Changes in renal function after switching from TDF to TAF in HIV-infected individuals: a prospective cohort study

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Summary: We assessed changes in renal function after replacing TDF with TAF in a national cohort of HIV-infected individuals. Among patients with established renal dysfunction, urinary protein-to-creatinine ratio and eGFR improved after the switch to TAF.

ABSTRACT

Background

Replacing tenofovir disoproxil fumarate (TDF) with tenofovir alafenamide (TAF) improves renal tubular markers in HIV-infected individuals, but the impact on estimated glomerular filtration rate (eGFR) remains unclear.

Methods

We included all participants from the Swiss HIV Cohort Study who switched from a TDF to a TAF-containing antiretroviral regimen or continued TDF. We estimated changes in eGFR and urine protein-to-creatinine ratio (UPCR) after 18 months using mixed-effect models.

Results

Of 3'520 participants (26.6% women, median age 50 years), 2'404 (68.5%) switched to TAF. Prior to switch, 1'664 (47.3%) had an eGFR <90 mL/min, and 1'087 (30.9%) a UPCR ≥15 mg/mmol. In patients with a baseline eGFR ≥90 mL/min, eGFR decreased with the use of TDF and TAF (-1.7 ml/min). Switching to TAF was associated with increases in eGFR of 1.5 mL/min (95% CI 0.5–2.5) if the baseline eGFR was 60-89 mL/min, and 4.1 mL/min (95% CI 1.6–6.6) if <60 mL/min. In contrast, eGFR decreased by 5.8 mL/min (95% CI 2.3–9.3) with the continued use of TDF in individuals with a baseline eGFR <60 mL/min. UPCR decreased after replacing TDF by TAF, independent of baseline eGFR.

Conclusions

Switching from TDF to TAF improves eGFR and proteinuria in patients with renal dysfunction.

Keywords

Tenofovir alafenamide, estimated glomerular filtration rate, urine protein-to-creatinine ratio, renal tubulopathy, antiretroviral therapy, comorbidities, switch.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NRTI) included in many first-line antiretroviral therapy (ART) regimens, and has been associated with renal side effects such as proximal renal tubulopathy and Fanconi syndrome [1-3]. Tenofovir alafenamide (TAF), a prodrug that reaches high intracellular tenofovir concentrations while maintaining 90% lower plasma levels than TDF, seems less likely to cause proximal renal tubulopathy [4-6]. Therefore, current ART guidelines favor TAF over TDF as a component of ART for HIV-infected patients who are at risk for kidney disease [7, 8].

Whereas the beneficial impact of TAF on markers of proximal renal tubulopathy seems clear, studies reporting changes in estimated glomerular filtration rate (eGFR) have shown mixed results [5, 6, 9-11]. However, patients with co-morbidities and established renal dysfunction were generally underrepresented in these studies. A phase three study assessed the impact of replacing TDF by TAF on renal function and did not show any improvement in eGFR after 48 and 96 weeks [12, 13]. Furthermore, the single-arm design of the trials enrolling patients with renal dysfunction did not allow the comparison of changes in renal function between patients on TDF and TAF. Finally, whether the impact of replacing TDF by TAF varies among patients with comorbidities other than renal dysfunction is unknown.

We used data from the Swiss HIV Cohort Study (SHCS) to estimate the impact of replacing TDF by TAF on eGFR and proteinuria, and assessed whether differences exist among patients with renal dysfunction and other comorbidities.

METHODS

Study population

The SHCS (www.shcs.ch) is a prospective multicenter cohort that enrolls close to 80% of all HIV-infected adults currently receiving ART in Switzerland [14]. Clinical and HIV-specific data as well as laboratory values are recorded at enrollment, and every 6 months thereafter. In addition to protocol-defined assessments, laboratory data from additional visits and hospitalizations at the study sites are also registered. All changes in ART and co-medications are recorded, and stopping reasons are required when any drug is changed. Local ethical committees of all cohort centers approved this cohort study and all patients provided a written informed consent.

We considered all participants with follow-up visits after January 1st 2016. Patients had to be on a TDF-containing ART for more than 30 days and (a) continue TDF until the end of the observation period (March 2019), or (b) switch from TDF to TAF. The decision to switch was at the discretion of the treating physician. We restricted our analyses to direct switches from TDF to TAF and excluded patients who were prescribed other NRTIs in between. Additionally, patients who discontinued TAF after the switch were excluded, but we explored related causes using stopping reasons given by the treating physician. Finally, to be included, patients needed to have at least two creatinine measurements before baseline and two measurements thereafter, with a minimum of one month interval between each other. The baseline date was defined as (a) switching date for patients on TAF, (b) October 1st 2016 for patients remaining on TDF (date of introduction of TAF into the Swiss market), or (c) registration date for patients remaining on TDF who joined the SHCS after October 1st 2016.

Outcomes and definitions

Our primary outcome was the change in eGFR between baseline and 18 months thereafter. We considered all available creatinine measurements 24 months before and 18 months after baseline date, and used the CKD-EPI equation to calculate the eGFR [15]. The main exposure of interest was switching from TDF to TAF compared to remaining on TDF. Secondary outcomes were improvements in eGFR ≥10% from baseline, and changes in proteinuria (expressed as urine protein-to-creatinine ratio in mg/mmol, normal value <15 mg/mmol). Arterial hypertension was defined as two measurements >140/90 mmHg or current antihypertensive treatment, diabetes mellitus as HbA1c ≥6.5% or current antidiabetic treatment, and osteoporosis as a T-score ≤-2.5 in any bone density measurement or history of fragility fracture. Chronic hepatitis B virus (HBV) infection was defined as the presence of a positive hepatitis B surface (HBs) antigen, and hepatitis C infection (HCV) as having a detectable HCV viral load at any time-point, irrespective of HCV treatment. A history of cardiovascular disease included the past occurrence of myocardial infarction, cerebral infarction, coronary angioplasty/stenting, coronary artery bypass grafting, venous thromboembolic events, or any procedure on peripheral arteries.

Statistical analyses

We compared patient characteristics between individuals who switched to TAF and those who remained on TDF using Fisher's exact and Wilcoxon rank-sum tests. We calculated mean changes (with 95% confidence intervals [CI]) in eGFR between baseline and 18 months thereafter, and used linear mixed-effect models to analyze the impact of switching from TDF to TAF on eGFR and proteinuria. Multivariable analyses were adjusted for the following factors at baseline: age, sex, African origin, CD4 cell count (categorized as above or below 500 cells/μL), time since TDF start, history of cardiovascular disease, arterial hypertension, diabetes, and infection with HBV or HCV. Since several drugs lead to higher serum creatinine levels through reduced creatinine secretion, the use of ritonavir, cobicistat, dolutegravir or cotrimoxazole were included as time-varying covariates in the eGFR analysis [16-18]. To account for non-linearity, we added time from baseline as a linear and quadratic term. We hypothesized that the impact of switching from TDF to TAF on eGFR differed according to eGFR at baseline (categorized as ≥ 90 mL/min, 60–89 mL/min and <60 mL/min), and included this parameter as an interaction term. Residual effects within categories of this variable were accounted for using a variable indicating the quartiles within each eGFR category at baseline. All covariates were tested for interaction with time and eGFR, but no other interaction terms were statistically significant. For proteinuria, we identified age, sex, African origin, diabetes, arterial hypertension and eGFR at baseline as potential confounders, and adjusted for them in our model. Additionally, we included an interaction term for eGFR at baseline (categorized as above) to explore the impact on proteinuria among these categories. All statistical analyses were performed using Stata 15.1 (Stata Corp, College Station, TX, USA) and R 3.5.2.

Sensitivity analyses

Since the inclusion of clinically indicated creatinine measurements (e.g. in the event of acute renal failure) could lead to an accumulation of high creatinine values that are not necessarily representative of the long-term renal function trajectory, we performed a sensitivity analysis which included only measurements taken at per-protocol cohort visits, every 6 months. The exclusion of patients with less than two creatinine measurements and those who switched from TDF to a different NRTI than TAF could have led to the overestimation of the impact of switching. Therefore, we performed an analysis including all individuals with any number of creatinine measurements, and including those who switched from TDF to a different NRTI after the baseline date. These individuals were categorized into the TDF group, and eGFR values were censored at the time of switch to a different NRTI. To minimize the potential impact of other ART changes on changes in eGFR, we performed an additional analysis including only individuals without any further ART changes other than the replacement of TDF with TAF after baseline. Finally, we explored the impact of co-administering boosted protease inhibitors (PI) with TDF and TAF using an interaction term indicating whether patients were on such a regimen at baseline.

RESULTS

Study population

Of 10'482 patients with active follow-up during the study period, 8'198 ever received TDF. For our main analyses, we excluded 3'129 individuals who switched from TDF to another NRTI, 80 who switched to TAF but discontinued TAF during the study period, and 1'469 who did not have enough creatinine measurements, leaving a study population of 3'520 patients (**Figure S1**). Of those, 2'407 (68%) had switched from TDF to TAF. Overall, 938 (26.6%) patients were women, the median age was 50 years (interquartile range [IQR] 43 to 56), and 535 (15.2%) were of African origin. HBV-coinfection was present in 243 (7.2%) individuals, and HCV infection in 448 (12.9%), of whom 75 (2.3% overall) had a detectable HCV-RNA at baseline. The median eGFR at baseline was 91.4 mL/min (IQR 77.5 to 104.2); 1'664 patients (47.3%) had an eGFR below 90 mL/min, and 194 (5.5%) had an eGFR below 60 mL/min.
Baseline characteristics by switch status are shown in **Table 1**. Patients who switched to TAF were older, less likely to be female or of African origin, and had a lower eGFR at baseline. Patients in the TAF group were more likely to have comorbidities such as arterial hypertension, diabetes, cardiovascular diseases or osteoporosis, and were more likely to be on an integrase inhibitor or PI-based ART regimen at baseline. Median follow-up time was similar in both groups (15.5 months for patients remaining on TDF vs. 14.7 months for those who switched to TAF), but the exposure to TDF before baseline was 1.1 year longer in those who switched to TAF compared to those remaining on TDF. Median eGFR at baseline was higher in the TDF group than in the TAF group (96.9 mL/min, IQR 83.4 to 108.3 vs. 89.0 mL/min, IQR 75.1 to 102.1, $p<0.0001$). Of all patients included in our analysis, 3'036 (86.3%) had proteinuria measurements available at baseline. The proportion of individuals with a urine protein-to-creatinine ratio ≥15 mg/mmol as well as median urine protein-to-creatinine ratio at baseline were similar between those who remained on TDF and those who switched to TAF.

Changes in eGFR over time

From baseline to 18 months thereafter, eGFR decreased by 1.7 mL/min (95% CI 0.8 to 2.7) in individuals who remained on TDF, and increased by 0.3 mL/min (95% CI -0.5 to 1.0) in those who switched to TAF. In multivariable analyses, switching from TDF to TAF was associated with a decrease in eGFR for patients with an eGFR at baseline ≥90 mL/min, and with an increase for patients with a baseline eGFR of 60–89 mL/min and below 60 mL/min (**Figure 1, Table 2**). Switching from TDF to TAF was associated with a predicted change in eGFR of -1.7 mL/min (95% CI -2.7 to -0.8) for patients with a baseline eGFR ≥90 mL/min, 1.5 mL/min (95% CI 0.5 to 2.5) for those with an eGFR of 60–89 mL/min, and 4.1 mL/min (95% CI 1.6 to 6.6) for individuals with an eGFR <60 mL/min. Patients remaining on TDF experienced a decrease in eGFR, irrespective of the eGFR at baseline, with the most prominent decrease seen among individuals with an eGFR <60 mL/min (**Table 2**).

Predictors of an increase in eGFR

Among patients who switched to TAF with a baseline eGFR below 90 mL/min, the likelihood of improving their eGFR of ≥10% after 12 months was similar among patients with different comorbidities and whether ART regimens included boosted protease inhibitors (PI) at baseline or not. Older individuals were less likely to improve their eGFR (adjusted odds ratio: 0.86 per 10 year step, 95% CI 0.72 to 1.01). When we restricted the analysis to individuals with an eGFR <60 mL/min, those on a boosted PI regimen were 50% less likely to experience an improvement of ≥10% after 12 months (**Figure 2**).

Changes in proteinuria

Crude and adjusted changes in proteinuria from baseline are shown in **Figure 3**. In patients remaining on TDF, urine protein-to-creatinine ratio remained stable at 18 months (0.7 mg/mmol, IQR -3.8 to 9.0), whereas it decreased in patients who switched to TAF (2.2 mg/mmol, IQR 1.5 to 8.0). In adjusted analyses, the urine protein-to-creatinine ratio increased by 3.1 mg/mmol (95% CI 0.4 to 5.8) in those who remained on TDF, compared to a decrease of 6.1 mg/mmol (95% CI 4.3 to 7.8) in patients who switched to TAF, 18 months after baseline. The decrease in urine protein-to-creatinine ratio after switching to TAF was most prominent in the group of patients with baseline eGFR measurements <60mL/min (15.5 mg/mmol, 95% CI 8.3 to 22.7), and in those with an eGFR 60–89 mL/min (7.1 mg/mmol, 95% CI 4.5 to 9.6) (**Figure S2**).

Reasons for discontinuation of TAF

Eighty individuals had TDF replaced by a TAF, but subsequently stopped it before the end of the observation period. The most common reasons given by the treating physician were “use of a study treatment” (n=16, 20%), “simplified treatment available” (n=11, 13.8%) and “patient’s wish”, which included ART discontinuation (n=10, 12.5%). Other reasons were “drug interactions” (n=4, 5%), “intended pregnancy” (n=3, 3.8%) and “treatment failure” (n=2, 2.5%). Toxicity accounted for 10 discontinuations (12.5%), with only one being attributed to renal toxicity (**Table S1**). The latter patient experienced renal dysfunction and proteinuria over time using TDF, which improved slightly after changing to TAF, but ART was eventually changed to a NRTI sparing regimen (raltegravir + boosted darunavir).

Sensitivity analyses

After restricting our analysis to creatinine values taken at pre-specified cohort visits, neither the slope nor the magnitude of creatinine trajectories changed substantially (mean number of creatinine measurements 6.1 vs. 11.7 in the full analysis dataset, **Figure S3**). Furthermore, including all patients irrespective of the number of available creatinine measurements and those who switched from TDF to a different NRTI than TAF after the baseline date did not change our findings (**Table S2**). No substantial changes could be observed after restricting the analysis to individuals without any additional changes made to their ART regimen other than replacement of TDF with TAF (973 [87.4%] of those remaining on TDF, and 1'220 [50.7%] of those switching to TAF, **Table S3**). In analyses stratified according to the use of a boosted PI at baseline, predicted changes in eGFR remained similar among individuals with a baseline eGFR ≥90 mL/min or 60–89 mL/min. However, the use of boosted PIs in patients with an eGFR below 60 mL/min who remained on TDF was associated with an eGFR decrease of 23.0 mL/min (95% CI 11.1 to 34.8) at 18 months, whereas the eGFR of those who switched to TAF remained stable at 18 months (1.6 mL/min, 95% CI -2.9 to 6.1). In contrast, individuals with an eGFR below 60 mL/min who switched to TAF without boosted PIs experienced an increase of 5.3 mL/min (95% CI 2.2 to 8.3) (**Table S4**).

DISCUSSION

In this nationwide cohort of HIV-infected individuals, the eGFR and urine protein-to-creatinine ratio improved among individuals with pre-existing renal dysfunction after switching from TDF to TAF, whereas these markers remained stable among patients without renal dysfunction. Our results support international guidelines recommending the replacement of TDF by TAF in individuals with renal dysfunction.

Most clinical trials have shown improvements in renal tubular markers on TAF-containing regimens compared to TDF, but failed to show significant changes in eGFR. Over time, ongoing tubular toxicity leads to the inflammation of the renal tubules, followed by a progressive loss of tubular cells and destruction of other renal structures, eventually reflected in the decreasing eGFR [19]. In our study, replacing TDF by TAF was not only followed by reductions in proteinuria, but also by an increase in eGFR among individuals with established renal dysfunction. These findings were independent of co-existing infections, cardiovascular or metabolic diseases. The magnitude of the improvements in both eGFR and proteinuria was highest in the group of patients with pre-established renal dysfunction who switched to TAF, suggesting a link between this specific treatment change and the partial reversal of TDF-induced tubular toxicity. Our findings contrast with previous studies in which improvements in renal function were mainly limited to decreases in renal tubular markers [5, 6, 9, 20]. Among 242 HIV-infected patients with renal impairment (eGFR of 30 to 69 mL/min) who switched to a TAF-based ART regimen, no significant change in eGFR was found at 48 and 96 weeks [12, 13]. These discrepancies could be attributed to the larger and more representative patient population of our study, including individuals with comorbidities and renal dysfunction. In line with our findings, a recent pooled analysis of 26 clinical trials comparing TDF and TAF found improvements in eGFR as well as renal tubular markers [21]. However, the latter study enrolled few individuals with pre-existing renal dysfunction.

The decline in eGFR among patients with a normal renal function at baseline was similar between patients on TDF and those switched to TAF, and was comparable to the physiological eGFR decline seen in ageing, healthy individuals [22]. These findings confirm and extend earlier results of a meta-analysis and a large observational study, in which renal adverse events were rare when TDF was given to individuals without renal dysfunction [2, 3]. In line with the results of previous studies, switching to TAF was associated with improvements in proteinuria among our study participants, irrespective of the eGFR at baseline [5, 6, 20]. Nevertheless, the renal benefit of replacing TDF by TAF in individuals with a normal eGFR but with proteinuria remains to be determined.

The use of TDF in combination with a boosted PI has been associated with a more pronounced decline in eGFR and higher rates of treatment discontinuations due to renal events, compared to regimens including TDF and another third agent [23, 24]. Protease inhibitors increase tenofovir plasma levels, which might lead to enhanced renal toxicity [25]. In line with those findings, individuals with renal dysfunction who continued TDF together with a boosted PI in our study experienced a marked decline in eGFR. However, patients on boosted PIs with an eGFR <60 mL/min who switched to TAF were less likely to improve their eGFR after 12 months compared to those without PIs. This finding has been replicated in earlier studies assessing changes in eGFR after stopping TDF, which suggested that renal function recovery takes longer in these individuals [26, 27]. This finding warrants confirmation in other studies, as this subgroup of patients was small.

Our study provides robust evidence on the renal benefits of replacing TDF by TAF among individuals with renal dysfunction on TDF, independent of the presence of other comorbidities. The association between the switch to TAF and eGFR changes remained significant across a range of sensitivity analyses. In contrast to most studies having explored the association between TAF and renal outcomes within clinical trials, ours is based on real world data from a nationally representative cohort, which consists of an ageing population with a high prevalence of non-communicable diseases [28]. Additionally, the considerable amount of individuals using TDF with renal dysfunction provided a unique opportunity to have a comparison group for our analyses. However, given the short follow-up time available on TAF-containing regimens, we were not able to provide evidence of a long-term benefit of TAF on renal function. Furthermore, time spent on TDF before baseline was slightly longer for patients switching to TAF compared to those remaining on TDF. In order to minimize the potential underestimation of the renal benefit of switching to TAF ,we included time on TDF before baseline in our multivariable analysis. Although we adjusted our multivariable models for the most important comorbidities and co-medications, the presence of other factors such as nephrotoxic drugs or other renal diseases might have led to the underestimation of the improvement in renal function after the switch from TDF to TAF. Since we used a single eGFR measurement for baseline stratification, we could not exclude the presence of regression to the mean. However, the similarity between the results obtained by using all available eGFR measurements for each patient (11.7 on average) and those seen when using only semi-annual, per-protocol measurements (6.1 on average), was reassuring in this regard. Finally, subgroup analyses, such as the one focusing on individuals treated with boosted protease inhibitors, were based on a small number of observations, and should therefore be regarded as exploratory.

In conclusion, our findings suggest that switching from TDF to TAF or to another TDF-free backbone should be considered in individuals with established renal dysfunction. In the absence of other risk factors for TDF-associated toxicity, continuing TDF in individuals with a normal renal function seems reasonable, and has the potential to reduce HIV-related costs

due to the availability of generic formulations of TDF. Additionally, since TAF seems to be associated with other adverse events such as increases in cholesterol levels and weight gain, longer-term follow-up from observational cohort studies is needed to confirm the safety and efficacy of TAF in individuals with comorbidities [29, 30].

FOOTNOTES

Potential conflicts of interest: BS reports support to his institution for travel grants from Gilead. BL has received travel grants, grants or honoraria from Gilead and ViiV. AC reports no conflict of interest. MC's institution has received a research grant from ViiV and Gilead and offered expert testimony for Abbvie, MSD, Gilead and Sandoz. HFG has received unrestricted research grants from Gilead Sciences (HIV cure grant) and Roche; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from Gilead Sciences, ViiV and Merck, Sandoz and Mepha. HK reports supports for travel grants from MSD and Gilead. MS reports no conflict of interest. EB reports support to his home institution for advisory boards and/or travel grants from MSD, Gilead Sciences, ViiV, Pfizer, Abbvie and Sandoz. PS reports no conflict of interest. CAF reports no conflict of interest. HF reports unrestricted educational grant supports to his home institution by Gilead Sciences, ViiV, Abbvie, Bristol-Myers Squibb and MSD outside the submitted work. AR reports support to his institution for advisory boards and/or travel grants from Janssen-Cilag, MSD, Gilead Sciences, Abbvie, and Bristol-Myers Squibb, and an unrestricted research grant from Gilead Sciences. All remuneration went to his home institution and not to AR personally, and all remuneration was provided outside the submitted work. GW reports support to his home institution for advisory boards and/or travel grants from MSD, Gilead Sciences and Abbvie, and an unrestricted research grant from Gilead Sciences.

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Table 1: Baseline characteristics of the study population

	Remained on TDF n = 1'113	Switched to TAF n = 2'407	p-value
Female sex (%)	359 (32.3)	579 (24.1)	<0.0001
Median age in years (IQR)	48 (41–54)	51 (43–57)	<0.0001
African origin (%)	227 (20.4)	308 (12.8)	<0.0001
Transmission group (%)			<0.0001
MSM	440 (40.8)	1195 (50.8)	
PWID	98 (9.1)	253 (10.8)	
other	541 (50.1)	903 (38.4)	
Median CD_4 count in cells/µL (IQR)	628 (485–816)	646 (487–835)	0.16
Median CD_4 nadir in cells/µL (IQR)	219 (111–314)	204 (106–309)	0.15
Chronic HBV infection (%)	80 (7.5)	163 (7.1)	0.70
Chronic HCV infection (%)	138 (12.5)	310 (13.1)	0.70
History of CV disease (%)	80 (7.2)	227 (9.4)	0.03
Diabetes (%)	64 (5.8)	185 (7.7)	0.04
Arterial hypertension (%)	590 (53.0)	1444 (60.0)	<0.0001
Osteoporosis (%)	42 (3.8)	179 (7.4)	<0.0001
Median eGFR in mL/min (IQR)	96.9 (83.4–108.3)	89.0 (75.1–102.1)	<0.0001
eGFR category (%)			<0.0001
≥90 mL/min	701 (63.0)	1155 (48.0)	
60-89 mL/min	389 (35.0)	1081 (44.9)	
<60 mL/min	23 (2.1)	171 (7.1)	
Median urine protein-to-creatinine ratio (IQR)	11.5 (7.6–21.0)	11.5 (7.8–20.0)	0.99
Urine protein-to-creatinine category (%)			0.87
<15 mg/mmol	554 (49.8)	1395 (58.0)	
15-50 mg/mmol	226 (20.3)	576 (23.9)	
>50 mg/mmol	85 (7.6)	200 (8.3)	
Missing	248 (22.3)	236 (9.8)	
Median time on TDF before baseline in years (IQR)	7.1 (4.7–10.3)	8.2 (5.2–11.0)	<0.0001
Third drug at baseline			<0.0001
Boosted protease inhibitor (%)	173 (15.5)	749 (31.1)	
Integrase inhibitor (%)	201 (18.1)	1'068 (44.4)	

NNRTI (%)	825 (74.1)	802 (33.3)

TDF = Tenofovir disoproxil fumarate, **TAF** = Tenofovir alafenamide, **IQR** = interquartile range, **MSM** = men who have sex with men, **PWID** = patients who inject drugs, **HBV** = hepatitis B virus, **HCV** = hepatitis C virus, **CV** = cardiovascular, **eGFR** = estimated glomerular filtration rate, **NNRTI** = Non-nucleoside reverse transcriptase inhibitor

Table 2: Predicted mean eGFR (95% confidence interval) over time according to the multivariable model

	eGFR at baseline ≥90 mL/min		eGFR at baseline 60–89 mL/min		eGFR at baseline below 60 mL/min	
	TDF (n = 701)	**TAF (n = 1'155)**	**TDF (n = 389)**	**TAF (n = 1'081)**	**TDF (n = 23)**	**TAF (n = 171)**
eGFR at baseline*	101.9 (101.5 to 102.4)	103.6 (102.8 to 104.5)	80.8 (80.3 to 81.2)	81.9 (81.0 to 82.8)	59.9 (58.6 to 61.2)	63.5 (61.2 to 65.8)
eGFR after 18 months	100.2 (99.5 to 101.0)	101.9 (100.9 to 102.9)	79.8 (78.8 to 80.8)	83.4 (82.4 to 84.4)	54.1 (50.2 to 58.0)	67.6 (65.0 to 70.1)
Change in eGFR after 18 months	-1.7 (-2.4 to -1.0)	-1.7 (-2.7 to -0.8)	-0.9 (-1.8 to -0.1)	1.5 (0.5 to 2.5)	-5.8 (-9.3 to -2.3)	4.1 (1.6 to 6.6)
Difference in eGFR of TAF vs. TDF after 18 months	-0.1 (-1.3 to 1.2)		2.5 (1.1 to 3.8)		9.9 (5.6 to 14.2)	

Predicted changes (with 95% confidence intervals) using a mixed effect model, adjusted for age, sex, ethnicity, CD_4 cell count at baseline, time since TDF start, use of ritonavir, cobicistat, dolutegravir or cotrimoxazole, presence of cardiovascular disease, arterial hypertension, diabetes, dyslipidemia and co-infection with hepatitis B and hepatitis C virus.

eGFR = estimated glomerular filtration rate, **TDF** = tenofovir disoproxil fumarate, **TAF** = tenofovir alafenamide

* Numbers represent modelled mean values that can differ from unadjusted values, and therefore do not always exactly fit into the range of eGFR values of a specific baseline group.

FIGURE LEGENDS

Figure 1: Predicted change (95% confidence interval) in eGFR over time

Stratified by eGFR at baseline. Predicted changes (with 95% confidence intervals) using a mixed effect model, adjusted for age, sex, ethnicity, CD4 cell count at baseline, use of ritonavir, cobicistat, dolutegravir or cotrimoxazole, presence of cardiovascular disease, arterial hypertension, diabetes, dyslipidemia and co-infection with hepatitis B and hepatitis C virus.

eGFR = estimated glomerular filtration rate, **TDF** = tenofovir disoproxil fumarate, **TAF** = tenofovir alafenamide

Figure 2: Predictors of an eGFR increase of ≥10% from baseline after 12 months in patients who switched to TAF (multivariable model)

Panel A: Patients on TAF with an eGFR at baseline <90 mL/min (n = 1'081).
Panel B: Patients on TAF with an eGFR at baseline <60mL/min (n = 171). * Per +10 years older.
CV = cardiovascular, **HBV** = hepatitis B virus, **HCV** = hepatitis C virus, **PI** = protease inhibitor

Figure 3: Change in proteinuria over time

Line/Ribbon: Predictions (95% confidence interval) using a mixed effect model (adjusted for sex, age, African origin, presence of diabetes, arterial hypertension and eGFR at baseline)

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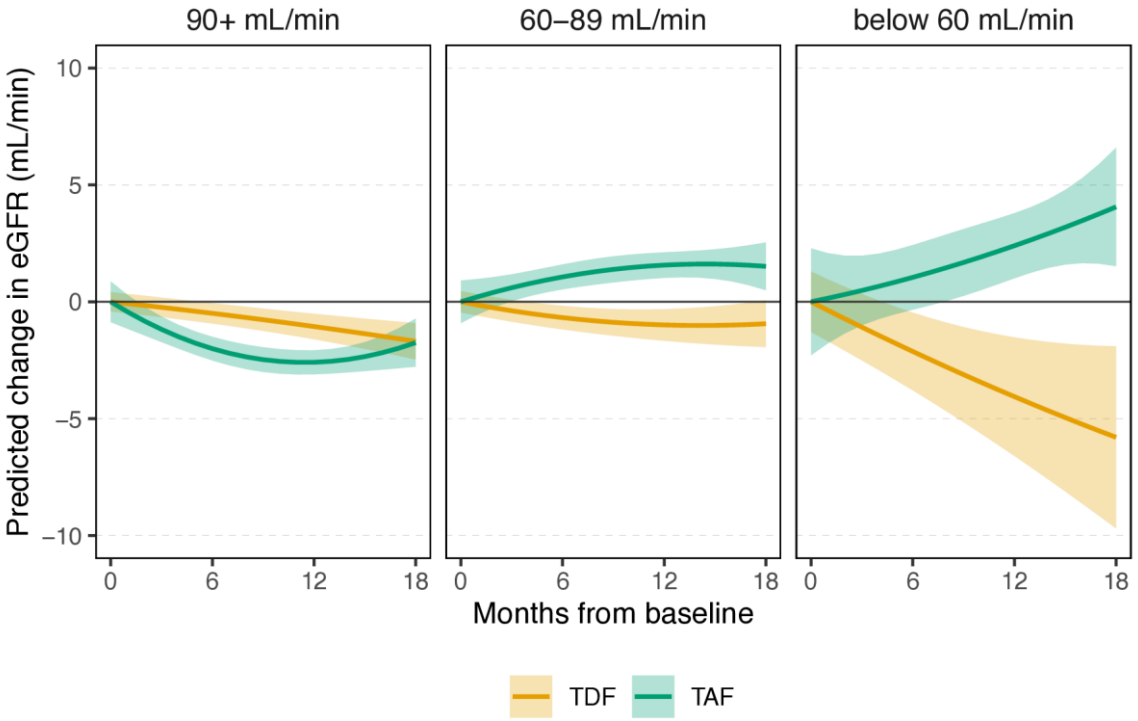
Figure 1



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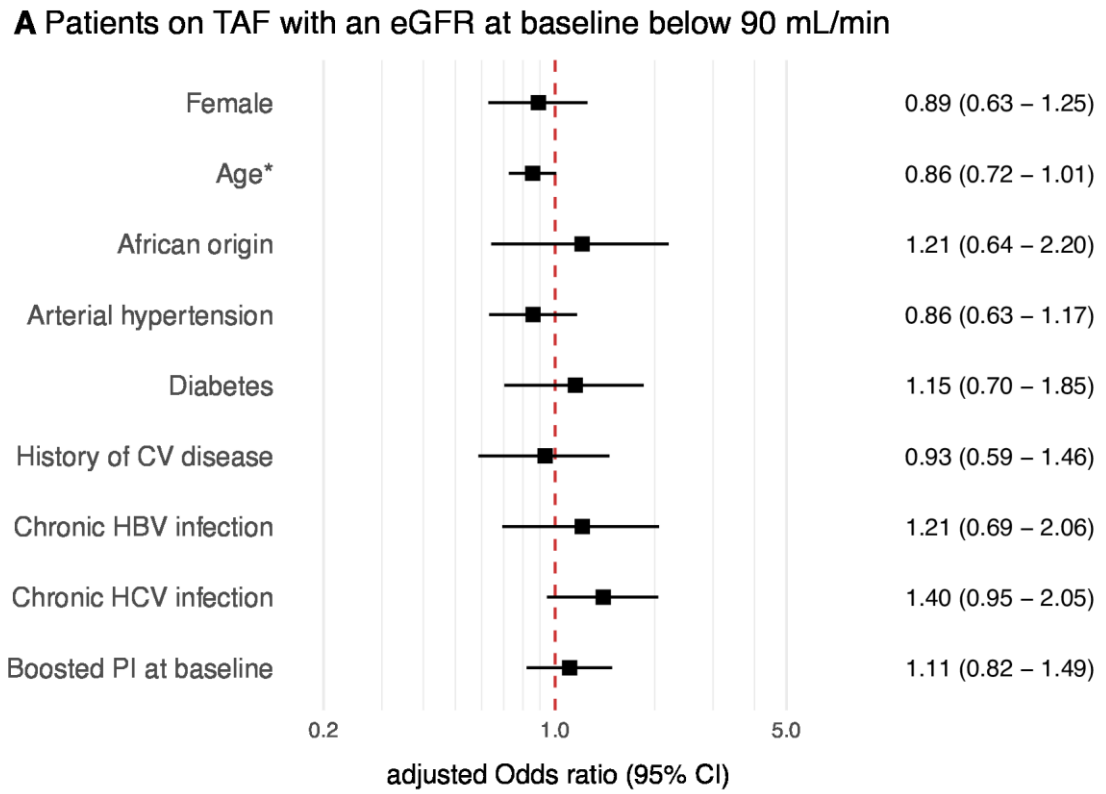
24 Figure 2A



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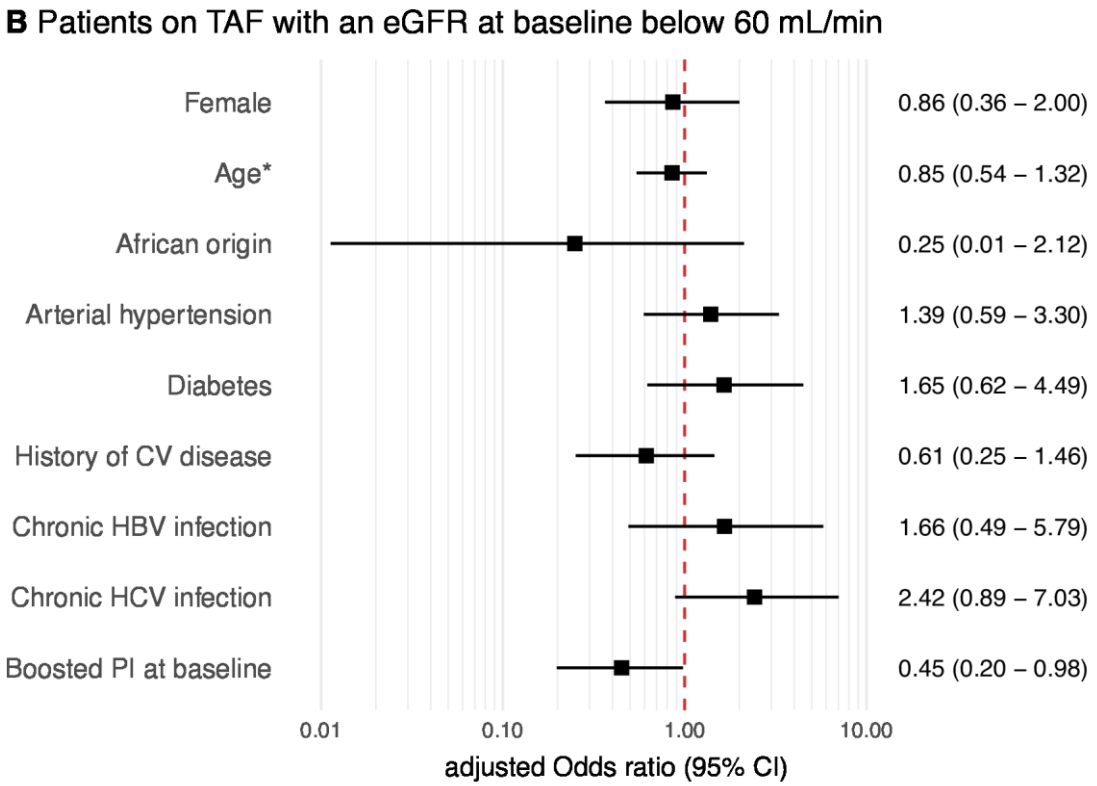
27 Figure 2B



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