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Evaluation of the Side Effects of Antiretroviral Treatment

Antiretroviral Tedavi Yan Etkilerinin Değerlendirilmesi

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Abstract

Introduction: The frequency of antiretroviral therapy (ART)-induced side effects varies in HIV-infected patients. In this study, we aimed to compare drug-induced side effects developing in patients receiving different ART regimens.

Materials and Methods: This study was performed after obtaining approval of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital's Ethics Committee (89513307/1009/515) on 30.12.2015. Ninety-five patients with HIV infection followed-up between January 2012 and December 2015 who received ART were included in this study. Their clinical and laboratory findings were evaluated retrospectively and possible drug-related side effects were investigated. Antiretroviral therapy regimens were compared using chi-square test and Fisher's exact test for categorical variables and with Mann-Whitney U test for numerical variables; changes in numerical variables were compared using Wilcoxon test. SPSS 22.0 software (Chicago, IL, USA) was used for data analyses.

Results: All cases were treated with regimens consisting of tenofovir/emtricitabine (TDF/FTC). Three patients restarted treatment after quitting for several months, thus 98 regimens administered to 95 patients were evaluated. Forty-nine of them received protease inhibitors (PIs), 44 received integrase inhibitors (INSTIs), and five received non-nucleoside reverse transcriptase inhibitors. The median (IQR) follow-up period was seven (4-13) months. None of the patients had renal function abnormality before ART but during treatment three (3.1%) of them needed renal dose adjustment for TDF/FTC. Compared to baseline values, there were significant differences in creatinine and creatinine clearance levels during treatment ($p<0.001$). Hyperlipidemia developed in 50% of the patients who did not have hyperlipidemia at start of treatment and this rate differed significantly between the PI and INSTI regimens (69% and 26%, respectively, $\chi^2=11.214$, $p=0.001$). Seventeen percent of the patients developed an elevation in ALT levels during the treatment, but none required treatment change for this reason. Treatment changes were made 27 times in 21 patients while 15 of these changes were due to probable side effects. Thus, of 125 treatment regimens, possible clinical side effects were observed in 30 (24%), 13 of which were diarrhea. Gastrointestinal side effects were observed in 26% with PI-based regimens and neuropsychiatric side effects were observed in 6% with INSTI-based regimens.

Conclusion: The most common side effects were hyperlipidemia (50%) and diarrhea (23%). Diarrhea was responsible for two-thirds of the ART switches in our study. It is important to monitor patients receiving ART for possible side effects. The results of longer and more comprehensive follow-up are needed to obtain more definitive data.

Keywords: HIV, antiretroviral therapy, tenofovir, dolutegravir, darunavir

Öz

Giriş: HIV ile enfekte hastalarda antiretroviral tedaviye (ART) bağlı gelişen yan etki sıklığı ve dağılımı değişiklik göstermektedir. Bu çalışmada, farklı ART rejimleri alan hastalarda görülen ilaç yan etkilerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma 30.12.2015 tarihinde İstanbul Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi Etik Kurul'u onayı (89513307/1009/515 sayılı) alınarak gerçekleştirildi. Ocak 2012-Aralık 2015 tarihleri arasında HIV enfeksiyonu tanısıyla izlemimize giren ve yeni ART başlanan, en az üç ay izlemde kalan 95 hasta kaydedildi. Hastaların klinik ve laboratuvar verileri retrospektif olarak incelendi, olası ilaç yan etkileri değerlendirildi. SPSS 22.0 Software (Chicago, IL, USA) programı kullanılarak ART rejimleri arasında kategorik değişkenler χ^2 testi ve Fisher's exact test, sayısal değişkenler Mann-Whitney U testi ile; sayısal değişkenlerdeki değişim Wilcoxon testi ile karşılaştırıldı.

Bulgular: Olgularımızın tamamına tenofovir/emtrisitabin (TDF/FTC) bazlı rejimler başlandı. Üç hasta değişen sürelerde tedaviye ara verdikten sonra tekrar tedavi altına alındı, böylece 95 hastaya uygulanan 98 farklı rejim değerlendirmeye alınmış oldu. Bunların 49'una proteaz inhibitörü (Pİ), 44'üne

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integraz inhibitörü (INSTI) ve beşine non-nükleozid revers transkriptaz inhibitörü bazlı rejimler başlandı. Medyan (IQR) izlem süresi yedi (4-13) ay oldu. Hiçbir hastada tedavi öncesi renal fonksiyon bozukluğu yokken üçünde (%3,1) izlem sırasında TDF/FTC'de renal doz ayarlaması yapıldı. Başlangıç değerlere göre tedavi sırasındaki kreatinin ve kreatinin klirensi değerlerinde anlamlı farklılık gözlendi (p<0,001). Başlangıçta hiperlipidemisi olmayan olguların %50'sinde tedavi altında hiperlipidemi ortaya çıktı. Proteaz inhibitörü bazlı rejimlerle INSTI bazlı rejimler karşılaştırıldığında istatistiksel olarak anlamlı bir farklılık vardı (sırasıyla, %69 ve %26, χ^2=11.214, p=0,001). Başlangıçta alanin aminotransferaz (ALT) yüksekliği olmayan olguların %17'sinde izlem sırasında ALT değerleri yükseklik gösterdi. Tedavi değişikliğine gidilmedi. Yirmi bir hastada 15'i yan etkilere bağlı olmak üzere toplam 27 kez tedavi değişikliği yapıldı. Böylece 125 tedavi rejiminin izlemi sırasında 13'ü diyare olmak üzere 30'unda (%24'ünde) olası klinik yan etki görüldü. Proteaz inhibitörü bazlı rejimlerde %26 oranında gastrointestinal, INSTI bazlı rejimlerde %6 oranında nöropsikiyatrik yan etki gözlendi.
Sonuç: Olgularımızda en sık görülen yan etki hiperlipidemi (%50) ve diyare (%23) oldu. Diyare varlığı üçte iki oranında ART değişikliği gerektirdi. Antiretroviral tedavi alan hastaların yan etkiler yönünden yakından izlenmesi önemlidir. Daha net sayısal veriler oluşturabilmek için daha uzun süreli ve kapsamlı izlem sonuçlarının değerlendirilmesi gerekmektedir.
Anahtar Kelimeler: HIV, antiretroviral tedavi, tenofovir, dolutegravir, darunavir

Introduction

The range of treatment options for HIV infection has increased since the first treatment regimen was described, and new and more effective regimens have improved the ease of use and success of treatment. While the number of patients has increased, the criteria for starting antiretroviral therapy (ART) have also been expanded and drugs have become more readily accessible[1]. According to data from the World Health Organization, as of mid-2016, the number of patients infected with HIV and receiving ART reached 18.2 million globally[2]. This means that a larger population of patients is undergoing ART, which leads to ART-related problems such as side effects, drug interactions, and resistance. Although new antiretrovirals cause fewer adverse events compared to earlier agents, longer lifespan also extends exposure to drug toxicity. Side effects may reduce the quality of life provided by successful treatment. This can in turn reduce adherence to treatment, resulting in treatment failure or resistance.

Studies conducted on the adverse effects of ART differ in terms of side effects evaluated, preferred treatment regimens, and treatment durations for these regimens. Therefore, each study reports different incidence rates for these side effects. The prevalence of nephrotoxicity associated with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is reported as 0.8-2%[3,4]. Hyperlipidemia associated with ART has been reported at rates of up to 70-80%[5].

Although many ART options are currently available, the ideal treatment should be individualized for each patient. The ability to predict the adverse effects that may occur with each regimen will enable more effective treatment. The aim of this study was to identify the prevalence, causes, and outcomes of adverse effects experienced by patients with HIV while receiving ART.

Materials and Methods

Patients: This study was performed after obtaining approval of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital's Ethics Committee (89513307/1009/515) on 30.12.2015. The medical records of 100 patients being followed by the Infectious Diseases and Clinic Microbiology Clinic for HIV infection between January 2012 and December 2015 were analyzed retrospectively. A total of 95 patients who were aged 18 or over, had recently started ART, and were followed up for at least three months were included in the study. Patients who were treated in other facilities, were followed without ART, or did not attend follow-up regularly after starting ART were excluded.

Data collection: The patients' medical records were screened and the following data were recorded in an Excel spreadsheet: demographic data; HIV-RNA, CD4 and CD8 counts, complete blood count, and biochemical parameters [fasting lipids, fasting glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, estimated glomerular filtration rate (eGFR), electrolytes, full urine test] at initial presentation and follow-up visits; ART started; any other drugs used; prophylactic antibiotics for opportunistic infections; follow-up notes; symptoms and findings at each visit; adverse effects experienced during ART; and any changes in treatment (with reasons).

Definitions: Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2); eGFR was calculated using the Cockcroft-Gault formula: (140 - age) x weight (kg)/(serum creatinine x 72)[6,7]. For women, this formula was multiplied by 0.85. Renal functions were assessed for each patient by calculating maximum creatinine and minimum eGFR during follow-up and the change in these values from baseline; eGFR levels below 60 mL/min during ART were considered nephrotoxicity[6,8].

Hyperlipidemia was defined as total cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, or triglyceride level >150 mg/dL[8]. For each patient, the presence of hyperlipidemia at beginning and during treatment and changes in lipid values were noted.

Elevated ALT was defined as 1.25 times the normal upper limit. Elevated ALT at beginning and during treatment and changes in ALT value were determined for each patient[8].

Statistical Analysis

The data entered in the Excel spreadsheet were statistically analyzed using SPSS 22.0 Software (Chicago, IL, USA). The patients' demographic, clinical, and laboratory parameters were analyzed using descriptive statistical methods [percentage for categorical variables and median, interquartile range (IQR), minimum, and maximum values for continuous data]. The patients were separated into groups based on ART regimen: protease inhibitor (PI), integrase inhibitor (INSTI), and non-nucleosite reverse transcriptase inhibitor (NNRTI). Statistical comparisons were performed between the two largest groups (PI and INSTI). Categorical variables were compared using chi-square (χ^2) test and Fisher's exact test when necessary, and numerical variables were compared using Mann-Whitney U test. Numerical data obtained at the beginning of treatment and during follow-up were compared using Wilcoxon test. P values <0.05 were considered statistically significant.

Results

Patient characteristics: Of the 95 patients included in our study, 84 (88%) were male and 11 (12%) were female, with ages ranging between 20 and 68. The median (IQR) age was 37 (30-47) years and median (IQR) BMI was 24 (22-26).

Comorbidities included diabetes in six patients, hypertension in five, cancer in four, hyperlipidemia in two, and coronary heart disease in a single patient. Four patients (4.2%) were HBsAg-positive, while HCV infection was not detected in any of the patients. Family history included diabetes for 37 (39%), coronary heart disease for 25 (26%), hypertension for 22 (23%), cancer for 17 (18%), and hyperlipidemia for four (4%) patients. Forty-four (46%) patients were smokers and nine (10%) used alcohol.

CD4+ lymphocyte count was <200/mm^3 in 35 (37%), 200-499/mm^3 in 43 (45%), and >500/mm^3 in 17 patients (18%). Only 10 (11%) patients exhibited acquired immunodeficiency syndrome defining disease.

Treatment and follow-up: Baseline laboratory values of all patients prior to treatment are summarized in Table 1 and the distribution of ART regimens initiated is shown in Table 2. All patients were on TDF/FTC-based regimens, and the most common combination was lopinavir/ritonavir (LPV/r), with 47%. Forty-six patients received PI, 44 received INSTI, and five were given NNRTI-based combinations. Depending on CD4 lymphocyte counts and serological results, some patients were also started on prophylactic antibiotherapy: 24 patients were given trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* (PCP) and/or toxoplasmosis, nine were given isoniazid for *Mycobacterium tuberculosis*, and two were given azithromycin for *Mycobacterium avium complex*.

For three patients receiving a PI-based combination, treatment was discontinued for periods ranging from 4 to 12 months, after which treatment and follow-up continued with the same regimen. Therefore, our analysis included clinical and laboratory findings presumed to be drug side effects developed during 98 different regimens in 95 patients.

Comparisons of selected laboratory findings prior to and during ART between groups are presented in Table 3.

Renal dysfunction: While none of the patients had renal dysfunction before treatment, three patients (3.1%) developed chronic kidney disease and required renal dose adjustment during TDF/FTC treatment. Two of these patients were taking PI-based and one was taking NNRTI-based regimens. None required dialysis. Maximum creatinine level among all patients during ART ranged between 0.52 and 1.93 mg/dL and had a median (IQR) of 0.91 (0.78-1.00) mg/dL. The median (IQR) minimum eGFR was 112 (96-132) mL/min and ranged between 36 and 163 mL/min. There were significant differences in eGFR and creatinine values during treatment compared to baseline values (p<0.001). Median (IQR) rate of increase in creatinine level was 0.16 (0.03-0.28), and the median (IQR) reduction rate in eGFR value was 0.15 (0.03-0.23). There was no significant difference between the ART regimens (Table 3).

Table 1. Patients' baseline laboratory values before start of antiretroviral therapy

	Median	IQR
HIV-RNA (copies/mL)	137,763	52,727-687,229
HIV-RNA ($\log_{10}$ copies/mL)	5.14	4.72-5.84
CD4 number (/mm^3)	297	120-423
CD8 number (/mm^3)	846	546-1301
WBC (/mm^3)	6250	5400-7400
Hb (g/dL)	14.2	12.8-15.3
PLT (x103/mm^3)	218	179-265
Glucose (mg/dL)	95	88-105
BUN (mg/dL)	13	11-16
Creatinine (mg/dL)	0.77	0.68-0.86
Phosphorus (mg/dL)	3.15	2.63-3.58
Total cholesterol (mg/dL)	161	132-189
HDL (mg/dL)	34	29-41
LDL (mg/dL)	97	75-131
Triglycerides (mg/dL)	115	86-196
ALT (U/L)	26	19-43
AST (U/L)	28	22-35
LDH (U/L)	209	187-231
CPK (U/L)	86	62.25-131.50
eGFR (mL/min)	134	116-154

CPK: Creatinine phosphokinase, eGFR: Estimated glomerular filtration rate, IQR: Interquartile range, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Hyperlipidemia: Thirty-seven patients (38%) had hyperlipidemia at baseline, and there was no difference in their distribution between the treatment groups. An additional 58 patients (59%) developed hyperlipidemia during ART. The proportion of patients who developed hyperlipidemia during follow-up was 67% (n=33) with PI-based regimens vs. 48% (n=21) with INSTI-based regimens (χ^2=5.748, p=0.017). A similar number of patients exhibited elevated blood lipids not quite reaching the hyperlipidemia threshold during treatment with PI regimens (n=32, 65%), while only 13 patients (30%) had elevated blood lipids during treatment with INSTI-based regimens (χ^2=16.124, p<0.001) (Table 3).

Fifty percent of the patients who did not have hyperlipidemia at baseline developed the condition during treatment. However, there was a statistically significant difference in the distribution of these patients between the PI-based regimen and INSTI-based regimen groups (69% vs. 26% respectively, χ^2=11.214, p=0.001). Diet and exercise were recommended to all patients. Only two patients with persistently high lipid levels despite dietary modification and exercise required antihyperlipidemic therapy. Antiretroviral therapy was not changed in any of the patients.

Table 2. Initial antiretroviral therapy regimen

ART regimen	n=95 (%)
TDF/FTC + LPV/r	45 (47.4%)
TDF/FTC + DTG	16 (16.8%)
TDF/FTC + EVG/c	15 (15.8%)
TDF/FTC + RAL	13 (13.7%)
TDF/FTC + EFV	5 (5.3%)
TDF/FTC + DRV/r	1 (1.1%)

c: Cobicistat, DRV: Darunavir, DTG: Dolutegravir, EFV: Efavirenz, EVG: Elvitegravir, FTC: Emtricitabine, LPV: Lopinavir, RAL: Raltegravir, r: Ritonavir, TDF: Tenofovir disoproxil fumarate

Elevated transaminase: Of the 98 regimens started, in 17 (17%) baseline ALT values were high, and there was no statistically significant difference between different treatment regimens (Table 3). Fourteen (17.3%) of the patients who did not have high ALT values at baseline exhibited elevated ALT during follow-up. Only three patients had extremely high values (>x5 normal upper limit); the others had slight elevation which normalized during follow-up. No other reason was found to account for this elevation. There was no significant difference between PI- and INSTI-based regimens (13% and 16% respectively, χ^2=0.217, p=0.642). Treatment was not changed for this reason in any of the cases. Thirty-five (36%) of the patients showed a reduction in ALT level during follow-up, even though some had ALT levels within normal range.

Creatinine phosphokinase (CPK) level: Twenty-three (29%) of all the cohort exhibited varying degrees of CPK elevation at different times during treatment. However, since CPK monitoring was not standardized in all patients and values were variable even in the same patient during follow-up, we did not perform advanced analysis or consider it appropriate to directly associate CPK levels with ART.

Table 3. Selected laboratory findings before and during antiretroviral therapy, and comparison between the two largest treatment groups

	All n=98	PI group n=49	INSTI group n=44	p
Follow-up time, median months (IQR)	7 (4-13)	10 (5-9)	6 (3-7)	**<0.001**
Pre-ART				
eGFR, median mL/min (IQR)	133 (114-152)	138 (121-158)	127 (112-143)	**0.025**
Creatinine, median mg/dL (IQR)	0.79 (0.68-0.87)	0.76 (0.61-0.84)	0.81 (0.72-0.89)	**0.025**
Elevated ALT, n (%)	17 (17.3)	9 (18.4)	7 (15.9)	0.754
Hyperlipidemia, n (%)	37 (38.0)	17 (34.7)	20 (45.5)	0.290
During ART				
eGFR <60 mL/min, n (%)	3 (3.1)	2 (4.1)	0 (0)	0.496
Minimum eGFR, median mL/min (IQR)	112 (96-132)	121 (102-134)	111 (96-124)	0.115
eGFR reduction rate, median (IQR)	0.14 (0.03-0.23)	0.16 (0.08-0.24)	0.14 (0.04-0.23)	0.634
Maximum creatinine, median mg/dL (IQR)	0.91 (0.78-1.00)	0.82 (0.73-0.94)	0.94 (0.85-1.01)	**0.007**
Creatinine increase rate, median (IQR)	0.16 (0.03-0.28)	0.16 (0.00-0.31)	0.14 (0.04-0.26)	0.902
Elevated ALT, n (%)	21 (21.4)	10 (20.4)	7 (15.9)	0.575
Hyperlipidemia, n (%)	58 (59.2)	33 (67.3)	21 (47.7)	**0.017**
Increased blood lipids, n (%)	48 (48.9)	32 (65.3)	13 (29.5)	**<0.001**
CPK ≥170 U/L, n (%)	23 (29.1)	8 (23.5)	14 (34.1)	0.315

eGFR: Estimated glomerular filtration rate, PI: Protease inhibitors, ART: Antiretroviral therapy, ALT: Alanine aminotransferase

Potential clinical side effects observed during initial ART regimen: Symptoms observed in follow-up during initial ART were considered to be potential clinical side effects of the drug in 22 (23%) of the patients. Fourteen (15%) of the adverse reactions were gastrointestinal, five were neuropsychiatric, two were musculoskeletal, and one patient experienced itching. The initial regimens were changed in 12 (13%) patients due to these clinical side effects.

ART changes: In addition to the 12 cases exhibiting clinical side effects, initial treatment was also changed in nine patients (9%) for other reasons such as nonadherence to treatment or drug unavailability. Treatment was changed a total of 27 times in 21 patients [(22%); changed twice in four patients and thrice in one patient]. The number of treatment changes and their distribution according to treatment regimen are shown in Table 4. Sixty-three percent of the changes involved the LPV/r-based regimen. Overall 33% of the patients receiving LPV/r had treatment change while 19% were due to diarrhea. Antiretroviral therapy regimen was changed in four (67%) of the six patients using efavirenz. There was a statistically significant difference in treatment changes between the INSTI-based regimens (9%) vs. the PI-based regimens (32%) (χ^2=9.960, p=0.002). Adverse events were the reason for 65% of PI regimen changes and 17% of INSTI regimen changes, but the difference was not statistically significant (χ^2=4.102, p=0.069).

Overall probable clinical side effects observed during follow-up: Ninety-five patients were followed under a total of 125 different regimens, including after treatment interruption (n=3) and regimen changes (n=27). Therefore, all regimens received by each patient were assessed and the frequency of probable clinical side effects was calculated as a fraction of 125. Probable clinical side effects were observed during follow-up in 30 (24%) of the regimens. Of these, 17 (14%) were gastrointestinal, including 13 (10%) patients with diarrhea; 10 (8%) were neuropsychiatric, with forgetfulness in five (4%) patients; two patients experienced widespread bone pain and weakness in the legs; and one patient complained of itching. The distribution of these clinical side effects by treatment regimen is shown in Table

Table 4. Treatment changes according to antiretroviral therapy regimen

ART regimen	n=125	Treatment change, n (%)	Change due to side effects, n (%)
TDF/FTC + LPV/r	52	17 (32.6%)	11 (21.1%)
TDF/FTC + EVG/c	29	1 (3.4%)	1 (3.4%)
TDF/FTC + DTG	19	0	0
TDF/FTC + RAL	18	5 (27.7%)	0
TDF/FTC + EFV	6	4 (66.6%)	3 (50%)
TDF/FTC + DRV/r	1	0	0

c: Cobicistat, DRV: Darunavir, DTG: Dolutegravir, EFV: Efavirenz, EVG: Elvitegravir, FTC: Emtricitabine, LPV: Lopinavir, RAL: Raltegravir, r: Ritonavir, TDF: Tenofovir disoproxil fumarate, ART: Antiretroviral therapy

Table 5. Clinical side effects experienced by the patients

Clinical side effects	All n=125 (%)	PI group n=53 (%)	INSTI group n=66 (%)	NNRTI group n=6	p*
Gastrointestinal	**17 (13.6)**	**14 (26.4)**	**2 (3)**	**1**	**<0.001**
Diarrhea	13 (10)	12 (22.6)	1 (1.5)	-	**<0.001**
Dyspepsia	2 (1.6)	1 (1.9)	-	1	0.445
Constipation	1 (0.8)	-	1 (1.5)	-	1.000
Nausea	1 (0.8)	1 (1.9)	-	-	0.445
Neuropsychiatric	**10 (8)**	**3 (5.7)**	**4 (6.1)**	**3**	1.000
Forgetfulness	5 (4)	3 (5.7)	1 (1.5)	1	0.322
Irritation, insomnia	4 (3.2)	-	3 (4.5)	1	0.253
Depression	1 (0.8)	-	-	1	-
Musculoskeletal	**2 (1.6)**	**2 (3.8)**	**-**	**-**	0.196
Leg weakness	1 (1)	1 (1.9)	-	-	0.445
Diffuse muscle pain	1 (1)	1 (1.9)	-	-	0.445
Itching	**1 (1)**	**-**	**1 (1.5)**	**-**	1.000

*Comparison between protease inhibitors and integrase inhibitor groups, not including non-nucleosite reverse transcriptase inhibitor.
PI: Protease inhibitors, NNRTI: Non-nucleosite reverse transcriptase inhibitor, INSTI: Integrase inhibitor

5. Adverse events were observed in 19 (36%) of the 53 patients receiving a PI regimen, including 14 (26%) gastrointestinal effects; in seven (10%) of the 66 patients receiving an INSTI regimen, four (6%) of which were neuropsychiatric; and in four (66%) of the six patients receiving a NNRTI regimen, including three (50%) neuropsychiatric side effects. In comparison of the PI and INSTI regimens with regard to clinical side effects, only gastrointestinal side effects exhibited a significant difference due to diarrhea ($p<0.001$).

Discussion

Various studies have reported the prevalence of side effects in patients receiving ART as varying between 34% and 40%[9,10]. Overall, the prevalence of side effects in the present study varied between 1% and 50%. The frequency of side effects differs in each study based on the preferred ART regimen and treatment duration. If the presumed side effects associated with ART are categorized as clinical findings and laboratory findings, it can be commented that clinical side effects occured in 24% of the patients in our study. In a Swiss cohort, reported side effects were 47% clinical and 27% based on laboratory findings[11]. However, it is not possible to make any real comparison with this study both because they assessed all laboratory abnormalities as side effects and because the drugs used at the time of the study were different and more toxic than those we used in this study.

The most common ART-associated side effects in previous studies are related to the gastrointestinal system[9,12]. In the present study, we also observed gastrointestinal side effects in 14% of our patients. Diarrhea accounted for about two-thirds of these gastrointestinal side effects. Among our treatment groups, gastrointestinal complaints were most common among patients on PI-based regimens (26%). Diarrhea occurred in 12 (23%) of the 14 patients with gastrointestinal complaints associated with PI regimens. In a meta-analysis, the incidence of moderate to severe diarrhea in 1469 patients taking LPV/r was 15.5%, and 1.3% of these patients had to discontinue treatment due to diarrhea[13]. In our study, 8% of all cases and 19% of LPV/r users required change in ART regimen because of diarrhea.

Another ART-related side effect observed in our study was hyperlipidemia. Fifty-nine percent of the patients developed hyperlipidemia during ART, but 38% of the patients had hyperlipidemia prior to treatment. In a separate assessment based only on patients who did not have hyperlipidemia at baseline, we determined that 50% developed hyperlipidemia during treatment. A comparison of the different treatment groups showed that hyperlipidemia developed more frequently with PI-based combinations than INSTI-based combinations and, even among patients who did not develop hyperlipidemia, blood lipids levels were significantly higher during treatment. Although ART regimen was not changed due to hyperlipidemia in any of our patients, two patients with persistent elevation despite dietary modifications and exercise received antihyperlipidemic therapy. None of the patients experienced cardiac events. In the FLAMINGO study, the darunavir/ritonavir group showed greater increase in triglyceride, total cholesterol, and LDL cholesterol levels compared to the dolutegravir group[14]. Stein et al.[15] found that patients using PI-based combinations had significantly different increases in triglyceride and total cholesterol levels compared to other treatment groups. In a study by Behrens et al.[16] including a small patient group, 71% of patients receiving PI developed hyperlipidemia and 44% of them had isolated hypertriglyceridemia. In our study, 69% of initially normolipidemic patients who received a PI-based regimen developed hyperlipidemia during treatment. In a 5-year cohort study by Tsiodras et al.[17] including 221 patients receiving ART, the cumulative incidences of hypertriglyceridemia and hypercholesterolemia were 19% and 24%, respectively, and PIs were found to be independently associated with hypertriglyceridemia and hypercholesterolemia. In their study, 240 mg/dL was accepted as the upper limit for total cholesterol and 500 mg/dL for triglyceride, which may explain why the incidences were lower compared to our results.

Another major ART-related side effect is nephrotoxicity, though the frequency varies. In a meta-analysis of 17 studies, kidney dysfunction was found to develop at a significantly higher rate in patients taking TDF compared to a control group not taking TDF[18]. In our study, all of the patients were receiving TDF/FTC-based combination treatments. Although none of our patients had renal dysfunction prior to treatment, eGRF value fell to below 50 mL/min in 3% of the patients after starting treatment and therefore the regimen was continued with an adjusted dose of TDF/FTC. In two of these three patients, eGRF increased after dose adjustment. Jin et al.[19] reviewed a total of 136 patients taking TDF/FTC and observed a sharp increase (>1.5 mg/dL) in serum creatinine in 4.9% of the patients, all of whom were in the PI group. In our study, two of the three patients who developed nephrotoxicity were receiving a PI-based regimen. A study by Baxi et al.[20] provided strong evidence the risk of renal dysfunction increased with longer exposure to TDF. The median follow-up time for patients in the present study was seven months. Therefore, the lower rate of nephrotoxicity observed in our study may be attributed to the shorter follow-up time compared to other studies. In a study by Lai et al.[21] including 27 patients using TDF, 81% exhibited phosphaturia, glycosuria, and bicarbonaturia as findings of proximal tubular damage, and this damage was largely reversible in 70% of cases. Although we observed significant differences between the PI and INSTI groups in terms of maximum creatinine levels during ART, they were not interpreted as significant since baseline eGFR and creatinine levels and treatment durations differed between the groups.

Some complications that may develop in the natural course of HIV infection as well as the patients' comorbidities may be disconsidered as adverse events caused by antiretroviral drugs, which presents a challenge in the differentiation and management of these complications. Therefore, the best approach in these cases would be to take antiretroviral side effects into consideration as well. An evaluation of factors associated with reduction in creatinine clearance in HIV patients showed that the use of PI, age over 50 years, presence of diabetes, hypertension, and CD4 count below 350 were significant factors[22]. Comorbidities were not included in our ART toxicity evaluation since the number of preexisting comorbidities in our patients was low.

ALT elevation was observed in 17% of the patients treated in our study. In a study by Núñez et al.[23] evaluating 222 patients, about 10% of the patients receiving ART were found to exhibit a sharp increase in transaminases; however, etiological studies suggested that reasons other than ART (alcohol, coinfections, etc.) might have been responsible for the hepatotoxicity. Although the incidence of hepatotoxicity caused by antiretroviral drugs is not known, it is reported that mild increases in ALT may occur during treatment. Increases in ALT levels observed in the present study were also mild in all but three of our patients, and returned to normal without requiring a regimen change. Therefore, it was concluded that the elevated ALT levels were not associated with the ART regimen used. With the exception of nonsteroidal anti-inflammatory drugs used by one patient, the reason for ALT elevation could not be determined.

During ART, 10 (8%) of the patients exhibited adverse neuropsychiatric effects, and treatment regimen was subsequently switched in four of those patients. Three of these patients were receiving an efavirenz-based combination and the symptoms disappeared after the regimen change. Previous studies have reported neuropsychiatric side effects in 50% of patients who used efavirenz, with the most common being sleeping disorders, followed by depression, dizziness, and anxiety[24]. In our study, the most common neuropsychiatric side effect was forgetfulness, followed by insomnia/nervousness and depression. Among the treatment groups in our study, neuropsychiatric side effects were observed in 50% of patients using a NNRTI-based combination. Although there were few patients in our population using efavirenz, the complication rate was comparable to those in other studies.

Two patients in our study using PI exhibited clinical side effects associated with the musculoskeletal system. Literature data indicate an incidence of 21.3% for ART-associated musculoskeletal side effects[12]. A 48-week study comparing abacavir/lamivudine with TDF/FTC revealed a significant 13% loss of bone mineral density in the TDF/FTC group[25]. Although bone mineral density was not routinely tested in our patient group, osteoporosis was identified in one patient with musculoskeletal complaints.

There are few studies examining side effects based on a variety of clinical and laboratory parameters together, as we did in the present study. Each study generally focuses on a single side effect. Since each study is based on different definitions or criteria for toxicity, it is difficult to make comparisons between them.

Approximately 20-25% of patients discontinue ART due to adverse events associated with treatment[1]. Of our patients, 12% required regimen changes due to side effects. However, a limitation of our study was the short follow-up period. This resulted in low rates of side effects, especially with new ART regimens. Although recent introduction of more effective and easier to use new treatment options has reduced the incidence of side effects, they should be evaluated for longer follow-up periods. Another limitation of our study was that there was no evaluation of comorbidity subgroups due to the limited number of patients.

Conclusion

The main findings of this study were that 50% of patients who were normolipidemic before ART developed hyperlipidemia during treatment, and severe renal dysfunction occured as a side effect of ART, albeit at a very low rate (3%). In addition, the most common clinical side effect was diarrhea, which occured in 10% of the patients. Diarrhea was severe enough to require a change in ART regimen in two-thirds of those patients. Regimens including PI group antiretrovirals caused the highest rate of side effects. In conclusion, for patients starting ART, it is important to consider the potential side effects and the patient's comorbidities when selecting a treatment regimen, and these issues should be kept in mind and evaluated together during follow-up.

Future studies that include larger patient populations that are followed for longer periods and evaluate multiple factors including comorbidities will provide more robust data concerning the side effects of ART.

Ethics

Ethics Committee Approval: This retrospective study was performed after obtaining approval of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital's Ethics Committee (89513307/1009/515) on 30.12.2015.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B., S.G., Concept: S.G., Design: S.B., S.G., S.Ö., Data Collection or Processing: S.B., S.G., Analysis or Interpretation: S.B., S.G., Literature Search: S.B., Writing: S.B.

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