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

Bernard Surial1, Bruno Ledergerber2, Alexandra Calmy3, Matthias Cavassini4, Huldrych F. Günthard4,5, Helen Kovari2, Marcel Stöckle6, Enos Bernasconi7, Patrick Schmid8, Christoph A. Fux9, Hansjakob Furrer3, Andri Rauch1, Gilles Wandeler1,10 and the Swiss HIV Cohort Study

1Department of Infectious Diseases, Bern University Hospital, University of Bern
2Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich
3Division of Infectious Diseases, Geneva University Hospital, University of Geneva
4Division of Infectious Diseases, University Hospital of Lausanne, University of Lausanne
5Institute of Medical Virology, University of Zurich
6Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel
7Division of Infectious Diseases, Regional Hospital of Lugano
8Division of Infectious Diseases, Canton Hospital of St Gallen
9Division of Infectious Diseases, Canton Hospital of Aarau
10Institute of Social and Preventive Medicine, University of Bern

Corresponding author:
Bernard Surial M. D., Department of Infectious Diseases, Inselspital, Bern University Hospital, 3010 Bern, Switzerland, bernard.surial@insel.ch

Alternate corresponding author:
Gilles Wandeler M.D., Department of Infectious Diseases, Inselspital, Bern University Hospital, 3010 Bern, Switzerland, gilles.wandeler@insel.ch

© The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.
Previous Presentations: Parts of the results were presented at the 10th IAS conference, 21-24 July 2019 in Mexico.

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.

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]. Neverthel...
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].
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.

Funding: This work was funded by the framework of the SHCS, supported by the Swiss National Science Foundation [SNF grant number 177499, SHCS project number 842]. GW was supported by a Professorship from the Swiss National Science Foundation [PP00P3_176944].

Authors’ contributions: BS, AR and GW designed the study. BS and GW drafted the first draft of the manuscript. BS and BL performed the statistical analyses. AR, HF, BL, AC, MC, HG, HK, MS, EB, PS, and CAF contributed to the conception of the study and revised the manuscript for substantial intellectual content. All authors read and approved the final manuscript.

REFERENCES


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remained on TDF n = 1'113</th>
<th>Switched to TAF n = 2'407</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>359 (32.3)</td>
<td>579 (24.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
<td>48 (41–54)</td>
<td>51 (43–57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>African origin (%)</td>
<td>227 (20.4)</td>
<td>308 (12.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transmission group (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSM</td>
<td>440 (40.8)</td>
<td>1195 (50.8)</td>
<td></td>
</tr>
<tr>
<td>PWID</td>
<td>98 (9.1)</td>
<td>253 (10.8)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>541 (50.1)</td>
<td>903 (38.4)</td>
<td></td>
</tr>
<tr>
<td>Median CD4 count in cells/µL (IQR)</td>
<td>628 (485–816)</td>
<td>646 (487–835)</td>
<td>0.16</td>
</tr>
<tr>
<td>Median CD4 nadir in cells/µL (IQR)</td>
<td>219 (111–314)</td>
<td>204 (106–309)</td>
<td>0.15</td>
</tr>
<tr>
<td>Chronic HBV infection (%)</td>
<td>80 (7.5)</td>
<td>183 (7.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Chronic HCV infection (%)</td>
<td>138 (12.5)</td>
<td>310 (13.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>History of CV disease (%)</td>
<td>80 (7.2)</td>
<td>227 (9.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>64 (5.8)</td>
<td>185 (7.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>550 (53.0)</td>
<td>1444 (60.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>42 (3.8)</td>
<td>179 (7.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median eGFR in mL/min (IQR)</td>
<td>96.9 (83.4–108.3)</td>
<td>89.0 (75.1–102.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR category (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥90 mL/min</td>
<td>701 (63.0)</td>
<td>1155 (48.0)</td>
<td></td>
</tr>
<tr>
<td>60-89 mL/min</td>
<td>389 (35.0)</td>
<td>1081 (44.9)</td>
<td></td>
</tr>
<tr>
<td>&lt;60 mL/min</td>
<td>23 (2.1)</td>
<td>171 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Median urine protein-to-creatinine ratio (IQR)</td>
<td>11.5 (7.6–21.0)</td>
<td>11.5 (7.8–20.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Urine protein-to-creatinine category (%)</td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>&lt;25 mg/mmmol</td>
<td>554 (49.8)</td>
<td>1395 (58.0)</td>
<td></td>
</tr>
<tr>
<td>15-50 mg/mmmol</td>
<td>226 (20.3)</td>
<td>576 (23.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;50 mg/mmmol</td>
<td>85 (7.6)</td>
<td>200 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>248 (22.3)</td>
<td>236 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Median time on TDF before baseline in years (IQR)</td>
<td>7.1 (4.7–10.3)</td>
<td>8.2 (5.2–11.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Third drug at baseline</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Boosted protease inhibitor (%)</td>
<td>173 (15.5)</td>
<td>749 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Integrase inhibitor (%)</td>
<td>201 (18.1)</td>
<td>1'068 (44.4)</td>
<td></td>
</tr>
<tr>
<td>NNRTI (%)</td>
<td>825 (74.1)</td>
<td>802 (33.3)</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 2: Predicted mean eGFR (95% confidence interval) over time according to the multivariable model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR at baseline ≥90 mL/min</strong></td>
<td><strong>eGFR at baseline 60–89 mL/min</strong></td>
<td><strong>eGFR at baseline below 60 mL/min</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF (n = 701)</td>
<td>TAF (n = 1'155)</td>
<td>TDF (n = 389)</td>
</tr>
<tr>
<td>eGFR at baseline*</td>
<td>101.9 (101.5 to 102.4)</td>
<td>103.6 (102.8 to 104.5)</td>
<td>80.8 (80.3 to 81.2)</td>
</tr>
<tr>
<td>eGFR after 18 months</td>
<td>100.2 (99.5 to 101.0)</td>
<td>101.9 (100.9 to 102.9)</td>
<td>79.8 (78.8 to 80.8)</td>
</tr>
<tr>
<td>Change in eGFR after 18 months</td>
<td>-1.7 (-2.4 to -1.0)</td>
<td>-1.7 (-2.7 to -0.8)</td>
<td>-0.9 (-1.8 to -0.1)</td>
</tr>
<tr>
<td>Difference in eGFR of TAF vs. TDF after 18 months</td>
<td>-0.1 (-1.3 to 1.2)</td>
<td></td>
<td>2.5 (1.1 to 3.8)</td>
</tr>
</tbody>
</table>

Predicted changes (with 95% confidence intervals) using a mixed effect model, adjusted for age, sex, ethnicity, CD4 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)
Figure 2A

A Patients on TAF with an eGFR at baseline below 90 mL/min

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.89 (0.63 – 1.25)</td>
</tr>
<tr>
<td>Age*</td>
<td>0.86 (0.72 – 1.01)</td>
</tr>
<tr>
<td>African origin</td>
<td>1.21 (0.64 – 2.20)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.86 (0.63 – 1.17)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.15 (0.70 – 1.85)</td>
</tr>
<tr>
<td>History of CV disease</td>
<td>0.93 (0.59 – 1.46)</td>
</tr>
<tr>
<td>Chronic HBV infection</td>
<td>1.21 (0.69 – 2.06)</td>
</tr>
<tr>
<td>Chronic HCV infection</td>
<td>1.40 (0.95 – 2.05)</td>
</tr>
<tr>
<td>Boosted PI at baseline</td>
<td>1.11 (0.82 – 1.49)</td>
</tr>
</tbody>
</table>
Figure 2B

B Patients on TAF with an eGFR at baseline below 60 mL/min

- Female: 0.86 (0.36 – 2.00)
- Age*: 0.85 (0.54 – 1.32)
- African origin: 0.25 (0.01 – 2.12)
- Arterial hypertension: 1.39 (0.59 – 3.30)
- Diabetes: 1.65 (0.62 – 4.49)
- History of CV disease: 0.61 (0.25 – 1.46)
- Chronic HBV infection: 1.66 (0.49 – 5.79)
- Chronic HCV infection: 2.42 (0.89 – 7.03)
- Boosted PI at baseline: 0.45 (0.20 – 0.98)

adjusted Odds ratio (95% CI)
Change in Protein-to-Creatinine ratio (mg/mmol)

Months since baseline

TDF

TAF