

Switching from TDF to TAF in HIV/HBV co-infected individuals with renal dysfunction - a prospective cohort study

Bernard Surial¹, Charles Béguelin¹, Jean-Philippe Chave², Marcel Stöckle³, Noémie Boillat-Blanco⁴, Thanh Doco-Lecompte⁵, Enos Bernasconi⁶, Jan Fehr^{7,8}, Huldrych F. Günthard^{7,9}, Patrick Schmid¹⁰, Laura N. Walti¹, Hansjakob Furrer¹, Andri Rauch^{*1}, Gilles Wandeler^{*1,11}, and the Swiss HIV Cohort Study

¹Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland

²Clinique de Monchoisi, Lausanne, Switzerland

³Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

⁴Division of Infectious Diseases, University Hospital of Lausanne, University of Lausanne, Lausanne, Switzerland

⁵Division of Infectious Diseases, Geneva University Hospital, University of Geneva, Geneva, Switzerland

⁶Division of Infectious Diseases, Regional Hospital of Lugano, Lugano, Switzerland

⁷Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

⁸Department of Public Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

⁹Institute of Medical Virology, University of Zurich, Zurich, Switzerland

¹⁰Division of Infectious Diseases, Cantonal Hospital of St Gallen, St Gallen, Switzerland

¹¹Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

* Authors contributed equally

Corresponding author

Gilles Wandeler M.D., Department of Infectious Diseases Inselspital, Bern University Hospital, 3010 Bern, Switzerland, gilles.wandeler@insel.ch, Phone: +41 78 775 85 33, Fax: +41 31 632 31 76

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Running Head: TAF in HIV/HBV and renal dysfunction

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Abstract

Background: Whereas tenofovir disoproxil fumarate (TDF) can lead to renal adverse events, tenofovir alafenamide (TAF) has a more favorable renal safety profile. However, the impact of replacing TDF with TAF on renal function and liver parameters among HIV/hepatitis B virus (HBV) co-infected individuals with renal dysfunction remains unclear.

Methods: We included all participants from the Swiss HIV Cohort Study with an HIV/HBV-coinfection who switched from TDF to TAF and had an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m² and a suppressed HIV viral load (<200 cp/mL). We assessed changes in eGFR, urine protein-to-creatinine ratio and alanine aminotransferase (ALT) after one year using mixed-effect models with interrupted time-series.

Results: Among 106 participants (15.1% women, median age 53 years), eGFR was 60-89 mL/min/1.73m² in 84 (79.2%) and <60 mL/min/1.73m² in 22 (20.8%) individuals at the time of switch. One year after the switch from TDF to TAF, individuals with an eGFR between 60-89 mL/min/1.73m² experienced increases in eGFR of 3.2 mL/min/1.73m² (95% confidence interval [CI] 1.2 to 5.2), while those with an eGFR <60 mL/min/1.73m² experienced improvements of 6.2 mL/min/1.73m² (95% CI 2.4 to 10.0). Urine protein-to-creatinine ratio decreased overall (-6.3 mg/mmol, 95% CI -10.0 to -2.7), and ALT levels declined in patients with elevated baseline levels (-11.8 IU/L, 95% CI -17.3 to -6.4) one year after replacing TDF with TAF.

Conclusions: Switching from TDF to TAF among HIV/HBV-coinfected individuals with renal impairment led to improvements in eGFR, a decline in proteinuria, and to ALT normalization in those with elevated ALT levels.

Keywords: HIV-HBV coinfection, antiretroviral therapy outcomes, renal function, liver toxicity, tenofovir alafenamide, non-communicable diseases.

INTRODUCTION

Tenofovir-based antiretroviral therapy (ART) is the mainstay of treatment for HIV/hepatitis B virus (HBV) co-infection. Whereas resistance to lamivudine develops in a significant proportion of HBV-infected individuals, HBV resistance to tenofovir is rare¹. Additionally, liver fibrosis seems to improve with the use of tenofovir, and its use is associated with a reduced incidence of cirrhosis and hepatocellular carcinoma²⁻⁴.

However, tenofovir disoproxil fumarate (TDF) has been associated with renal side effects such as proximal renal tubulopathy⁵. Moreover HBV infection itself can lead to glomerular and tubular renal injury and, rarely, to the development of end-stage renal disease⁶. Tenofovir alafenamide (TAF) is a prodrug with a favorable renal safety profile compared to TDF,

mainly because tenofovir plasma concentrations are reduced by approximately 90%^{7,8}. Because the studies which confirmed the renal safety of TAF in HIV/HBV-infected individuals mainly enrolled individuals without renal impairment^{7,9}, we evaluated the impact of replacing TDF with TAF on eGFR, urine protein-to-creatinine ratio and alanine aminotransferase (ALT) levels in HIV/HBV co-infected individuals with renal dysfunction using data from the Swiss HIV Cohort Study (SHCS).

METHODS

Study design and population

This multicenter prospective cohort study included all HIV/HBV-coinfected individuals with an eGFR below 90 mL/min/1.73m², who had TDF replaced by TAF. The SHCS (www.shcs.ch) is a national cohort that enrolls close to 80% of all adults living with HIV currently receiving ART in Switzerland¹⁰. All data including laboratory measurements, changes in ART and co-administered medications are recorded prospectively at enrollment and every 6 months thereafter. Eligible participants were 18 years or older, had a positive hepatitis B surface antigen (HBsAg) or detectable HBV DNA, a suppressed HIV viral load (<200 cp/mL), were on a TDF-containing ART regimen for at least 6 months, and had an eGFR below 90 mL/min/1.73m². Pregnant women and individuals with decompensated liver cirrhosis were excluded. Data was collected between January 2014 and February 2020. Local ethical committees of all cohort centers approved this study and all patients provided written informed consent.

Outcomes and definitions

Primary outcomes were changes in eGFR (calculated using the CKD-EPI formula¹¹) and urine protein-to-creatinine ratio (normal <15 mg/mmol) in the year before and the year after switch from TDF to TAF. Secondary outcomes were HBV and HIV suppression and HBsAg

loss one year after the switch, as well as changes in serum ALT in the year before and the year after the switch. We considered all data collected at protocol-defined follow-up visits within two years prior and 18 months after switching to TAF. Normal ALT levels were defined as ≤ 25 IU/L for women and ≤ 35 IU/L for men¹². Liver fibrosis was assessed using transient elastography (TE), or AST-to-platelet ratio index (APRI) if TE was unavailable. Significant fibrosis was defined as liver stiffness >7.0 kPa or APRI >1.5 , and cirrhosis as liver stiffness >11.0 kPa or APRI >2.0 . Diabetes mellitus was defined as HbA1c $\geq 6.5\%$ or current antidiabetic treatment, hepatitis C virus infection (HCV) as having a detectable HCV viral load prior to switch, and hepatitis D (HDV) co-infection as having a positive HDV serology. Hazardous alcohol use was assessed using the AUDIT-C score and defined as ≥ 3 points in women and ≥ 4 points in men¹³.

Statistical analysis

Baseline characteristics were presented using descriptive statistics, and Fisher's exact test or Wilcoxon rank sum tests were used for group wise comparisons. Correlation coefficients were calculated using Spearman's rank correlation. We used linear mixed-effect models with interrupted time-series to compare changes in eGFR, urine protein-to-creatinine ratio and ALT levels between the year before and the year after the switch to TAF¹⁴. Analyses for eGFR and urine protein-to-creatinine ratio were adjusted for baseline age, sex, ethnicity, diabetes and treatment for arterial hypertension. Use of integrase inhibitors, atazanavir, lopinavir, rilpivirine, cobicistat and cotrimoxazole were added as time-varying covariates in renal analyses to account for their potential impact on eGFR. Urine protein-to-creatinine ratio analyses were further adjusted for eGFR at baseline. Analyses of ALT changes were adjusted for baseline age, sex, body mass index (BMI), HIV transmission group (persons who inject drugs, men who have sex with men, other), HCV infection, and HBV replication status. In the

latter analysis, hazardous alcohol consumption and the use of efavirenz (EFV) were included as time-varying covariates. All analyses were performed using R version 3.6.2.

RESULTS

Study population

Of 466 individuals with a positive HBsAg and active follow-up, 224 switched from TDF to TAF. After excluding eight individuals with a HIV viral load above 200 cp/mL, and 110 individuals with an eGFR ≥ 90 mL/min/1.73m², 106 individuals formed the study population. Sixteen (15.1%) participants were female, 20 (18.9%) were of African origin, and the median age was 53 years (interquartile range [IQR] 48-58, **Table**). Baseline eGFR was between 60–89 mL/min/1.73m² in 84 (79.2%) and below 60 mL/min/1.73m² in 22 (20.8%) individuals. Patients with an eGFR below 60 mL/min/1.73m² were older, more likely to receive a treatment for arterial hypertension, and had lower CD4 cell counts and higher urinary protein-to-creatinine ratios compared to individuals with an eGFR of 60-89 mL/min/1.73m². The median follow-up time on TAF was similar between both groups (14.6 months [IQR 12.5 – 16.2] in individuals with an eGFR of 60-89 mL/min/1.73m², and 14.1 months [IQR 12.4 – 16.9] in those with an eGFR below 60 mL/min/1.73m²). Sixty-three patients (59.4%) had only TDF replaced by TAF, the rest of the ART regimen remaining unchanged. The most common reasons for stopping TDF were the prevention of toxicity (37.1%), established renal toxicity (17.1%) and treatment simplification (11.4%).

Changes in eGFR and urine protein-to-creatinine ratio

Adjusted changes in eGFR are shown in the **Figure (Panel A)**. Individuals with an eGFR between 60-89 mL/min/1.73m² experienced changes in eGFR of -1.9 mL/min/1.73m² in the last year on TDF (95% CI -3.3 to -0.5), which increased to 3.2 mL/min/1.73m² one year (95% CI 1.2 to 5.2) after switching to TAF (p-value for slope difference 0.001). The use of

TDF in individuals with an eGFR below 60 mL/min/1.73m² led to a decline in eGFR (-4.9 mL/min/1.73m² in the year prior to switch, 95% CI -7.5 to -2.2), and switching to TAF was associated with improvements in eGFR (6.2 mL/min/1.73m² one year after the switch, 95% CI 2.4 to 10.0, p-value for slope difference <0.001).

One year after switching to TAF, 58 (54.7%) individuals had urine protein-to-creatinine ratio values available, and the main demographic and clinical characteristics, including eGFR at baseline, were similar between the group with and without follow-up data. After adjusting for covariates, the use of TDF was associated with a change in urine protein-to-creatinine ratio of 0.9 mg/mmol in the last year prior to switch (95% CI -2.5 to 4.3), and switching to TAF led to a change in urine protein-to-creatinine ratio of -6.3 mg/mmol one year after the switch (95% CI -10.0 to -2.7, p-value for slope difference 0.01). Changes in urine protein-to-creatinine ratio after one year did not correlate with changes in eGFR over time (correlation coefficient -0.02, p=0.91). Our findings on eGFR and urine protein-to-creatinine ratio remained similar after restricting the analyses to individuals who had the replacement of TDF by TAF as the only ART change (Table S1, <http://links.lww.com/QAI/B499>).

HIV and HBV outcomes and changes in ALT levels

One year after switching from TDF to TAF, 97 of 98 (99.0%) individuals with available HIV RNA follow-up measurements had a suppressed viral load (<200 cp/mL). HBV viral load was suppressed (<50 IU/mL) in 64 of 66 (97.0%) individuals with available follow-up measurements. One individual with detectable HIV and HBV viral loads reported suboptimal adherence, and the other individual with detectable HBV DNA did not have a suppressed HBV viral load at the time of switch. HBsAg loss was observed in four (8.7 %) out of 42 individuals with HBsAg measurements available one year after switching to TAF.

Thirty-six individuals (34.0%) had elevated ALT levels at baseline, 14 (13.2%) had significant fibrosis, and 6 (5.7%) had liver cirrhosis. Among those with elevated ALT levels,

one individual (4.2%) had a detectable HBV viral load at baseline, compared to 3 (4.2%) among those with normal ALT levels. In adjusted analyses individuals with normal ALT levels at baseline experienced ALT changes of -1.3 IU/L (95% CI -3.8 to 1.2) in the year before and of -0.1 IU/L (95% CI -3.6 to 3.5) in the year after switching to TAF. In individuals with elevated ALT levels, the use of TDF was associated with increases in ALT of 5.9 IU/L per year (95% CI 2.1 to 9.8), whereas they experienced marked decreases of -11.8 IU/L per year (95% CI -17.3 to -6.4) after the switch to TAF (**Figure Panel B**). EFV was the third drug used in 5 individuals (7.1%) with normal ALT levels and in 6 individuals (16.6%) with elevated ALT levels at baseline. In addition to switching to TAF, all but one of them received a non-EFV containing regimen. Restricting the analyses to individuals without EFV use or to individuals who only had TDF replaced by TAF did not change our findings (**Table S2**, <http://links.lww.com/QAI/B499>).

DISCUSSION

In our nationwide cohort, switching from TDF to TAF in HIV/HBV co-infected individuals with renal dysfunction was associated with improvements in eGFR and urinary protein-to-creatinine ratio, and led to the maintenance of HIV and HBV viral suppression. Additionally, patients with elevated ALT levels experienced significant ALT reductions after switching to TAF. These findings provide strong evidence of the benefits of replacing TDF by TAF in HIV/HBV-coinfected patients with moderate renal dysfunction.

In line with results from previous interventional studies we found high HBV suppression rates one year after starting TAF^{7,9}. However, earlier studies included mostly individuals with normal renal function and showed modest improvements in eGFR or a lower rate of decline with the use of TAF when compared with TDF⁷. In the present study switching to TAF was associated with improvements in renal function, which was most pronounced in individuals

with a baseline eGFR below 60 mL/min/1.73m². Changes in eGFR were not correlated with improvements in urinary protein-to-creatinine ratios, as switching from TDF to TAF led to reductions in proteinuria irrespective of the eGFR at baseline.

One third of our study population had elevated ALT levels at baseline, and the replacement of TDF with TAF was associated with a reduction in ALT levels in this sub-population, independent of other risk factors. For instance, the association remained similar after excluding individuals on EFV-based ART, and after restricting the analysis to individuals who had TDF replaced by TAF without further modifications in their ART regimen. In registrational trials, TAF was associated with faster rates of ALT normalization compared to TDF in HBV mono-infected and HIV/HBV co-infected patients^{7,9}. However, as all but one individual had a suppressed HBV viral load at baseline in our study, more efficient HBV suppression cannot explain our results. Altogether, these findings raise the possibility that TDF may cause some degree of liver toxicity, which seems to be at least partially reversible after switching to TAF. The potential for liver toxicity of TDF has been observed in a large cohort study of HIV mono-infected individuals, which found a strong relationship between TDF and elevated transaminases¹⁵. Further studies are needed to confirm our finding and generate potential explanations.

Our study is among the first to evaluate the benefit of using TAF among HIV/HBV co-infected individuals with renal dysfunction. The use of interrupted time-series allowed us to compare dynamic changes in outcomes between the year before and after the switch, while minimizing confounding by variables which remain constant over time¹⁴. Although selection bias or confounding by indication are possible in cohort studies, we were able to include the large majority of patients in all analyses, except in the one focusing on urinary protein-to-creatinine ratio. However, as the main demographic and clinical characteristics of individuals with and without available proteinuria follow-up measurements did not differ significantly,

our results remain valid. The robustness of the ALT analyses is challenged by the low number of individuals with elevated levels at baseline, the brief follow-up period of one year, and the possibility of a regression to the mean effect. Finally, given that paired baseline and follow-up transient elastography measurements were unavailable for most individuals, the analyses on ALT levels could not be stratified by the underlying degree of fibrosis.

Conclusion

Switching from TDF to TAF among HIV/HBV co-infected individuals with renal impairment led to improvements in eGFR, a decline in proteinuria, and to ALT normalization in those with elevated ALT levels. The use of TAF in those individuals seems to be safe and effective, and switching from TDF to TAF should be considered among co-infected individuals with renal impairment or with otherwise unexplained ALT elevations.

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NOTES

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Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C, Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

Author's contribution:

BS, CB, AR and GW designed the study. BS and GW prepared the first draft of the manuscript. BS performed the statistical analyses. JPC, MS, NB, TD, EB, JF, HFG, PS, LW, and HF contributed to the conception of the study, data collection and revised the manuscript for substantial intellectual content. All authors read and approved the final manuscript.

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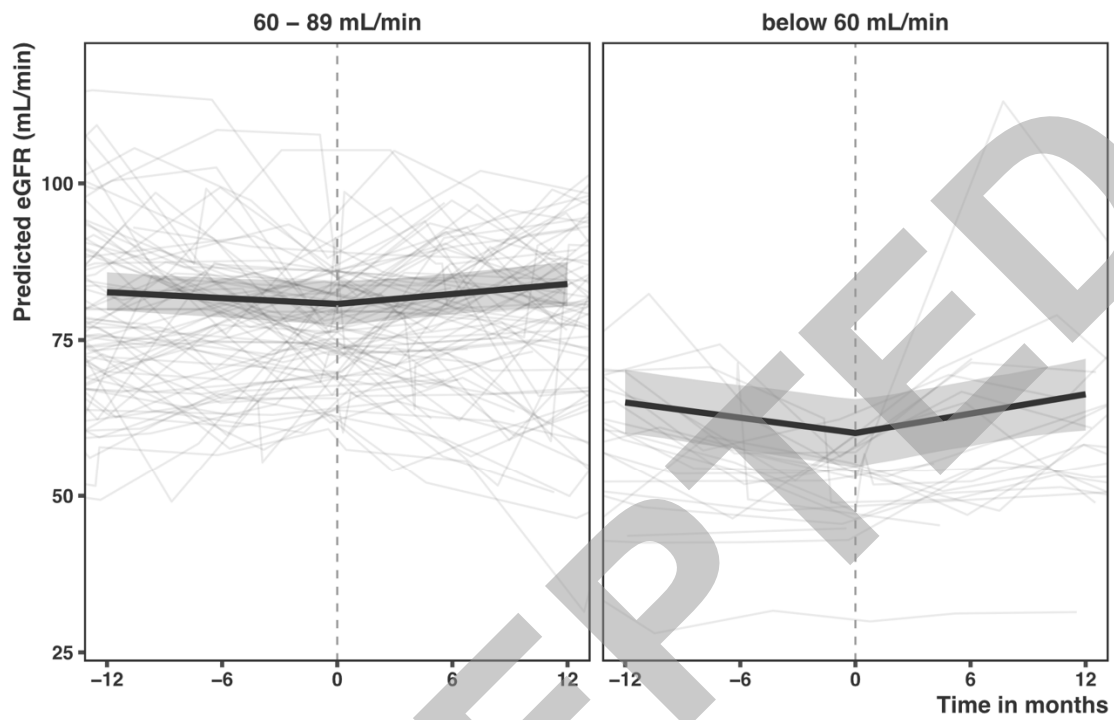
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Figure Adjusted changes in eGFR and ALT levels after switching from TDF to TAF

A Changes in eGFR after switching from TDF to TAF



B Changes in ALT after switching from TDF to TAF

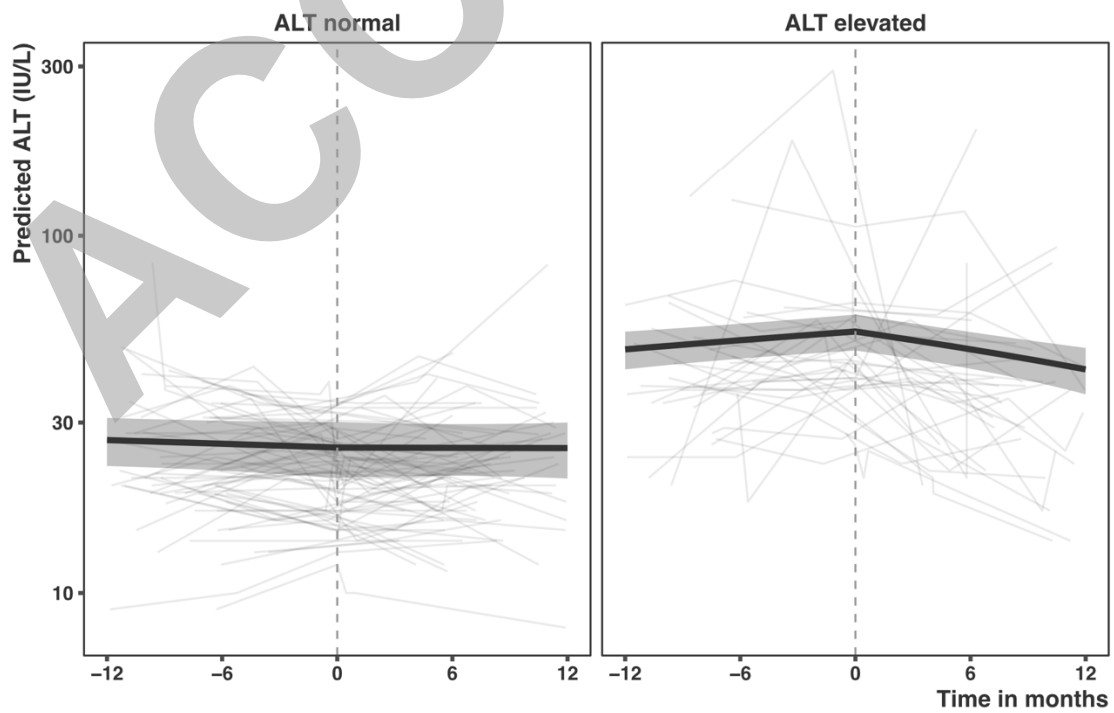


Figure legend Adjusted changes in eGFR and ALT levels in the year before and the year after switching from TDF to TAF

Panel A: Changes in eGFR according to the multivariable model stratified by eGFR at baseline (60-89 mL/min/1.73m² vs. below 60 mL/min/1.73m²). Adjusted for age, sex, ethnicity, diabetes, treatment for arterial hypertension and the time-updated use of integrase inhibitors, atazanavir, lopinavir, rilpivirine, cobicistat and cotrimoxazole.

Panel B: Changes in ALT levels according to the multivariable model stratified by ALT levels at baseline (normal vs. elevated*). Adjusted for baseline age, sex, body mass index, transmission risk (persons who inject drugs, men who have sex with men, other), hepatitis C virus infection, hepatitis B virus replication at time of switch, and time-updated for hazardous alcohol consumption and efavirenz use.

* ALT >25 for women and >35 for men.

The dashed line represents the time of switch from TDF to TAF. **eGFR** estimated glomerular filtration rate, **ALT** alanine aminotransferase, **TDF** tenofovir disoproxil fumarate, **TAF** tenofovir alafenamide.

Table Characteristics of the study population at the time of switch from TDF to TAF

	eGFR 60-89 mL/min (n = 84)	eGFR below 60 mL/min (n = 22)	p- value
Female (%)	13 (15.5)	3 (13.6)	1.00
Median age in years (IQR)	51.5 (48 - 57)	54.5 (50.3 - 69.8)	0.02
African origin (%)	17 (20.2)	3 (13.6)	0.69
PWID (%)	4 (4.8)	2 (9.1)	0.60
Median CD4 count (cells/ μ L)	593 (426-806)	462.5 (274.3-636.3)	0.04
Hepatitis D infection (%)	5 (6.0)	2 (9.1)	0.96
Chronic HCV infection (%)	2 (2.4)	2 (9.1)	0.40
Diabetes (%)	5 (6.0)	3 (13.6)	0.45
Treated for arterial hypertension (%)	23 (27.4)	12 (54.5)	0.03
Median eGFR in mL/min (IQR)	78.2 (71.3-83.8)	53.0 (47.5-55.2)	<0.001
Median urine protein-to-creatinine ratio in mg/mmol (IQR)	11.5 (8.8-18.1)	21.4 (15.9-64.4)	0.01
Urine protein-to-creatinine ratio (%)			0.01
>50 mg/mmol	4 (4.8)	5 (22.7)	
Missing	23 (27.4)	5 (22.7)	
Median ALT in IU/L (IQR)	27.0 (20.5-38.3)	23.0 (17.0-38.0)	0.23

ALT elevated* (%)	30 (35.7)	6 (27.3)	0.82
Grade 1 (<2.5 ULN, %)	28 (33.3)	6 (27.3)	
Grade 2 (≥2.5 to <5 times ULN, %)	1 (1.2)	0	
Grade 3 (≥5 to <10 times ULN, %)	1 (1.2)	0	
Grade 4 (≥ 10 times ULN, %)	0	0	
Significant fibrosis ¹ (%)	13 (15.5)	1 (4.5)	0.29
Cirrhosis ² (%)	6 (7.1)	0	0.34
Median time on TDF in years (IQR)	10.2 (6.5 – 12.2)	11.4 (9.2 - 14.5)	0.11
Switch from TDF to TAF without changes in other components (%)	48 (57.1)	15 (68.2)	0.49
Third drug before switch (%)			0.27
Dolutegravir	16 (19.0)	6 (27.3)	
Rilpivirine	12 (14.3)	6 (27.3)	
Darunavir	11 (13.1)	4 (18.2)	
Elvitegravir	10 (11.9)	0	
Efavirenz	10 (11.9)	1 (4.5)	
Other	25 (29.8)	5 (22.7)	

eGFR estimated glomerular filtration rate, **IQR** interquartile range, **MSM** men having sex with men, **PWID** persons who inject drugs, **HCV** hepatitis C virus, **APRI** AST to platelet ratio index. **ULN** Upper limit of normal.

*ALT >25 for women and >35 for men, according to AASLD recommendations.

¹TE >7.0 kPa or APRI >1.5

²TE >11.0 kPa or APRI > 2.0

ACCEPTED