD4+ lymphocyte count of PLHIV at the time of first admission was determined as 478.81±297.8 (3-1539) cells/mm^3. The mean Human immunodeficiency virus RNA at the time of first admission was 325703±47830 (24-16410000) copies/mL.

During the follow-up of PLHIV, 7.7% (n=11) had type 2 diabetes, 7.7% (n=11) hypertension, 6.3% (n=9) osteoporosis/osteopenia, 3.5% (n=5) hyperlipidemia, 2.8% (n=4) cardiovascular disease, 2% (n=3) asthma, 0.7% (n=1) chronic renal failure and 0.7% (n=1) hypothyroidism.

Reasons for testing PLHIV; self-will in 41.7% (n=63), research for disease in 27.8% (n=42), pre-surgical examination in 13.3% (n=19), before blood and organ donation in 4% (n=6), before marriage in 4% (6), during pregnancy in 1.3% (n=2), and before other admissions in 8.6% (n=13) (Table 2).

In 23.2% (n=35) of PLHIV, the treatment started was changed. The most common reason for changing treatment was intolerance and/or toxicity in 12.6% (n=19) of patients. Other reasons were as follows: pregnancy in 4% (n=6), treatment non-compliance in 2.6% (n=4), patients' own request in 2% (n=3), and physician's decision for simplified treatment in 2% (n=3). In our study, HIV RNA level above 50 copies/ml at the 24th week of HAART was defined as virological unresponsiveness. Virological success was achieved in all PLHIV. There was no change in treatment due to virological unresponsiveness in the study. Among the treatment changes due to intolerance and/or toxicity, 15 patients underwent changes due to osteopenia/

Table 1. Human immunodeficiency virus (HIV) transmission routes in people living with HIV

	Number (n)	Percentage (%)
Heterosexual intercourse	113	74.8
Men who have sex with men	33	21.9
Bisexual intercourse	3	2.0
Cause unknown	2	1.3
Total	151	100

osteoporosis (Figure 1). In our study, it was observed that tenofovir disoproxil fumarate (TDF)-based regimens were started in 9 PLHIV who developed osteoporosis/osteopenia. A decrease in bone mineral density was found in the dual energy X-ray absorptiometry (DEXA) evaluation in the follow-up of 6 PLHIV. Changes were made due to low glomerular filtration rate (GFR) in two individuals receiving TDF treatment. Changes were made in one of the two individuals with low GFR due to nausea-vomiting and one due to hypersensitivity. The characteristics of the patients whose treatment was changed due to toxicity were summarized in Table 3.

Individuals living with human immunodeficiency virus were using the following antiretroviral drugs in various combinations: TDF, emtricitabine (FTC), dolutegravir (DTG), tenofovir alafenamide (TAF), elvitegravir/cobicistat (ELV/co), bictegravir sodium (BIC), raltegravir (RAL), abacavir (ABC), lamivudine (LAM), efavirenz (EFV), lopinavir/ritonavir, rilpivirine. The regimens used by PLHIV in first-line treatment are summarized in Table 4.

The regimens received by PLHIV after treatment changes were as follows: Transition was made from TDF-containing regimens to ABC or TAF-containing regimens (seven individuals receiving TDF+FTC+DTG to TAF+FTC+ELV/co treatment, five individuals receiving TDF+FTC+DTG to ABC+LAM+DTG treatment, two individuals receiving TDF+FTC+ELV/co to TAF+FTC+ELV/co treatment, one individual receiving TDF+FTC+RAL to ABC+LAM+DTG treatment) in 15 individuals with osteopenia/osteoporosis in order to eliminate intolerance and/or toxicity. In our study, it was observed that TDF-based regimens were started in nine PLHIV with osteoporosis/osteopenia, and treatment was changed due to a decrease in bone mineral density detected in the DEXA of six PLHIV. Treatment was changed due to low GFR in two PLHIV using TDF. In one of these, the regimen was changed to a regimen containing TAF (from TDF+FTC+ELV/co to TAF+FTC+ELV/co) and to an ABC-containing regimen (from the TDF+FTC+RAL to ABC+LAM+DTG). A change was made from TDF+FTC+EFV regimen to the TDF+FTC+DTG regimen due to nausea/vomiting in one individual and hypersensitivity in another. It was changed to the regimens containing a single tablet (TAF+FTC+BIC, ABC+LAM+DTG) in three PLHIV due to their own request and in three PLHIV due to the physician's decision in order to simplify the treatment. Due to treatment non-compliance in four PLHIV, it was switched to single tablet regimens (TAF+FTC+RCC in three PLHIV, ABC+LAM+DTG in one PLHIV). Changes were made from regimens containing ELV/co and DTG to regimens containing RAL due to pregnancy in six PLHIV.

Table 2. Reasons for requesting tests for human immunodeficiency virus infection

	Number (n)	Percentage (%)
Patient's own request	63	41.7
While investigating the cause of a disease	42	27.8
Before the surgical operation	19	12.6
Before blood donation	6	4
Premarital	6	4
Pregnant screening	2	1.3
Other*	13	8.6
Total	151	100

*Other; job application, health report application, application for departure abroad, application for military service

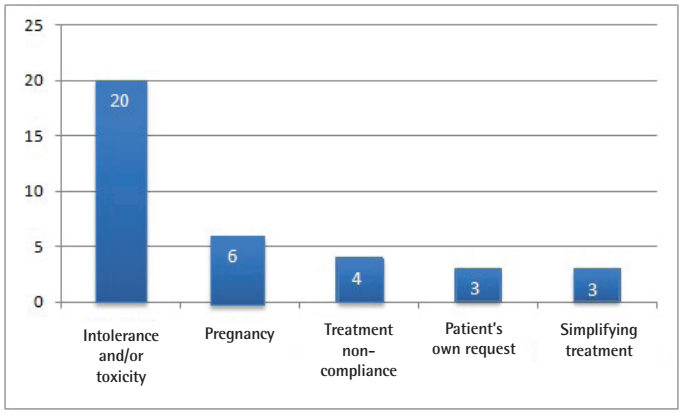

Figure 1. Causes of treatment change

Discussion

It is known that HIV is transmitted sexually in 46.1% of PLHIV in Turkey, and the route of transmission in 68.6% of these reported sexually transmitted cases is heterosexual intercourse. In addition, the transmission route in 1% of the cases is intravenous drug use, and the transmission route in 52.57% is unknown[2]. In some studies conducted in our country, the rate of transmission via sexual contact was found to be 65-89%[9,10]. In our study, the most common route of transmission was sexual contact (96.7%). It was reported that 74.8% of them were transmitted by heterosexual intercourse, and 21.9% by MSM. In our study, the number of patients whose transmission route was unknown was two, and this was considered a very low number according to the data of the Ministry of Health. The reason for this may be that the forms filled during the first admission are reported to the Ministry of Health and these forms are not updated afterwards. In addition, it may be due to the fact that PLHIV do not want to tell the transmission route during the first admission. In our study, we learned the transmission routes of PLHIV in our later follow-ups, which might lead to the low number of individuals whose transmission route was unknown.

In a study conducted in our country, it was shown that %37 of PLHIV were diagnosed during routine tests[10]. In another study conducted in our country, 47.2% of the individuals diagnosed

Table 3. Characteristics of patients who underwent treatment change due to toxicity

Type of toxicity (n)	Age	Gender	Beginning treatment regimen	Subsequent treatment regimen	Change period (month)	Laboratory	
Osteopenia/osteoporosis (n=6)						**DEXA**	
	54	M	TDF+FTC+DTG	TAF+FTC+ELV/Co	17	-0.4	-1.4
	67	M	TDF+FTC+DTG	TAF+FTC+ELV/Co	19	0.3	-1.5
	50	M	TDF+FTC+RAL	ABC+LAM+DTG	24	-0.9	-3.2
	39	M	TDF+FTC+DTG	TAF+FTC+ELV/Co	12	0.4	-1.7
	45	M	TDF+FTC+DTG	TAF+FTC+ELV/Co	13	0.6	-1.3
	47	M	TDF+FTC+DTG	TAF+FTC+ELV/Co	48	-0.9	-2.5
Nephrotoxicity (n=2)						**eGFR**	
	28	**M**	TDF+FTC+ELV/co	TAF+FTC+ELV/co	18	**90**	**68**
	40	**F**	TDF+FTC+RAL	ABC+LAM+DTG	26	**110**	**85**
Nausea (n=1)	24	**M**	TDF+FTC+EFV	TDF+FTC+DTG			
Hipersensitivity (n=1)	50	**F**	TDF+FTC+EFV	TDF+FTC+DTG			

DEXA: Dual energy X-ray absorptiometry, M: Male, F: Female, TDF: Tenofovir disoproxil fumarate, FTC: Emtricitabine, DTG: Dolutegravir, TAF: Tenofovir alafanamide, ELV/co: Elvitegravir/cobicistat, RAL: Raltegravir, ABC: Abacavir, LAM: Lamuvidin, EFV: Efavirenz, eGFR: Glomerular filtration rate

Table 4. The regimens used by individuals living with human immunodeficiency virus in first-line treatment

Treatment regimens	Number (n)	Percentage (%)
TDF/FTC+DTG	53	35.1
TAF/FTC/ELV/co	39	25.8
TAF/FTC/BIC	26	17.2
TDF+FTC+RAL	13	8.6
TDF+FTC+ELV/co	6	4
ABC+LAM+DTG	6	4
TDF+FTC+EFV	4	2.6
TDF+FTC+Lop/r	3	2
RPV+DTG	1	0.7

TDF: Tenofovir disoproxil fumarate, FTC: Emtricitabine, DTG: Dolutegravir, TAF: Tenofovir alafanamide, ELV/co: Elvitegravir/cobicistat, RAL: Raltegravir, ABC: Abacavir, LAM: Lamuvidin, EFV: Efavirenz, Lop/r: Lopinavir/ritonavir, RPV: Rilpivirine

with HIV infection were diagnosed with tests performed before donating blood, before marriage or operation[11]. In another study, PLHIV were most frequently diagnosed due to opportunistic infections (39%)[12]. In our study, the patient's own request (41.7%) was the most common cause of diagnostic testing, and the second most common cause (27.8%) was investigating a disease. We think that the reason why the self-diagnosis in PLHIV is higher compared to other studies may be due to the increased awareness about HIV transmission today.

Guidelines recommend starting treatment for all individuals diagnosed as having HIV, regardless of CD4 cell count. In our study, it was determined that TDF/FTC+DTG was given to 53 PLHIV, TAF/FTC/ELV/co to 39 PLHIV, and TAF/FTC/BIC to 26 PLHIV as initial treatment. There may be treatment changes in PLHIV due to various reasons such as drug resistance, patient's own request, side effects, or difficulties in drug supply[13]. In a study conducted in our country, it was found that treatment changes were made in 25.9% of PLHIV and the two most common reasons were non-compliance with treatment and side effects[9]. In another study, the most common reasons for treatment change were drug intolerance/toxicity (30.9%) and simplification of treatment (26.7%)[14]. In another study conducted in our country, in which 3019 PLHIV were included, it was shown that the treatment was changed in 11.6% (n=379) of PLHIV in the first year, and the two most common reasons were intolerance/toxicity and simplification of treatment, respectively[15]. In a study conducted in Italy, the rate of treatment change in HAART was found to be 36.1% in the first year. The three most common reasons for changing treatment were toxicity (19%), treatment non-compliance (21%), and simplification of treatment (29%)[16]. In our study, it was determined that the two most common reasons for treatment change were intolerance/toxicity and pregnancy. In our study, it was observed that TDF-based regimens were started in nine PLHIV who developed osteoporosis/osteopenia. In addition, a decrease in bone mineral density was detected with DEXA in the follow-up of six PLHIV. For this reason, drug changes were made in order to prevent potential toxicity in PLHIV with osteoporosis/osteopenia in whom TDF was started, and in whom a decrease in bone mineral density was detected in the follow-ups.

In our study, the second most common reason for drug change was pregnancy. Those who were treated with dolutegravir and ELV/co were switched to treatments with raltegravir. The reason for this was that there was a warning in the guidelines at the time of initiation of treatment that a neural tube defect could occur in relation to dolutegrevir treatment in pregnant women. In addition, treatment changes were made in patients using ELV/

co in the 2nd and 3rd trimesters of pregnancy due to the concern that the volume of distribution of these drugs might decrease and their blood levels may decrease to subtherapeutic levels[7]. The use of dolutegravir during pregnancy was associated with a small increased risk of neural tube defects, but no neural tube defects were observed when dolutegravir was started during pregnancy[17]. Today, current guidelines suggest that dolutegravir can be used after the 8th week of pregnancy[7]. Over the years, the recommendations of the guides may change. Therefore, drug changes may occur.

The incidence of nephrotoxicity associated with TDF is around 0.8-2% in studies[18,19]. In another study conducted in our country, it was shown that 1.9% (n=4) of PLHIV without renal failure at the beginning had a decrease in GFR, so treatment changes were made[14]. In our study, treatment changes were made due to low GFR in two individuals who received TDF treatment during their follow-up. It was remarkable that diabetes was a comorbidity in these two PLHIV. In another study evaluating 2425 PLHIV receiving TDF, kidney dysfunction developed in 4.2% of PLHIV[20]. As a result, we recommend paying attention to the comorbidities of PLHIV and individualizing the treatment, no matter what treatment they have received.

Studies conducted at different times in the same cohort have shown a decrease in the rate of virological unresponsiveness[16]. In our study, no virological unresponsiveness was found. We think that this may be due to better virological efficacy due to the use of more effective, better tolerated and less toxic drugs.

Study Limitations

The limitation of our study was that the number of PLHIV was low and our study included regional data. At the same time, patient follow-up by a single faculty member and the retrospective nature of the study were other limitations.

Conclusion

In conclusion, the main reasons for changing the initial HAART regimen are to simplify treatment and minimize drug toxicity in order to improve adherence and quality of life. In addition, current treatment options include drugs that are more effective, better tolerated, and less toxic than regimens used in the early years of HAART. Therefore, initial HAART optimization is important for both virological efficacy and tolerability. Long-term toxicity and persistence appear to be key features in the choice of first-line HAART.

Ethics

Ethics Committee Approval: The study was approved by the Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine of Retrospective Ethics Committee (reference no: 06, date: 22.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ç., Concept: M.Ç., E.S.P., S.O., Y.Ö., Design: M.Ç., E.S.P., S.O., Y.Ö., Data Collection or Processing: M.Ç., T.B., E.S.P., S.O., Y.Ö., Analysis or Interpretation: M.Ç., T.B., E.S.P., Literature Search: M.Ç., T.B., Writing: M.Ç.

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