



# Prevalence of nephropathy and proximal tubule disorder in human immunodeficiency virus patients under tenofovir therapy

Foroogh Sabzghabaei<sup>1</sup>, Afsaneh Sedighi<sup>2\*</sup>, Raziye Shahi<sup>2</sup>, Vahid Mahmoodi<sup>2</sup>, Jahanbakhsh Khamseh<sup>2</sup>, Neda Rahimian<sup>2</sup>

<sup>1</sup>Department of Medicine, Firoozabadi Hospital, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Internal Medicine, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran

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## ABSTRACT

**Introduction:** Tenofovir is a common therapy in human immunodeficiency virus (HIV) patients.

**Objective:** This study was carried out to determine the prevalence of nephropathy and proximal tubule disorder in HIV patients under tenofovir therapy.

**Patients and Methods:** In this study, 160 HIV patients under tenofovir therapy were enrolled and the prevalence of nephropathy and proximal tubule disorder was determined and compared.

**Results:** We found, the proximal tubule involvement in 25%, 6.8%, 2.2% and 0% in first year, 2–5 years, 6–10 years and 11–18 years of disease involvement respectively, ( $P = 0.02$ ). The mean glomerular filtration rate (GFR) diminution was 2.15%, 10.53%, 12.6% and 17.79%, in the first, 2–5, 6–10, and 11–18 years, respectively, again showing a significant difference between years ( $P = 0.02$ ). Proteinuria was seen in 13.1% of patients.

**Conclusion:** We concluded that GFR diminution and proximal tubule involvement are common and important to be managed in HIV-positive patients under tenofovir therapy, and discontinuation of drug has no positive effect on GFR.

### Implication for health policy/practice/research/medical education:

This study reflects complications related to administration of tenofovir in human immunodeficiency virus (HIV) patients and could serve as a practical guide for HIV specialists in administration of HIV antiviral therapy.

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## Introduction

Human immunodeficiency virus (HIV) is one of the most common fatal infectious diseases found worldwide and the highly active antiretroviral therapy (HAART) is the most recommended therapeutic option for these patients (1). However, no single therapy is approved for HIV patients (1,2). Tenofovir is a nucleoside transcriptase inhibitor acting via interaction with function of RNA-related DNA polymerase, leading to viral inhibition and it is a first-line HIV treatment in many countries in patients with urinary excretion (1,2).

Tenofovir is contraindicated in renal failure patients (3–5). It can result in proximal tubule involvement similar to Fanconi syndrome with a normal anion gap and with

hypophosphatemia, hyperphosphaturia, hypokalemia, hypouricemia, tubular proteinuria, glycosuria, aminoaciduria, and osteomalacia (4–7). On renal biopsy, acute extensive tubular necrosis in proximal kidney tubules is found (8–10). Some of the alterations are reversible (3,11,12).

## Objectives

Tenofovir is a common therapy in HIV patients, and nephropathy is its main therapeutic adverse effect. Hence, considering the necessity for the preservation of renal function in these patients amidst scarcity of studies on Iranians, this study was conducted to determine prevalence of nephropathy and proximal tubule disorder

in HIV patients under tenofovir therapy in Iran.

## Patients and Methods

### Study design

In this cohort, 160 consecutive HIV patients under tenofovir therapy from September 2018 to April 2020 were enrolled. The exclusion criteria were chronic kidney disease stage 4 and end-stage renal disease. Data were collected through a checklist. The variables included age, gender, age of onset, duration of treatment, background diseases, smoking, alcohol use, drug/opium use, vital signs, glomerular filtration rate (GFR), creatinine, urea, uric acid (UA), sodium, and potassium. The UA, creatinine, and urea were checked every three months. In cases with increase in creatinine, the tenofovir was discontinued, and the effect on GFR level was assessed. The prevalence of nephropathy and proximal tubule disorder was determined in patients and was compared by other variables.

### Data analysis

Data analysis was carried out by the SPSS version 25.0 software. The different types of tests employed included ANOVA, Chi-squared, independent sample *t* test, and post-hoc Tukey's assays. *P* values under 0.05 were considered as statistically significant.

## Results

In this study, 101 (63.1%) patients were male and the mean (standard deviation) age was 43.3 years (11.2 years) (range; 9–72 years). In total, 82 cases (51.3%) were married. The mean (standard deviation) body mass index (BMI) was 24.9 kg/m<sup>2</sup> (4.5 kg/m<sup>2</sup>). Around 31 cases (19.4%) had academic literacy. Duration of HIV in “less than five years”, “between 5 and 10 years” and “more than 10 years” were in 42.5%, 29.3% and 18.2% of subjects respectively. However, the average duration was 6.6 years (4.3 years). As shown in Table 1, the main transmission route was sexual relationship (45%). Continuous non-steroidal anti-inflammatory drug (NSAID) use over the last year was reported in 60.6% of cases and 30% of cases were smokers too. In addition, 1.9% of patients were also using intravenous opioids. The history of background diseases is shown in Table 2. The mean serum creatinine was 0.96 mg/dL, 0.98 mg/dL and 1.09 mg/dL in baseline, after six months and at the final stage, respectively. GFR decrease was one of the causes of tenofovir discontinuation in 55% of cases. The other causes are shown in Table 3. The laboratory results are shown in Table 4.

The first and second therapeutic regimens in patients are shown in Table 5. The mean GFR initially was 89.98 (17.78) and the finally 77.95 (18.62), showing a significant difference (*P* = 0.001). The GFR level lower than 90 mg/dL was increased by 74.4%.

There was GFR decrease in 84.4% of cases compared

**Table 1.** Route of HIV transmission in patients

Route	No.	%
Partner	38	23.8
Sexual relationship	72	45.0
Blood	48	30.0
Maternal	2	1.3
Total	160	100.0

**Table 2.** Disease background of patients

Disease	No.	%
DM	4	2.5
Tuberculosis	18	11.3
HTN	6	3.8
CKD	11	6.9
HBV	4	2.5
HCV	30	18.8

**Table 3.** Causes for tenofovir discontinuation in patients

Cause	No.	%
Osteopenia	9	45.0
Lack of response	6	30.0
GFR decrease and osteopenia	5	25.0
Total	20	100.0

**Table 4.** Laboratory results of patients

Test	Mean	SD	Minimum	Maximum
AST (unit/L)	26.25	14.54	5	116
ALT (unit/L)	32.34	19.91	7	132
LDL-c (mg/dL)	100.41	32.01	27	219
HDL-c (mg/dL)	45.03	12.79	20	97
TG (mg/dL)	154.23	90.99	42	562
WBC-FIRST (per µL)	5651.04	1951.74	5	12540
WBC-LAST (per µL)	6049.98	2343.52	6	19800
CD4-FIRST (per µL)	389.28	334.08	1	3028

with measurements conducted before the treatment. In total, 13.1% of the patients had proteinuria, including 1+, 2+ and 3+ in 8.8%, 2.5% and 1.9% of cases, respectively. The GFR alteration rates are shown in Table 6. Only inhalational opium use (*P* = 0.001), as shown in Table 7, was related to GFR alterations in patients. The mean CD4 count was initially 389.28 (334.08), and the final mean GFR level was 620.94 (284.24), showing a significant difference (*P* = 0.001). CD4 count was increased by 83.1%, with a mean increase of 319.4 (188.6) and mean decrease of 235.24 (422.29). There was a significant correlation between CD4 count and GFR level (*P* = 0.001).

In this study, the proximal tubule involvement was 25%, 6.8%, 2.2%, and 0% in the first year, at 2–5 years, at 6–10 years and at 11–18 years, respectively, showing a

**Table 5.** Utilized therapeutic regimens in the patients

	No.	%
<b>Initial regimen</b>		
TDF + FTC + ATV/r	16	10.0
TDF + FTC + LPV/r	2	1.3
TDF + FTC + EFV	104	65.0
TDF + FTC + RAL	3	1.9
TDF + FTC + RAL + ATV/r	3	1.9
TDF + FTC + DTG	4	2.5
DTG + 3TC + TAF	1	0.6
EFV + 3TC + TAF	2	1.3
FTC + TAF + ATV/r	1	0.6
TDF + 3TC + ATV/r	6	3.8
TDF + EFV + 3TC	12	7.5
3TC + TDF + LPV/r	2	1.3
TDF + ATV/r + 3TC	1	0.6
AZT + EFV + 3TC	1	0.6
ABC + TDF + LPV/r	1	0.6
NV + TDF + FTC	1	0.6
<b>Second regimen</b>		
3TC + EFV + ABC	6	3.8
ATV/r + 3TC + ABC	2	1.3
3TC + TAF + EFV	1	0.6
AZT + 3TC + ATV/r	3	1.9
3TC + ATV/r + DTG	1	0.6
3TC + AZT + DTG	1	0.6
FTC + TAF + EFV	3	1.9
3TC + AZT + EFV	2	1.3
FTC + 3TC + DTG	1	0.6
TDF + 3TC + ATV/r	1	0.6
TDF + FTC + EFV	2	1.3
EFV + 3TC + TAF	3	1.9
ABC + DTG + RTV + 3TC	1	0.6

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir; EFV, efavirenz; RAL, raltegravir; DTG, dolutegravir; 3TC, lamivudine; TAF, tenofovir alafenamide; AZT, Zidovudine; ABC, abacavir; NVP, nevirapine; RTV, ritonavir.

**Table 6.** GFR alteration rates in patients (mL/min/1.73 m<sup>2</sup>)

GFR	Mean	SD	Minimum	Maximum
Mean increase	12.04	12.74	0.0	51.00
Mean decrease	-16.48	12.68	-50.00	-1.00

significant difference ( $P = 0.02$ ). The mean GFR decrease was 2.15%, 10.53%, 12.6% and 17.79%, in the first year, at 2–5 years, at 6–10 years, and at 11–18 years, respectively, showing a significant difference ( $P = 0.02$ ). Tenofovir discontinuation was not related to last GFR level ( $P = 0.4$ ).

## Discussion

In this study, the rate and extent of nephropathy due to tenofovir use was determined in HIV-positive cases. Proximal tubule disorders were seen in 25%, 6.8% and 2.2% in the first year, at 2–5 years, and at 6–10 years of tenofovir use; however, thereafter no cases were seen until 18 years later. It was related to duration of use. The mean rate of GFR

**Table 7.** GFR measurements based on other variables

NSAID	Mean first GFR	SD	P value
No	88.25	16.87	0.3
Yes	91.09	18.48	
NSAID	Mean last GFR	SD	
No	76.81	17.31	0.5
Yes	78.69	19.47	
Smoking	Mean first GFR	SD	
Yes	94.43	15.18	0.07
No	88.57	18.63	
Smoking	Mean last GFR	SD	
Yes	79.19	15.50	0.5
No	77.46	19.85	
Opium use	Mean first GFR	SD	
Yes	89.67	21.93	0.9
No	89.98	17.87	
Opium use	Mean last GFR	SD	
Yes	67.11	15.68	0.001
No	80.25	18.43	
Diabetes	Mean first GFR	SD	
Yes	86.75	12.42	0.6
No	90.06	18.0	
Diabetes	Mean last GFR	SD	
Yes	82.75	33.45	0.6
No	77.83	18.25	
TB history	Mean first GFR	SD	
Yes	91.72	20.76	0.6
No	89.75	17.54	
TB history	Mean last GFR	SD	
Yes	77.67	16.47	0.9
No	77.99	18.92	
Hypertension	Mean first GFR	SD	
Yes	92.17	23.86	0.9
No	89.89	17.69	
Hypertension	Mean last GFR	SD	
Yes	68.17	11.97	0.7
No	78.33	18.75	

fall was 2.15%, 10.53%, 12.6% and 17.79% in the first year, at 2–5 years, at 6–10 years and at 11–18 years, respectively, showing a significant difference. For this reason, this effective and potent drug may be administered in the first treatment year and then can be replaced with other drugs for safety. The GFR improvement was not attained with tenofovir discontinuation, showing the irreversibility of the nephropathy in patients. Of 160 patients, 21 cases had overt proteinuria (3+), which underwent kidney biopsy. In one case, there was tubulointerstitial lesions due to HIV-associated nephropathy. In addition, there was one case of focal segmental glomerulosclerosis (FSGS) and the other with diabetic nephropathy. This is in line with the study conducted by previous authors; however, with a smaller sample size. This study showed that kidney involvement in HIV patients has shifted from HIVAN to immune-complex GN and diabetic nephropathy and FSGS cases.

The study by De Waal et al on 15156 cases showed, patients with lower initial GFR had a higher rate of renal

adverse effects (13). Moreover, Weaver et al, reported that of 24 HIV-positive cases under tenofovir therapy, 42% had reversible outcomes (3). However, in our study with a larger same size, the irreversible cases were more common. In another study on 213 Brazilian patients, the cardiovascular disease rate was higher in cases undergoing tenofovir therapy (4). However, in our study, no comparison was conducted with other drugs due to some limitations.

In the study by Waheed et al, on 15 cases under tenofovir therapy, of total patients, 11 patients had GFR more than 90 and the duration of treatment was considered 64 months (5). The mean GFR was decreased from 104 mL/min to 69 mL/min and then it was improved but not completely after drug discontinuation. This similarly shows the irreversible pattern. Herlitz et al, reported a rate of 61% for acute kidney injury and 15% for anuria (6). The difference in results of their survey may be due to a smaller sample size compared with our study.

A cross-sectional study on 101 patients showed that creatinine rise, proteinuria and tubular dysfunction were present in 7%, 37% and 15% of cases, respectively (7). However, these rates were lower in our study due to a shorter follow-up length. Gerard et al, assessed 53 patients under tenofovir therapy for 13 months (8). They found, GFR was decreased at a rate of 7.8 mL/min versus the control group. However, we had no control group for comparison and such design may be pursued in future studies. Crane et al reported a mean GFR decrease rate of 7 mL/min, leading to a rate of less than 60 mL/min in 2% of cases, similar to our study (9).

A review study by Jafari et al showed that older age, opium or NSAIDs use, low weight, low CD4+ count and high-dose and long-term tenofovir therapy were related to renal disorders in HIV cases under tenofovir therapy (14). Among these factors, only low CD4 cell count was related to nephropathy. Liu et al assessed 823 adult cases with GFR over 90 mL/min. They found, 21.6% had renal failure with an S-shaped pattern of renal function (15). The difference was especially higher between the first and fourth year of tenofovir therapy. Hence, tenofovir may be administered in the first year of treatment and then replaced with other agents.

Hoang et al reported that 8.5% out of 400 cases under tenofovir therapy had renal dysfunction that was related to older age, lower BMI and no exposure to isoniazid therapy (16). Anthropometric and demographic variables and tuberculosis treatment in our study were not related to renal function. Accordingly, Gupta et al, showed the importance of the type of salt used in tenofovir. This may be a possible cause of differences between results of various studies (17).

## Conclusion

In this study, we concluded that GFR diminution and

proximal tubule involvement are common and important to be managed in HIV-positive patients under tenofovir therapy, since discontinuation of the drug has no positive effect on GFR. Regarding the results, treatment with tenofovir in the initial two years is rational and then replacement with other drugs may be considered. However, further studies with a larger sample size and multi-center sampling can lead to more definitive results.

## Limitations of the study

Main limitations of our study are a smaller sample size and a shorter patient follow-up period. Further studies with a larger sample size and long-term-follow up are recommended.

## Authors' contribution

AS, FS and KE were the principal investigators of the study. RS, JKh, VM and NR were involved in preparing the concept and design of this study. VM and JKh revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revising the manuscript and critically evaluating the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of the Iran University of Medical Sciences approved this study. The institutional ethics committee of the Iran University of Medical Sciences approved all study protocols (IR.IUMS.FMD.REC1396.9511160009). Accordingly, written informed consent was obtained from all participants before any intervention. This study was part of the M.D. thesis of Mahmoodi being pursued at this university (Thesis#2952). Besides, ethical issues (including plagiarism, data fabrication and repeat publication) have been completely addressed by the authors.

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