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eGFR-EPI changes among HIV patients who switch from F/TDF to F/TAF while maintaining the same third agent in the Spanish VACH cohort

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ABSTRACT

Background: Evidence from clinical practice on the effects of switching from emtricitabine/tenofovir disoproxil fumarate (F/TDF) to emtricitabine/tenofovir alafenamide (F/TAF)-based triple-therapy (TT) regimens on renal parameters is limited.

Objective: This retrospective analysis evaluated the effects on renal function of switching from F/TDF to F/TAF-based TT regimens with no change in third agent among people living with HIV (PLWH).

Methods: Data were from a multicenter Spanish PLWH cohort. Patients with a baseline estimated glomerular filtration rate (eGFR-EPI) measurement, ≥ 1 follow-up measurement, ≥ 30 days treatment with F/TAF, and who switched from F/TDF to F/TAF with no change in third agent were included. Multivariate mixed linear models were used to evaluate change from baseline over time in eGFR-EPI. eGFR-EPI changes before and after switch were analyzed in a matched patient subgroup.

Results: Overall, 340 patients were included. Mean (95% CI) eGFR-EPI in patients with baseline eGFR-EPI < 90 ml/min/1.73m² ($n = 125$) was 79.6 (78.0; 81.2) ml/min/1.73m² at baseline and 81.3 (79.9; 82.7) ml/min/1.73m² at 12 months after switch. In the patient-matched subgroup ($n = 175$), median annual eGFR-EPI declined -4.24 ml/min/1.73m² while on F/TDF and increased $+0.93$ ml/min/1.73m² after switch to F/TAF

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($P < 0.0001$). In patients with baseline eGFR-EPI < 90 mL/min/1.73m², median annual eGFR-EPI increased +4.19 mL/min/1.73m² after switch ($P < 0.0001$).

Conclusion: Switching from F/TDF to F/TAF-based TT regimens while maintaining the same third agent numerically improved eGFR-EPI in PLWH with baseline eGFR-EPI < 90 mL/min/1.73m². eGFR-EPI improved significantly when comparing progression while on F/TDF vs progression after switch, confirming beneficial renal effects of switching to F/TAF in a clinical practice setting.

KEYWORDS: HIV, estimated glomerular filtration rate, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, switch, retrospective

Introduction

Tenofovir disoproxil fumarate (TDF) is a prodrug of the HIV nucleotide reverse transcriptase inhibitor tenofovir and has been commonly used in antiretroviral therapy (ART) for many years. Although TDF is better tolerated than older nucleoside reverse transcriptase inhibitors, its primary limitations are renal toxicity and decreases in bone mineral density.¹ Use of TDF in patients with HIV is associated with an increased risk of chronic kidney disease and proximal tubular dysfunction, a decline in estimated glomerular filtration rates (eGFR), and changes in urinary markers of renal function.²⁻⁵ An observational study found that the incidence of moderate or severe TDF-associated renal toxicity (defined as eGFR-EPI < 60 mL/min) in Spain was 29.2 cases per 1000 person-years.⁶

Another approved prodrug of tenofovir, tenofovir alafenamide (TAF), is associated with a significantly lower plasma concentration of the active metabolite tenofovir (TFV) compared to TDF and it is now widely used.⁷⁻¹⁰ A pooled analysis of 26 trials indicated that compared with those receiving TAF-containing regimens, participants receiving TDF-containing regimens reported higher cumulative incidences of proximal renal tubulopathy (0.34% versus 0%, $P < 0.001$) and discontinuations due to renal adverse events (0.47% versus 0.05%, $P < 0.001$).¹¹ In the clinical trial setting, switching from emtricitabine/tenofovir disoproxil fumarate (F/TDF) to emtricitabine/tenofovir alafenamide (F/TAF)-based triple therapy (TT) regimens has been shown to improve renal parameters.¹²⁻¹⁶ The lower renal toxicity associated with F/TAF compared with F/TDF is thought to be related to the significantly lower plasma concentration of TFV with TAF, since TFV-associated renal toxicity is concentration dependent.^{8,17,18}

Clinical practice data regarding the impact of switching from F/TDF to F/TAF on renal outcomes among people living with HIV (PLWH) are lacking globally. Only one other study in a clinical practice setting has been conducted, and a significant increase in eGFR-EPI (75.4 to 87.1 mL/min/1.73 m²) was observed 12 months after the switch in patients with baseline eGFR-EPI < 90 mL/min/1.73 m².¹⁹ Other

clinical practice data are limited to case reports and one case series.²⁰⁻²⁴ The case series of 10 patients with F/TDF-induced renal toxicity who switched to F/TAF-based regimens reported no change in median eGFR-EPI (61 mL/min at baseline) after the switch.²¹ It was speculated that the lack of improvement in eGFR-EPI may be due to the irreversible renal damage or other comorbidities such as hypertension that also contributed to the kidney disease. In addition to comorbidities, other factors such as sodium and potassium intake can influence changes in eGFR-EPI and contribute to the eGFR-EPI variation observed in the general population.²⁵ Such variations may explain some of the discrepancies among the clinical practice data for eGFR-EPI changes after switching from F/TDF-based to F/TAF-based regimens.

The objective of this analysis was to evaluate the effects on renal function of switching from an F/TDF to an F/TAF-based regimen with no change in third agent among PLWH in a large Spanish cohort.

Materials and methods

A retrospective analysis was performed using data from the VACH cohort. The VACH cohort is a prospectively recruited Spanish cohort of 14,833 HIV-infected adult patients from 23 investigational centers across Spain with the enrolment since 1997. Demographic data, HIV risk factors, Centers for Disease Control and Prevention (CDC) stage according to 1993 definitions, HIV-1 treatment initiation date, the specific antiretroviral regimens used, the date of change of every drug and the reasons for change, CD4 cell count, plasma HIV RNA levels, blood cell counts and blood chemistry tests are prospectively collected in an electronic case record form according to standardized criteria. Additional details on the data collection in VACH have been previously described.²⁶ All patients participating in the VACH cohort gave their consent to the use of anonymous data for epidemiologic studies. The study was reviewed and approved by Ethics Review Board of Cantabria.

Table 1 Patient demographics and clinical characteristics

At time of switch	eGFR-EPI at time of switch			P-Value	Subgroup population* (n = 175)
	All Switches (N = 340)	≥ 90 mL/min/1.73 m ² (n = 215)	<90 mL/min/1.73 m ² (n = 125)		
Male, n (%)	276 (81)	176 (82)	100 (80)	0.67	143 (81)
Age, yr, median (IQR)	47 (39; 53)	45 (36; 51)	50 (44; 56)	<0.0001	48 (40; 53)
Age >50 yr, n (%)	120 (35)	61 (28)	59 (47)	<0.01	68 (39)
HCV+, n (%)†	72/216 (33)	49/130 (38)	23/86 (27)	0.09	42/101 (42)
BMI kg/m ² , median (IQR)	23.9 (21.6; 26.8)	23.8 (21.3; 26.1)	24.4 (22.5; 27.7)	0.02	24.1 (21.9; 26.5)
eGFR-EPI mL/min/ 1.73 m ² , median (IQR)	95.7 (80.8; 104.4)	102.0 (96.8; 107.4)	76.6 (70.8; 81.8)	<0.0001	95.1 (79.2; 102.2)
CD4+, cells/mm ³ , median (IQR)	588 (389; 834)	588 (379; 836)	588 (407; 825)	0.70	576 (328; 803)
CD4+ ≥500 cells/ mm ³ , n (%)	220 (65)	139 (65)	81 (65)	0.98	108 (62)
CD4+ nadir cells/ mm ³ , median (IQR)	208 (90; 341)	247 (104; 367)	168 (75; 305)	0.03	163 (71; 284)
HIV RNA <50 copies/mL, n (%)	282 (83)	177 (82)	105 (84)	0.69	134 (77)
Pre-switch time on F/TDF, yr, median (IQR)	1.4 (0.7; 1.9)	1.3 (0.6; 1.8)	1.5 (0.8; 2.0)	0.10	0.1 (0.1; 0.2)
Time on F/TAF, d, median (IQR)	381 (284; 605)	404 (296; 630)	353 (263; 520)	0.01	338 (274; 499)
Time on ART, yr, median (IQR)	8.5 (2.3; 17.3)	7.8 (2.1; 17.3)	9.9 (3.3; 17.3)	0.40	10.1 (3.5; 18.5)
Time since HIV diagnosis, yr, median (IQR)	10.8 (4.4; 21.0)	10.5 (2.9; 21.2)	12.1 (5.2; 20.7)	0.22	14.5 (6.2; 24.1)

ART, antiretroviral therapy; BMI, body mass index; d, days; eGFR-EPI, estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration); F/TDF, emtricitabine/tenofovir disoproxil fumarate; F/TAF, emtricitabine/tenofovir alafenamide; IQR, interquartile range; yr, years; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

*The subgroup population consisted of patients in the full study population with available eGFR-EPI data at the start of the F/TDF regimen.

†Data were not available for all patients.

Patient populations

The primary analyses were performed on all patients meeting the selection criteria and in subgroups of patients with eGFR-EPI at baseline of <90 and ≥90 mL/min/1.73 m². To evaluate annual eGFR-EPI changes before and after the switch from F/TDF to F/TAF, analyses were also performed in a matched subgroup of patients with eGFR-EPI data during both the F/TDF and the F/TAF regimens (patient-matched subgroup).

Patient selection criteria

Patients at least 18 years of age who switched from F/TDF to F/TAF with no change in the third agent and who had eGFR-EPI data at the time of switch (baseline) from F/TDF to F/TAF up to March 2018 were included. Patients were also required to have been treated with F/TAF for at least 30 days and to have at least one follow-up eGFR-EPI measurement after the first month on F/TAF. To be included in the patient-matched subgroup, patients were also required to have at least one eGFR-EPI measurement at F/TDF start.

Data collection

Demographic characteristics extracted from the database were age, sex, race/ethnicity, weight, and body mass index. Clinical characteristics extracted from the database were the third agent of the therapeutic regimen, risk group of HIV transmission, CD4+ count, CD8+ count, HIV RNA copies, number of previous regimens, time since the first ART regimen, presence of comorbidities (e.g. diabetes, arterial hypertension, HCV, previous cardiovascular disease), and eGFR-EPI. If multiple follow-up eGFR-EPI measurements were available, the measurement closest to the relevant timepoint was selected. Dropouts and treatment changes were also collected. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (eGFR-EPI) equation and updated for age during the course of the study.

Endpoints

Baseline was defined as the time of switch from F/TDF to F/TAF. The primary endpoint analyzed was the change from baseline in eGFR-EPI over time.

Median annual eGFR-EPI changes before and after the switch from F/TDF to F/TAF were analyzed in the patient-matched subgroup.

Statistical analysis

Descriptive summaries were presented for baseline demographics and clinical characteristics. Comparisons between categorical groups were done with use of χ^2 and Fisher's exact tests. Student's *t* test was used for continuous variables. All *P* values were 2-tailed. To evaluate change from baseline over time in eGFR-EPI, multivariate mixed linear models were used with adjustment (at time of switch) for age, sex, HIV-RNA level, CD4+ count, baseline eGFR-EPI, time on previous F/TDF regimen prior to switch, time on F/TAF, time on ART, and time from HIV diagnosis as well as an interaction term between baseline eGFR-EPI and time on F/TAF. Predicted eGFR-EPI values were obtained by applying the multivariate mixed linear model regression to each patient's covariate values and averaging over the subgroup of interest.

For the patient-matched subgroup analysis, annualized median eGFR-EPI change while on F/TDF versus while on F/TAF was compared by Wilcoxon matched pairs signed rank test.

Results

In total, 340 patients were included; 81% were male and 35% were ≥ 50 years of age (Table 1). The baseline median eGFR-EPI was 95.7 ml/min/1.73 m² and 37% of patients had eGFR-EPI <90 ml/min/1.73 m². The median time on ART, on the previous F/TDF TT regimen, and on the F/TAF TT regimen was 8.5, 1.4, and 1.0 years, respectively. Patients with baseline eGFR-EPI <90 ml/min/1.73 m² were older and had a lower CD4 nadir compared with patients with baseline eGFR-EPI ≥ 90 ml/min/1.73 m² (Table 1). Most of the treatment switches were from E/C/F/TDF to E/C/F/TAF (Table 2).

Change of eGFR-EPI over time in the F/TAF regimen (adjusted for characteristics at the time of switch)

In the overall study population, the multivariate mixed model showed that age and baseline eGFR-EPI negatively impacted the change in eGFR after the switch from F/TDF, while longer time on F/TAF had the opposite effect of increasing eGFR-EPI change from baseline (with a lower positive impact for those with lower baseline eGFR-EPI as indicated by the interaction term) ($P < 0.0001$ for all). Sex, HIV RNA level, CD4+ counts, time on F/TDF prior to switch, time on

Table 2 Distribution of regimen switches

Switches (N = 340)	Proportion (%)
E/C/F/TDF to E/C/F/TAF	61
F/TDF + DRV/c to F/TAF + DRV/c	12
F/TDF + DTG to F/TAF + DTG	10
F/TDF + RAL to F/TAF + RAL	6
F/TDF + NVP to F/TAF + NVP	3
F/TDF + ETV to F/TAF + ETV	2
F/TDF + ATV/c to F/TAF + ATV/c	2
Other (less than 2% of patients)	5

ATV, atazanavir; C, cobicistat;/c, cobicistat used as booster; DRV, darunavir; DTG, dolutegravir; E, elvitegravir; ETV, etravirine; F, emtricitabine; NVP, nevirapine; RAL, raltegravir; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

ART, and time from diagnosis were not significantly associated with the change in eGFR-EPI (Table 3).

The impact of covariates was directionally identical in the subgroup analyses of patients with baseline eGFR-EPI above or below 90 ml/min/1.73 m². Statistical significance was also consistent with findings observed in the overall study population with the exception of age for which a null impact could not be ruled out in the eGFR-EPI < 90 ml/min/1.73 m² subgroup.

Predicted mean (95% CI) eGFR-EPI values were 94.3 (92.8; 95.9) at baseline and 94.2 (92.8; 95.5) ml/min/1.73 m² at 12 months after the switch from F/TDF to F/TAF in the overall study population, and 79.6 (78.0; 81.2) and 81.3 (79.9; 82.7) ml/min/1.73 m², respectively, in the subgroup of patients with a baseline eGFR-EPI <90 ml/min/1.73 m² (Figure 1). At 24 months after the switch, the predicted eGFR-EPI was 94.0 (92.8; 95.2) ml/min/1.73 m² in the overall study population and 83.0 (81.7; 84.3) ml/min/1.73 m² in the subgroup of patients with a baseline eGFR-EPI <90 ml/min/1.73 m² (Figure 1).

Patient-matched eGFR-EPI over time

In the patient-matched subgroup that had eGFR-EPI information from start of the F/TDF TT regimen through switch to the F/TAF TT regimen ($n = 175$), there was a statistically significant change in eGFR-EPI progression from before to after the switch ($P < 0.0001$; Table 4). Median annual eGFR-EPI while on F/TDF declined -4.24 ml/min/1.73 m², whereas median annual eGFR-EPI after switch to F/TAF increased $+0.93$ ml/min/1.73 m² ($P < 0.0001$). In patients with baseline eGFR-EPI <90 ml/min/1.73 m², median annual eGFR-EPI while on F/TDF declined -8.24 ml/min/1.73 m², whereas median annual eGFR-EPI after switch to F/TAF increased $+4.19$ ml/min/1.73 m² ($P < 0.0001$; Table 4).

Table 3 Mixed linear model results for adjusted eGFR-EPI change from baseline over time, overall and by baseline eGFR-EPI class*

Patient group	Coefficient [95% Confidence Interval], P-Value		
	All (n = 331†)	eGFR – EPI ≥90 mL/min/1.73 m ² at switch (n = 208)	eGFR – EPI < 90 mL/min/1.73 m ² at switch (n = 123)
Age, per year	-0.25 [-0.34; -0.16], p < 0.001	-0.33 [-0.44; -0.22], p < 0.001	-0.13 [-0.29; 0.03], p = 0.122
Sex (male as reference group)	0.53 [-1.45; 2.51], p = 0.599	-0.40 [-2.71; 1.91], p = 0.734	2.37 [-1.14; 5.88], p = 0.186
Log (HIV RNA)	-0.18 [-0.63; 0.26], p = 0.425	-0.16 [-0.67; 0.35], p = 0.533	-0.24 [-1.05; 0.57], p = 0.564
Log (CD4 cell count)	0.19 [-0.93; 1.31], p = 0.741	-0.06 [-1.27; 1.15], p = 0.926	1.5 [-0.93; 3.93], p = 0.225
Baseline eGFR – EPI, mL/min/1.73 m ²	-0.21 [-0.27; -0.15], p < 0.001	-0.19 [-0.32; -0.05], p = 0.007	-0.23 [-0.41; -0.04], p = 0.016
Time on F/TAF, days	0.03 [0.01; 0.04], p < 0.001	0.04 [0.01; 0.07], p = 0.005	0.05 [0.01; 0.09], p = 0.022
Baseline eGFR – EPI*Time on F/TAF, days	-0.0003 [-0.0004; -0.0002], p < 0.0001	-0.0004 [-0.0007; -0.0001], p = 0.003	-0.0006 [-0.0011; -0.00005], p = 0.032
Time on F/TDF prior to switch, per month	0.03 [-0.02; 0.08], p = 0.236	0.01 [-0.05; 0.06], p = 0.865	0.07 [-0.01; 0.15], p = 0.098
Time on antiretroviral therapy, years	0.04 [-0.08; 0.16], p = 0.515	0.11 [-0.03; 0.25], p = 0.126	-0.07 [-0.28; 0.14], p = 0.503
Time since HIV diagnosis, years	0.01 [-0.09; 0.11], p = 0.815	0.02 [-0.10; 0.14], p = 0.747	0.01 [-0.17; 0.19], p = 0.885
Constant	30.69 [19.02; 42.36], p < 0.0001	32.73 [14.96; 50.50], p < 0.0001	17.91 [-5.61; 41.43], p = 0.136

eGFR-EPI, estimated glomerular function rate (Chronic Kidney Disease Epidemiology Collaboration); F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/disoproxil fumarate; HIV, human immunodeficiency virus.

*Predicted values were obtained by applying the fitted multivariate models to each patient’s covariate values and averaging over the group of interest. The following formulas were applied:

For all patients:

$$eGFR-EPI = 30.69 + 0.03 * (\text{days on TAF}) - 0.25 * \text{Age} - 0.21 * (\text{eGFR-EPI switch}) - 0.0003 * (\text{eGFR-EPI switch}) * (\text{days on TAF}).$$

For patients with eGFR-EPI at time of switch <90 mL/min/1.73 m²:

$$eGFR-EPI = 17.91 + 0.05 * (\text{days on TAF}) - 0.13 * \text{Age} - 0.23 * (\text{eGFR-EPI switch}) - 0.0006 * (\text{eGFR-EPI switch}) * (\text{days on TAF}).$$

For patients with eGFR-EPI at time of switch ≥90 mL/min/1.73 m²:

$$eGFR-EPI = 32.73 + 0.04 * (\text{days on TAF}) - 0.33 * \text{Age} - 0.19 * (\text{eGFR-EPI switch}) - 0.0004 * (\text{eGFR-EPI switch}) * (\text{days on TAF}).$$

†2 outliers identified in the residual analysis were excluded, 7 patient regimens had missing values for at least one of the covariates and thus excluded from the regression.

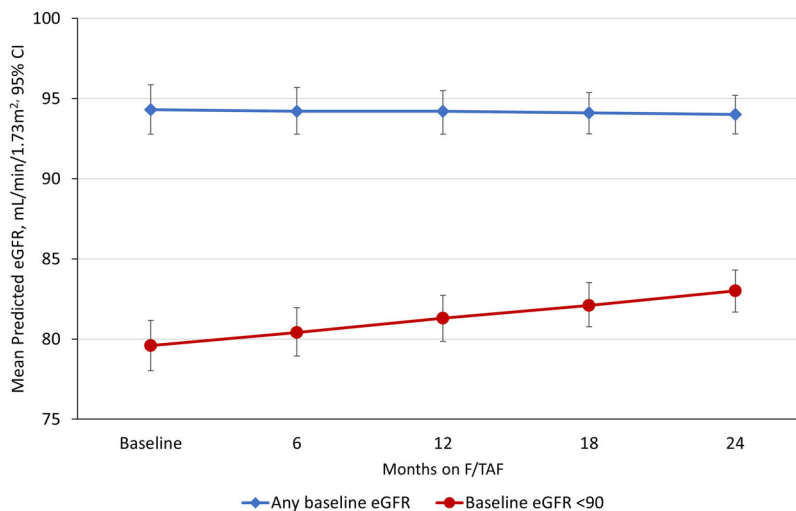


Figure 1 Mean predicted eGFR-EPI values* after switching from F/TDF to F/TAF (N = 331). eGFR-EPI, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

*Predicted values were obtained by applying the fitted multivariate models to each patient’s covariate values and averaging over the group of interest. The following formulas were applied:

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For patients with eGFR-EPI at time of switch ≥90 mL/min/1.73 m²:

$$eGFR-EPI = 32.73 + 0.04 * (\text{days on TAF}) - 0.33 * \text{Age} - 0.19 * (\text{eGFR-EPI switch}) - 0.0004 * (\text{eGFR-EPI switch}) * (\text{days on TAF})$$

Table 4 Subgroup analysis of patient-matched annual eGFR-EPI change

Patient Group	F/TDF Regimen	F/TAF Regimen	P-Value
All (N = 175)			
eGFR-EPI change, annualized median (IQR)	-4.24 (-10.37; -0.48)	+0.93 (-2.67; 6.34)	<0.0001
eGFR-EPI ≥ 90 mL/min/1.73 m ² at switch (n = 107)			
eGFR-EPI change, annualized median (IQR)	-2.79 (-7.56; 0.36)	-0.28 (-4.64; 3.59)	<0.01
eGFR-EPI < 90 mL/min/1.73 m ² at switch (n = 68)			
eGFR-EPI change, annualized median (IQR)	-8.24 (-16.46; -2.09)	+4.19 (-0.10; 9.88)	<0.0001

eGFR-EPI, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; IQR, interquartile range.

Discussion

In this cohort of PLWH, switching from F/TDF to F/TAF-based TT regimens while maintaining the same third agent improved eGFR with baseline eGFR-EPI < 90 mL/min/1.73 m². Furthermore, eGFR-EPI significantly improved when comparing the progression of individual patients while on F/TDF to progression after the switch to F/TAF. The median annual change in eGFR-EPI declined on F/TDF but increased on F/TAF, in a sample with a median follow-up time on F/TAF of 1 year. Together these data suggest a beneficial effect on renal safety of a switch from F/TDF to F/TAF-based TT regimens on eGFR-EPI in this cohort.

Similar to the results found in the current Spanish cohort, in a study conducted in a German cohort of PLWH there was a significant increase in eGFR-EPI (75.4 to 87.1 mL/min/1.73 m²) 12 months after switching from a F/TDF to F/TAF-based TT regimen in patients with baseline eGFR-EPI < 90 mL/min/1.73 m².¹⁹ The percentage of patients in the overall study cohort with normal eGFR-EPI (≥ 90 mL/min/1.73 m²) increased from 42% at baseline to 62% at 12 months. In both studies, the results indicate that patients with baseline eGFR-EPI < 90 mL/min/1.73 m² experience more benefit when switching from F/TDF to F/TAF-based regimens compared with those who had normal baseline eGFR-EPI, although the studies were not designed to compare differences between these groups. For patients in the Spanish cohort with eGFR-EPI < 90 mL/min/1.73 m², the positive association between time on F/TAF and eGFR-EPI change shown in the mixed linear model highlighted the benefits of F/TAF for long-term treatment, especially considering the natural eGFR decline with age. A small retrospective study found no significant change in eGFR-EPI overall after a switch from F/TDF- to F/TAF-based regimens, but lower pre-switch eGFR-EPI was a strong predictor of post-switch eGFR-EPI improvement.¹⁸ These data suggest that an eGFR-EPI < 90 mL/min/1.73 m² may be one indicator for considering a switch from a F/TDF-based regimen to a F/TAF-based regimen; however, other markers of renal function may be impacted in patients with normal eGFR-EPI.

The generalizability to PLWH is a strength of this study as the VACH cohort includes PLWH with comorbidities and disease characteristics that may exclude them from clinical trials. Another strength is the patient-matched subgroup analysis, where the eGFR-EPI before and after regimen switch was analyzed with each patient serving as his/her own comparator. This eliminates confounding from differences between treatment groups, such as the presence of cardiovascular disease, which can have an impact on renal function. Limitations of the study include those inherent to observational studies, including potentially heterogeneous data collection among the various physicians and missing data for some of the variables. Moreover, while confounding factors have been adjusted for in the regression model, confounding by indication remains a possibility.

The results of the current study of PLWH support clinical trial data indicating that switching from F/TDF-based regimens to F/TAF-based regimens has a beneficial effect on renal dysfunction. Switching reversed the decline in eGFR-EPI associated with TDF in patients with baseline eGFR-EPI < 90 mL/min/1.73 m².

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author, RT. The data are not publicly available due to restrictions [e.g. their containing information that could compromise the privacy of research participants].

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