OPEN

Switching From TDF to TAF in HIV/HBV-Coinfected Individuals With Renal Dysfunction—A Prospective Cohort Study

Bernard Surial, MD,[a] Charles Béguelin, MD,[a] Jean-Philippe Chave, MD,[b] Marcel Stöckle, MD,[c] Noémie Boillat-Blanco, MD,[d] Thanh Doco-Lecompte, MD,[e] Enos Bernasconi, MD,[f] Jan Fehr, MD,[g,h] Huldrych F. Günthard, MD,[g,i] Patrick Schmid, MD,[j] Laura N. Walti, MD,[a] Hansjakob Furrer, MD,[a] Andri Rauch, MD,[a] Gilles Wandeler, MD,[a,k] and the Swiss HIV Cohort Study

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)-coinfected 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/1.73 m^2 and a suppressed HIV viral load (<200 cp/mL). We assessed changes in eGFR, urine protein-to-creatinine ratio, and alanine aminotransferase (ALT) after 1 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/1.73 m^2 in 84 (79.2%) and <60 mL/min/1.73 m^2 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 and 89 mL/min/1.73 m^2 experienced increases in eGFR of 3.2 mL/min/1.73 m^2 (95% confidence interval [CI] 1.2 to 5.2), whereas those with an eGFR <60 mL/min/1.73 m^2 experienced improvements of 6.2 mL/min/1.73 m^2 (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) 1 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.

From the [a]Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland; [b]Division of Infectious Diseases, La Source Hospital, Lausanne, Switzerland; [c]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; [d]Division of Infectious Diseases, University Hospital of Lausanne, University of Lausanne, Lausanne, Switzerland; [e]Division of Infectious Diseases, Geneva University Hospital, University of Geneva, Geneva, Switzerland; [f]Division of Infectious Diseases, Regional Hospital of Lugano, Lugano, Switzerland; [g]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [h]Department of Public and Global Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland; [i]Institute of Medical Virology, University of Zurich, Zurich, Switzerland; [j]Division of Infectious Diseases, Cantonal Hospital of St Gallen, St Gallen, Switzerland; and [k]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.

Supported by an investigator-initiated trial grant from Gilead Sciences (NCT03115736), and within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (SNF grant number 177499, SHCS project number 842) and by the SHCS research foundation. G.W. was supported by a Professorship from the Swiss National Science Foundation (PP00P3_176944). The funder had no role in study design, collection of the data, analysis and interpretation of the results, and the decision to publish.

Presented in part at the 17th EACS conference; November 6–9, 2019, Basel, Switzerland.

B.S. reports support to his home institution for travel grants from Gilead. C.B., J.-P.C., and T.D.-L. report no conflict of interest. E.B. reports support to his institution for advisory boards and/or travel grants from Gilead, MSD, ViiV, Abbvie, Sandoz, and Pfizer. J.F. reports no conflict of interest. H.F.G. has received unrestricted research grants from Gilead Sciences; fees for data and safety monitoring board membership from Merck; and consulting/advisory board membership fees from Gilead Sciences, ViiV, Sandoz, and Mepha. P.S. reports no conflict of interest. L.N.W. reports support to her home institution for advisory boards or travel grants from MSD and Gilead Sciences. H.F. received unrestricted educational grant from Abbvie, ViiV, Gilead Sciences, MSD, Janssen, and Sandoz paid to the institution. A.R. 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 A.R. personally, and all remuneration was provided outside the submitted work. G.W. 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.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

A.R. and G.W. contributed equally. B.S., C.B., A.R., and G.W. designed the study. B.S. and G.W. prepared the first draft of the manuscript. B.S. performed the statistical analyses. J.-P.C., M.S., N.B.-B., T.D.-L., E.B., J.F., H.F.G., P.S., L.W., and H.F. 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.

Correspondence to: Gilles Wandeler, MD, Department of Infectious Diseases, Inselspital, Bern University Hospital, 3010 Bern, Switzerland (e-mail: gilles.wandeler@insel.ch).

Key Words: HIV/HBV coinfection, antiretroviral therapy outcomes, renal function, liver toxicity, tenofovir alafenamide, non-communicable diseases

(*J Acquir Immune Defic Syndr* 2020;85:227–232)

INTRODUCTION

Tenofovir-based antiretroviral therapy (ART) is the mainstay of treatment for HIV/hepatitis B virus (HBV) coinfection. Whereas resistance to lamivudine develops in a significant proportion of HBV-infected individuals, HBV resistance to tenofovir is rare.[1] In addition, liver fibrosis seems to improve with the use of tenofovir, and its use is associated with a reduced incidence of cirrhosis and hepatocellular carcinoma.[2–4]

However, tenofovir disoproxil fumarate (TDF) has been associated with renal side effects, such as proximal renal tubulopathy.[5] Moreover HBV infection itself can lead to glomerular and tubular renal injury and, rarely, to the development of end-stage renal disease.[6] Tenofovir alafenamide (TAF) is a prodrug with a favorable renal safety profile compared with TDF mainly because tenofovir plasma concentrations are reduced by approximately 90%.[7,8] Because the studies that 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 estimated glomerular filtration rate (eGFR), urine protein-to-creatinine ratio, and alanine aminotransferase (ALT) levels in HIV/HBV-coinfected 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/1.73 m^2, 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 Switzerland.[10] 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/1.73 m^2. Pregnant women and individuals with decompensated liver cirrhosis were excluded. Data were 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 chronic kidney disease epidemiology collaboration (CKD-EPI) formula[11]] 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 1 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 2 years before and 18 months after switching to TAF. Normal ALT levels were defined as ≤25 IU/L for women and ≤35 IU/L for men.[12] Liver fibrosis was assessed using transient elastography (TE) or aspartate aminotransferase-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 ≥6.5% or current antidiabetic treatment, hepatitis C virus infection (HCV) as having a detectable HCV viral load before switch, and hepatitis D virus (HDV) coinfection as having a positive HDV serology. Hazardous alcohol use was assessed using the Alcohol Use Disorders Identification Test Consumption score and defined as ≥3 points in women and ≥4 points in men.[13]

Statistical Analysis

Baseline characteristics were presented using descriptive statistics, and Fisher exact test or Wilcoxon rank sum tests were used for group wise comparisons. Correlation coefficients were calculated using Spearman's rank correlation coefficient. 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 TAF.[14] 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, HIV transmission group (persons who inject drugs, men who have sex with men, and others), 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 8 individuals with a HIV viral load above 200 cp/mL and 110 individuals with an eGFR ≥90 mL/min/1.73 m^2, 106 individuals formed the study population. Sixteen (15.1%) participants were women, 20 (18.9%) were of African origin, and the median age was 53 years (interquartile range [IQR] 48–58, Table 1). Baseline eGFR was between 60 and 89 mL/min/1.73 m^2 in 84 (79.2%) and below 60 mL/min/1.73 m^2 in 22 (20.8%) individuals. Patients with an eGFR below 60 mL/

min/1.73 m^2 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 with individuals with an eGFR of 60–89 mL/min/1.73 m^2. 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/1.73 m^2, and 14.1 months (IQR 12.4–16.9) in those with an eGFR below 60 mL/min/1.73 m^2]. 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 mean changes in eGFR are shown in the Figure 1A. Individuals with an eGFR between 60 and 89 mL/min/1.73 m^2 experienced changes in eGFR of −1.9 mL/min/1.73 m^2 in the last year on TDF [95% confidence interval (CI) −3.3 to −0.5], which increased to 3.2 mL/min/1.73 m^2 1 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/1.73 m^2 led to a decline in eGFR (−4.9 mL/min/1.73 m^2 in the year before switch, 95% CI −7.5 to −2.2), and switching to TAF was associated with improvements in eGFR (6.2 mL/min/1.73 m^2 1 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 before 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 1 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 1 year did not correlate with changes in eGFR over the course of 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 (see Table S1, Supplimental Digital Content, 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). The 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 4 (8.7%) of the 42 individuals with HBsAg measurements available 1 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 with 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 (Fig. 1B). 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 (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/B499).

DISCUSSION

In our nationwide cohort, switching from TDF to TAF in HIV/HBV-coinfected 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. In addition, 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 1 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 TDF.[7] In this 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/1.73 m^2. Changes in eGFR were not correlated with improvements in urinary protein-to-creatinine ratios because 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 subpopulation, 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

TABLE 1. 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*
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/μL)	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† (%)	13 (15.5)	1 (4.5)	0.29
Cirrhosis‡ (%)	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)	
Others	25 (29.8)	5 (22.7)	

HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate; PWID, persons who inject drugs, ULN, upper limit of normal.
*ALT >25 for women and >35 for men, according to recommendations of the American Association for the Study of Liver Diseases (AASLD).
†TE >7.0 kPa or APRI >1.5.
‡TE >11.0 kPa or APRI > 2.0.

compared with TDF in HBV-monoinfected and HIV/HBV-coinfected 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-monoinfected individuals, which found a strong relationship between TDF and elevated transaminases.[15] 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-coinfected 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, whereas minimizing confounding by variables that remain constant over the course of time.[14] Although selection bias or confounding by indication is possible in cohort studies, we were able to include most 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 1 year, and the possibility of a regression to the mean effect. Finally, given that paired baseline and follow-up TE measurements were unavailable for most individuals, the analyses on ALT levels could not be stratified by the underlying degree of fibrosis.

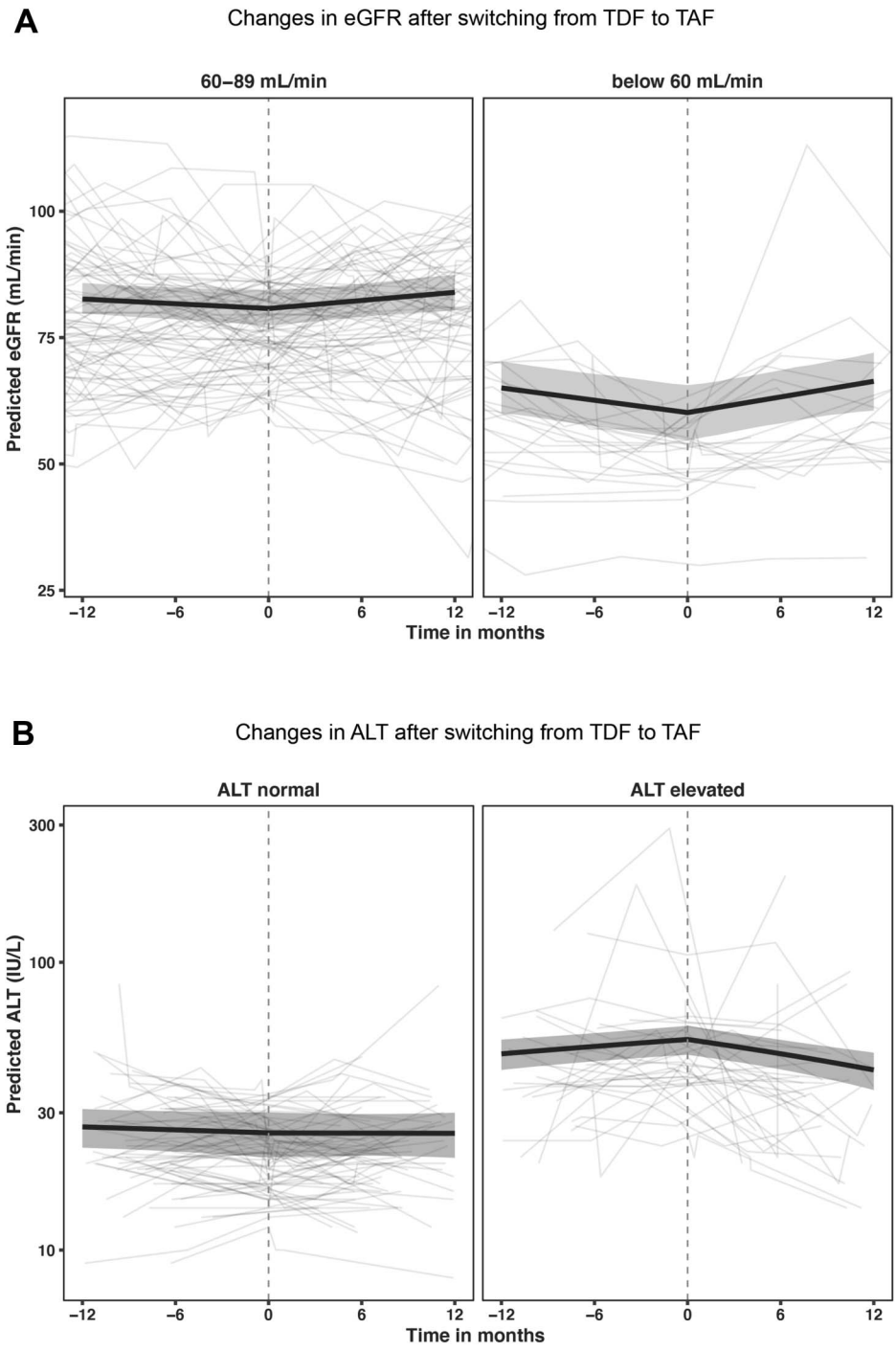

FIGURE 1. Adjusted changes in eGFR and ALT levels in the year before and the year after switching from TDF to TAF. (A) Changes in eGFR according to the multivariable model stratified by eGFR at baseline (60–89 mL/min/1.73 m^2 vs. below 60 mL/min/1.73 m^2). Adjusted for age, sex, ethnicity, diabetes, treatment for arterial hypertension, and the time-updated use of integrase inhibitors, atazanavir, lopinavir, rilpivirine, cobicistat, and cotrimoxazole. (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, and others), HCV infection, HBV replication at time of switch, and time-updated for hazardous alcohol consumption and efavirenz use. *ALT >25 for women and >35 for men. The bold line represents predicted mean values, the shaded area its 95% confidence intervals, and thin lines represent individual patient profiles. The dashed line represents the time of switch from TDF to 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. The use of TAF in those individuals seems to be safe and effective, and switching from TDF to TAF should be considered among coinfected individuals with renal impairment or with otherwise unexplained ALT elevations.

ACKNOWLEDGMENTS

The authors thank all patients, doctors, and nurses associated with the Swiss HIV Cohort Study (SHCS), Alexandra Scherrer and Anna Traytel from the SHCS data center, Danièle Perraudin and Marianne Amstutz from the SHCS coordination center, and especially Daniela Hirter and Christine Brülisauer and Melanie Lacalamita for collecting and maintaining the study data. The members of the SHCS are Anagnostopoulos A, Battegay M, Bernasconi E, Böni J,

Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert CR (Chairman of the Mother & Child 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, and Yerly S.

The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

REFERENCES

1. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci.* 2015;60:1457–1464.
2. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet.* 2013;381:468–475.
3. Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. *Hepatology.* 2017; 66:1444–1453.
4. Wandeler G, Mauron E, Atkinson A, et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: relevance for screening strategies. *J Hepatol.* 2019;71:274–280.
5. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS.* 2007;21:1273–1281.
6. Fabrizi F, Cerutti R, Ridruejo E. Hepatitis B virus infection as a risk factor for chronic kidney disease. *Expert Rev Clin Pharmacol.* 2019;12: 867–874.
7. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol.* 2018;68:672–681.
8. Podany AT, Bares SH, Havens J, et al. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. *AIDS.* 2018;32: 761–765.
9. Gallant J, Brunetta J, Crofoot G, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. *J Acquir Immune Defic Syndr.* 2016;73:294–298.
10. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: the Swiss HIV Cohort study. *Int J Epidemiol.* 2010;39:1179–1189.
11. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612.
12. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67:1560–1599.
13. Bush K, Kivlahan DR, McDonell MB, et al. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med.* 1998;158:1789–1795.
14. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol.* 2017;46:348–355.
15. Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drugs and risk of chronic alanine aminotransferase elevation in human immunodeficiency virus (HIV)-monoinfected persons: the data collection on adverse events of anti-HIV drugs study. *Open Forum Infect Dis.* 2016;3:ofw009.