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The Effects of Antivirals for Human Immunodeficiency Virus Treatment on Renal Functions

HIV Tedavisinde Kullanılan Antivirallerin Böbrek Fonksiyonuna Etkilerinin Araştırılması

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Abstract

Objective: Turkey is among the countries with a low incidence of the human immunodeficiency virus (HIV) infections. When HIV cases are decreasing worldwide, our country is among the countries where the number of patients is rapidly increasing. Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and abacavir are the drugs used for HIV treatment in Turkey. The estimated glomerular filtration rate (eGFR) is widely used as a kidney function indicator. This study aimed to investigate the effects of TDF and TAF-based regimens on renal function.

Materials and Methods: During the study period, 104 patients who are HIV-positive underwent treatment with an antiretroviral therapy (ART) regimen, of whom 60 fulfilled the inclusion criteria and were included in the study. This study retrospectively examined the effects of TAF and TDF-based regimens on eGFR and other routine parameters.

Results: Patients receiving TDF-based regimens revealed significantly increased serum creatinine and decreased eGFR levels compared to pre-treatment levels. Conversely, patients receiving a TAF-based regimen did not show significant changes in eGFR or serum creatinine levels.

Conclusion: Our data indicate that eGFR levels decrease with a TDF-based regimen. Thus, with TDF as a component of the ART regimen, eGFR levels should be carefully monitored. TDF-free regimens should be used in patients who are predicted to have impaired renal function and those with renal function changes during treatment.

Keywords: Human immunodeficiency virus, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate, renal function, glomerular filtration rate

Öz

Giriş: Türkiye, insan immün yetmezlik virüsü (HIV) enfeksiyonu insidansının düşük olduğu ülkeler arasındadır. İnsan immün yetmezlik virüsü olgularının tüm dünyada azalmakta olduğu bir dönemde ülkemiz hasta sayılarının hızla arttığı ülkeler arasında yer almaktadır. Tenofovir disoproksil fumarat (TDF), tenofovir alafanamid (TAF) ve abacavir Türkiye’de HIV tedavisinde kullanılan ilaçlardır. Tahmini glomerüler filtrasyon hızı (eGFR), böbrek fonksiyonunun bir göstergesi olarak yaygın şekilde kullanılmaktadır. Bu çalışmada TDF ve TAF bazlı rejimlerin böbrek fonksiyonu üzerindeki etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışma süresi boyunca, 104 HIV pozitif hastaya bir antiretroviral tedavi (ART) rejimi ile tedavi uygulandı. Bunlardan dahil edilme kriterlerini karşılayan 60 hasta çalışmaya alındı. Bu çalışmada retrospektif olarak TAF ve TDF tabanlı rejimlerin eGFR ve diğer rutin parametreler üzerindeki etkileri incelendi.

Bulgular: TDF bazlı rejimi alan hastalarda, tedavi öncesi seviyelere kıyasla serum kreatinin seviyelerinde anlamlı bir artış ve eGFR seviyelerinde anlamlı bir düşüş vardı. Bunun tersine, TAF bazlı rejimi alan hastalar, eGFR veya serum kreatinin seviyelerinde önemli değişiklikler göstermedi.

Sonuç: Verilerimiz, TDF bazlı rejim kullanıldığında eGFR seviyelerinin düştüğünü göstermektedir. Bu nedenle, TDF, ART rejiminin bir bileşeni olarak kullanılıyorsa, eGFR seviyeleri dikkatle izlenmelidir. Bu nedenle; böbrek fonksiyonlarında sıkıntı olabileceği öngörülen hastalarda ve tedavisi sırasında böbrek fonksiyon değişiklikleri görülen hastalarda TDF içermeyen rejimler kullanılmalıdır.

Anahtar Kelimeler: İnsan immün yetmezlik virüsü, tenofovir disoproksil fumarat, tenofovir alafanamid fumarat, böbrek fonksiyonu, glomerüler filtrasyon hızı

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Introduction

Approximately, 38 million people worldwide are infected with the human immunodeficiency virus (HIV). Of the infected people, 81% are aware of their HIV status and only 26 million are receiving treatment. Approximately, 1.7 million new cases and 690 thousand deaths occur annually worldwide^[1]. Turkey is among the countries with low HIV prevalence, but the number of new cases reported has been increasing over the years.

The widespread use of combined antiretroviral therapy (cART) has improved the life expectancy of patients who are HIV-positive^[2]. Tenofovir disoproxil fumarate (TDF), a nucleotide analog, and reverse transcriptase inhibitor are widely used in most countries for HIV treatment. It is among the most cost-effective drugs against HIV worldwide and is used as a conventional component of cART for HIV treatment^[3,4]. Additionally, TDF has been approved in case of pre-exposure prophylaxis to prevent HIV transmission for those at high risk of contracting this virus^[5].

In Turkey, TDF, tenofovir alafenamide (TAF), and abacavir-based ARTs are used for HIV treatment. The estimated glomerular filtration rate (eGFR) is commonly used as a kidney function indicator^[6,7]. Studies show that TDF is associated with decreased glomerular filtration rate (GFR) and renal dysfunction^[8-13].

In this study, we retrospectively examined the effects of TAF and TDF-based regimens on kidney function tests and other routine parameters in HIV-positive patients.

Materials and Methods

Study Design and Patients

This retrospective, observational, single-center study, analyzed the medical records of 104 patients who were followed up in the Infectious Diseases Clinic due to HIV infection between January 2018 and July 2020. Forty-four cases were excluded for various reasons. Routine parameters, including sodium, potassium, chloride, urea, creatinine, calcium, eGFR, HIV RNA levels, CD4+ cell counts, and comorbidities, were retrospectively examined at the beginning of the antiviral treatment and for 3, 6, and 12 months. Patients with prior HIV treatment, under 18 years of age, and coinfecting with hepatitis B or C virus were excluded from the study.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 23.0 for Mac (SPSS Inc., Chicago IL, USA). Categorical variables were compared using the chi-square or Fisher Exact test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test between treatment groups. The Wilcoxon signed-rank test was used to compare non-normally distributed variables

at different time points in each treatment group. A p value of <0.05 was considered statistically significant.

This study was performed with the approval of Hatay Mustafa Kemal University Faculty of Medicine Retrospective Ethics Board (reference number: 27.07.2020-27, date: 27.07.2020).

Results

During the study period, 104 patients who are HIV-positive underwent treatment with an ART regimen. Of whom, 60 patients fulfilled the inclusion criteria of the study. The study flowchart is presented in Figure 1.

Of the 60 patients who are HIV-positive and are included in the study, 47 (78.3%) were male and 13 (22.7%) were female, and the median age was 33.5 (25.5-45.5) years. Comorbidities were present in 6.7% (n=4) patients, and 23.7% patients (n=14) were diagnosed with acquired immunodeficiency syndrome (AIDS) without comorbidities. Only patients without prior ART were included. Table 1 presents the patients' baseline characteristics according to treatment groups.

TDF-based regimen was given to 41 (68.3%) patients while TAF-based regimen in 19 (31.7%). No significant differences were found between the treatment groups in terms of age, gender, the presence of AIDS during ART onset, and the presence of

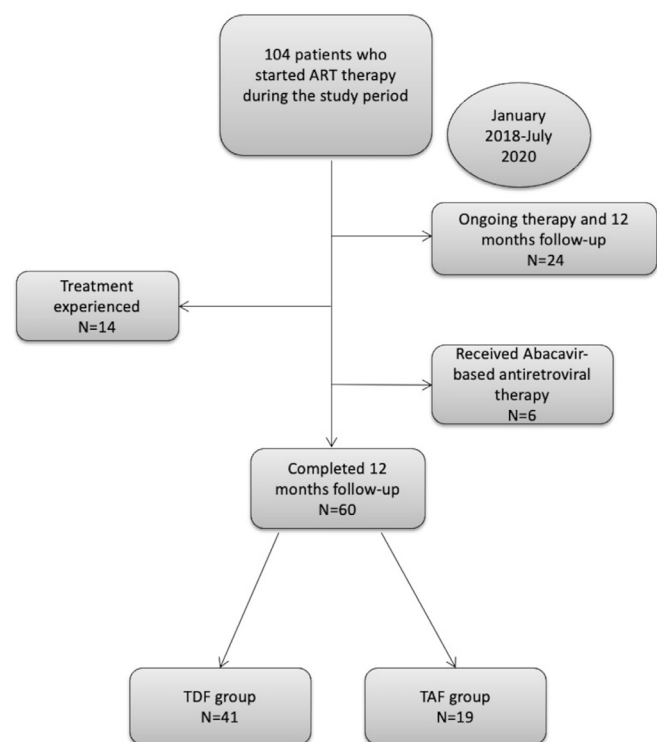


Figure 1. Flowchart showing the selection of the study group
ART: Antiretroviral therapy, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide

comorbidities ($p=0.679$, $p=0.194$, $p=0.188$, and $p=0.297$, respectively). However, basal serum creatinine and potassium levels were significantly higher in patients receiving TAF-based regimen than those receiving TDF-based regimen ($p=0.027$ and $p=0.047$, respectively) (Table 1).

A significantly increased serum creatinine levels were seen in patients receiving TDF-based regimen after three months, with significantly decreased eGFR levels, compared to the pre-

treatment levels ($p=0.003$ and $p=0.001$, respectively). However, this trend did not continue after three months (Figure 2). Conversely, patients receiving a TAF-based regimen did not show significant changes in eGFR or serum creatinine levels even after 12 months.

The serum potassium levels significantly increased after three months of the TDF-based regimen. The serum phosphate levels started to decrease after three months and significantly

Table 1. Baseline characteristics of patients according to the treatment groups

	TDF group (n=41)	TAF group (n=19)	p value
Age, years	33.5 (26-42)	34 (24-51)	0.679
Gender, male	30 (73.2)	17 (89.5)	0.194
AIDS at diagnosis	12 (30.0)	2 (10.5)	0.188
Comorbidity	4 (9.8)	0 (0)	0.297
Creatinine, mg/dL	0.78 (0.65-0.90)	0.86 (0.79-0.98)	0.027*
eGFR, %	111.5 (104-125)	109 (93-125)	0.395
Sodium, mmol/L	139 (137-140)	139 (139-141)	0.409
Potassium, mmol/L	4.2 (4.1-4.4)	4.4 (4.2-4.8)	0.047*
Chlorine, mmol/L	105 (104-106)	105 (103-106)	0.776
Phosphate, mmol/L	3.4 (3-3.8)	3.1 (2.7-3.5)	0.316
Calcium, mmol/L	9.3 (9-9.7)	9.5 (9.1-9.9)	0.255

*Statistically significant. Categorical data are expressed as n (%) and continuous data as median (interquartile range: 25th and 75th percentile).

eGFR: Estimated glomerular filtration rate

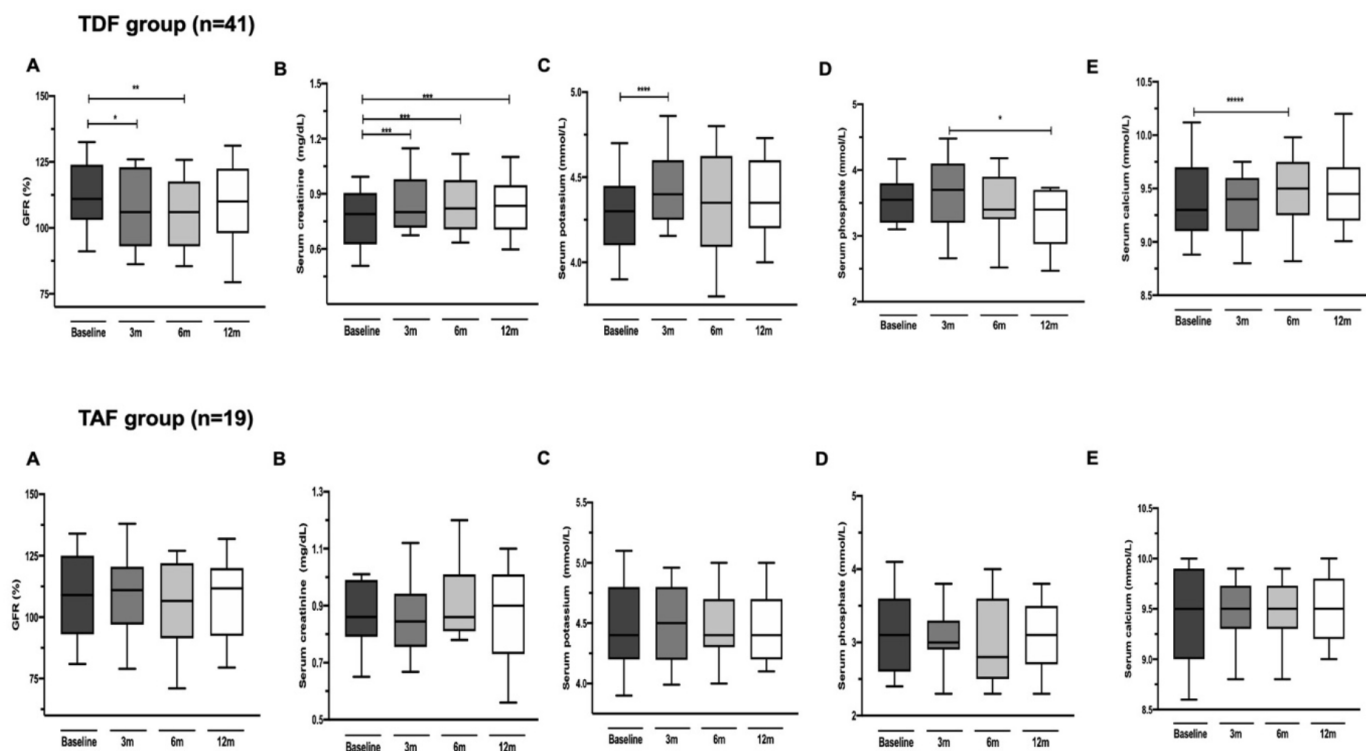


Figure 2. The comparison of (A) GFR, (B) serum creatinine, (C) serum potassium, (D) serum phosphate, and (E) serum calcium parameters in the TDF and TAF groups at different time points after administration

GFR: Glomerular filtration rate, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide

decreased after 12 months of the TDF-based regimen. Significantly increased serum calcium levels were seen after six months of TDF-based regimen; however, no such changes were seen in patients receiving TAF-based regimen.

Discussion

A single-center, observational study by Nishijima et al.^[8] revealed that long-term TDF exposure decreases renal function in HIV-1 patients with low body weight. A meta-analysis study by Cooper et al.^[9] revealed a statistically significant decrease in creatinine clearance and renal dysfunction with a TDF-based regimen. However, another meta-analysis study conducted by Wang et al.^[14] revealed that TAF and TDF have similar tolerability, safety, and efficacy. With a TAF-based regimen, fewer side effects related to bone density and renal functions were found in the treatment of HIV-1 patients with or without prior treatments. Our study revealed decreased eGFR levels in patients receiving TDF-based regimens, especially in the first three months but no decreased GFR levels even after 12 months in patients receiving TAF-based regimens. Similarly, a study by Obiri-Yeboah et al.^[15] revealed that eGFR levels decrease after six months in patients receiving TDF-based regimens despite normal serum creatinine and urea levels. Our data revealed that when using TDF, eGFR levels decreased, which is consistent with the data from previous studies. Therefore, if TDF is used as a component of the initial ART regimen, eGFR levels should be more carefully monitored. Additionally, TDF-free regimens should be used in patients who are predicted to have impaired renal function and those with renal function changes during treatment. A previous study revealed that hypophosphatemia, proteinuria, and eGFR level reduction were commonly found with TDF-based regimens in pediatric patients^[16]. Another study revealed that long-term TDF use may cause renal toxicity with hypophosphatemia, unlike zidovudine-, lamivudine-, and nevirapine-based regimens^[17]. Our study revealed that serum phosphate levels started to decrease after three months in patients receiving the TDF-based regimen and significantly decreased at 12 months of the therapy; however, no changes were observed in patients receiving the TAF-based regimen. Therefore, it can be speculated that TAF-based regimens are better in terms of renal function.

An observational cohort study revealed significant improvement in eGFR levels in patients who were switched from TDF- to TAF-based regimens^[18]. Similarly, another multicenter prospective study revealed that the transition from TDF to TAF improved eGFR levels and proteinuria in patients with renal dysfunction^[19]. Furthermore, another study revealed that proteinuria, albuminuria, proximal renal tubular function, and bone mineral density were all improved after switching from TDF- to TAF-based regimens^[20]. Another study compared the two regimens and revealed that those receiving TAF experienced significantly

smaller changes in estimated creatinine clearance, renal tubular proteinuria, and bone mineral density^[21]. These studies provide more support for renal safety of TAF and switching from TDF to TAF in those who experience progressive renal function deterioration, whereas our study excluded patients who were switched from TDF to TAF. Data on this subject in Turkey is inadequate, thus we think that more multicenter studies that involve a larger number of cases are needed.

Studies have suggested that low CD4+ cell counts, high baseline creatinine levels, older age, concomitant nephrotoxin exposure, comorbidities, use of didanosine and potent protease inhibitors, and low body mass are risk factors for renal toxicity^[22]. Moreover, TDF exposure, aging, and comorbidities were also reported as renal toxicity determinants among HIV-positive patients. Thus, regular renal function monitoring has been recommended in such high-risk individuals^[23]. Turkey has a low HIV prevalence; however, the number of cases has been gradually increasing. Therefore, we think that larger studies that investigate the risk factors for renal toxicity are needed.

Study limitations include its retrospective design, regional data investigation, and the small number of cases. Nevertheless, our data is limited and raises attention to this important topic in Turkey.

Conclusion

Our study results revealed reduced eGFR levels in patients receiving TDF-based regimens. Based on our findings and previous studies, with the use of TDF as an initial ART regimen component, kidney function tests should be more carefully monitored. Additionally, a TAF-based regimen should be preferred in regions where it is available. Multicenter future studies that involve a larger number of cases and compare different regimens are warranted.

Ethics

Ethics Committee Approval: This study was performed with the approval of Hatay Mustafa Kemal University Faculty of Medicine Retrospective Ethics Board (reference number: 27.07.2020-27, date: 27.07.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ç., T.B., F.H.T., Concept: M.Ç., F.H.T., Design: M.Ç., T.B., Data Collection or Processing: M.Ç., T.B., F.H.T., Analysis or Interpretation: M.Ç., T.B., F.H.T., Literature Search: M.Ç., T.B., F.H.T., Writing: M.Ç., T.B., F.H.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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