Switching to tenofovir alafenamide fumarate or abacavir in HIV patients with tenofovir disoproxil fumarate associated renal dysfunction: the randomized clinical BACTAF-study and the retrospective BACTAF-R cohort-study.

I.E.A. Wijting, C. Rokx, A. Verbon, B.J.A. Rijnders; on behalf of the BACTAF study-team.

ABSTRACT

Introduction

Tenofovir disoproxil fumarate (TDF)-containing combination antiretroviral therapy (cART) for HIV is associated with renal dysfunction through accelerated estimated glomerular filtration rate (eGFR)-decline. Whether a switch to tenofovir alafenamide (TAF) is non-inferior to abacavir (ABC) containing cART in patients with TDF-associated eGFR-decline is unknown.

Methods

The BACTAF-studies are two multicenter studies: a randomized clinical non-inferiority trial (NCT02957864) and a retrospective cohort-study. The interim analyses of both studies combined are presented here. Eligible patients (aged ≥18 years), HIV-RNA suppressed (<50 c/ml) on TDF-containing cART with an accelerated eGFR-decline, were switched to TAF or ABC. Exclusion criteria were non-TDF-related causes of eGFR-decline, eGFR <30 ml/min at switch, HLA-B5701 carriers, cardiovascular disease, ABC resistance, or hepatitis B or C virus infections. The primary endpoint was an at least 50% eGFR-recovery at week 48 after TDF-discontinuation.

Results

A total of 250 patients discontinued TDF, including 35 in the randomized trial. In total 131 switched to TAF, and week 48 data on eGFR were available in 81 TAF and 102 ABC patients respectively. In the trial, patients who switched from TDF to TAF had mean 29.0 (standard deviation (SD) 22.0) mL/min eGFR decline and ABC patients had 27.5 (SD 25.8) over 8 and 6 years respectively. The mean eGFR in TAF and ABC were 72.9 (SD 15.0) and 67.9 (SD 14.8) mL/min at TDF-discontinuation. After 48 weeks, mean eGFR increased 8.4 and 6.4 mL/min in TAF and ABC ($p<0.001$) and were comparable between groups (difference: 2.0mL/min, 95%CI: -5.3 – 1.5, $p>0.1$). Subgroups of 21/81 (25.9%) patients on TAF and 30/102 patients (29.4%) on ABC showed more than 50% eGFR-recovery at week 48. HIV-RNA remained suppressed in at least 95% of all patients.

Conclusions

In patients with a TDF-related accelerated eGFR-decline, Switching to TAF is non-inferior ABC in terms of eGFR stabilization and recovery rates after TDF discontinuation.

INTRODUCTION

In HIV treatment guidelines, one of the recommended nucleoside reverse transcriptase inhibitors (NRTI) is tenofovir disoproxil fumarate (TDF).[1,2] However, in particular after long-term use, treatment with TDF can be associated with nephrotoxicity which occurs in two different, often overlapping ways: an accelerated decline in estimated glomerular filtration rate (eGFR), more than the anticipated eGFR-decrease of approximately 1 ml/min/year),[3] and proximal tubular dysfunction (PTD).[4,5] Whether and to what extent TDF-associated nephrotoxicity is reversible, is currently not fully elucidated by the available cohort studies. In particular, few studies have examined the reversibility of eGFR decline during TDF therapy. Also problematic is that these studies all included substantial proportions of patients with comorbidities which could also cause eGFR-declines, for which was not always corrected in multivariable models, and often the recovery of eGFR was ill-defined.[7–13] A decreased eGFR and proteinuria are associated with increased morbidity and mortality (e.g. cardiovascular disease, acute renal failure).[14] Therefore, reliable data on the reversibility of TDF-associated renal impairment are of importance. Two alternative NRTI backbones can be used to substitute the TDF-containing backbone abacavir (ABC) combined with lamivudine (3TC) or tenofovir alafenamide fumarate (TAF) combined with emtricitabine (FTC).[1] Importantly, both FTC and 3TC have not been associated with renal toxicity. Until 2016, only an ABC-containing NRTI-backbone was available as alternative for a TDF-containing backbone. This could be problematic because it is absolutely or relatively contraindicated in certain subpopulations. For example, patients who carry HLA-B5701-alleles may develop hypersensitivity-reactions, and an association between ABC-exposure and cardiovascular events in patients at risk has been reported repeatedly.[15,16] In 2016, a TAF containing NRTI-backbone became available, offering an alternative for ABC in case of TDF-related renal dysfunction. TDF and TAF share the same active component, tenofovir, but TAF-administration results in 90% lower mean plasma tenofovir-concentrations and higher intracellular tenofovir-concentrations in CD4 T-lymphocytes, with comparable viral suppression.[17,18] Especially the resulting lower kidney tenofovir concentration is thought to contribute to a more favorable renal safety profile. Indeed in trials, both ABC and TAF showed excellent renal safety profiles in patients without renal dysfunction.[19,20] However, comparative data on renal safety and recovery of TDF-associated renal impairment after a switch from TDF to ABC or TAF are lacking. Since both compounds are used to tackle TDF related renal dysfunction in HIV, we hypothesized that a switch from TDF to TAF is non-inferior to a switch to ABC in recovery of a TDF-associated eGFR-decline.

METHODS

The BACTAF-study (Switching to Tenofovir Alafenamide Fumarate or aBACavir in patients with Tenofovir Disoproxil Fumarate associated eGFR-decline) was a multi-center, non-inferiority trial in seven Dutch hospitals and one Belgian hospital: Erasmus MC Rotterdam, Slotervaart MC Amsterdam, Rijnstate Arnhem, OLVG Amsterdam, UMCG Groningen, ETZ Tilburg, and Maasstad Hospital Rotterdam in the Netherlands, and UZ Leuven in Belgium. Patients on TDF with FTC or 3TC and a TDF-associated eGFR-decline (definition below) switched to TAF/FTC or ABC/3TC, with continuation of the third antiretroviral agent, and they were followed for 96 weeks. The data presented here are an interim analysis of the combined result from a retrospective observational cohort study and a randomized clinical trial, so patients in the retrospective observational study had been using TDF before inclusion, but had already switched to TAF or ABC. Eligible patients both for the prospective and the retrospective study were adults, with plasma HIV-RNA < 50 c/mL for ≥ 24 weeks on unchanged TDF-containing cART. TDF exposure had to be for one year at minimum. Most importantly, in all included patients an accelerated TDF-associated eGFR-decline was present at the time of TDF discontinuation. This was defined as 1) a mean decline of > 3 ml/min/year since TDF initiation provided that there had been at least 5 years of TDF exposure, and/or 2) an eGFR < 70 ml/min with an eGFR at TDF initiation of > 90 ml/min, and/or 3) a > 25% eGFR-decline since TDF initiation. The eGFR was calculated according to the CKD-EPI method. Patients with other causes of eGFR-decline due to e.g. hypertension, diabetes mellitus, and exposure to known nephrotoxic medication were all excluded, as were HLA-B5701 carriers, those with prior documented cardiovascular disease, patients with hepatitis B or C virus infections, eGFR < 30 ml/min at screening for the prospective study (or at ABC or TAF initiation in the retrospective study), and the presence of intermediate or higher levels of resistance to ABC according to the Stanford University HIV drug database.[21] The primary endpoint was the proportion of patients on TAF versus ABC with adequate eGFR-recovery 48 weeks after TDF-discontinuation. An adequate eGFR-recovery was defined as an at least 50% recovery of the eGFR decrease that had occurred during TDF exposure. Secondary renal endpoints are the proportion of patients with an at least 50% recovery of the eGFR decrease at week 24, an at least 25% recovery of the eGFR decrease at weeks 24 and 48, and the mean eGFR changes over 48 weeks. The data presented here are an interim analysis of the combined result from the retrospective observational cohort study and the randomized clinical trial. The secondary endpoints are therefore described without interferential comparisons. Non-renal and renal secondary endpoints reported here are the proportions of patients with HIV-RNA < 50 c/mL, fasting serum lipids, adverse events (AE), and changes in the presence of dipstick proteinuria (patients in the cohort only) and PTD markers (patients in the randomized clinical trial only). The following measurements were considered markers for PTD, which was defined by the presence of at least 2 of the following: 1) serum phosphate (PO4) < 0.8 mmol/L, 2) fractional

excretion of phosphate (FePO4) > 20% and > 10% with hypophosphatemia, 3) serum uric acid < 0.20 mmol/L in males and < 0.12 mmol/L in females, 4) fractional excretion of uric acid (FeUA) > 20% and > 15% in hypouricemic patients, 5) urine protein to creatinine (UPCR) > 15 mg/mmol, 6) urine albumin to protein ratio (UAPR) < 0.4 in patients with an increased UPCR, and 7) normoglycaemic glucosuria.[22] Serum lipids (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and TC:HDL-ratio) were measured, although not routinely so in the patients from the retrospective cohort study as systematic lipid measurements are not part of standard care. As dolutegravir, rilpivirine, elvitegravir/cobicistat, and darunavir/cobicistat (DTG, RPV, EVG/COBI, and DRV/COBI) all decrease the tubular creatinine excretion, exposure to these drugs increases serum creatinine thereby artificially decreasing serum creatinine based glomerular filtration estimations. Mean eGFR decrease in phase 3 trials with these drugs was estimated at mean 10 mL/min. Therefore, in patients on a TDF-containing backbone without DTG, RPV, or EVG/COBI, or DRV/COBI as part of their cART but who switched to an ABC- or TAF-containing backbone combined with either DTG, RPV, or COBI, 10 mL/min was added to all eGFR-measurements to compensate for this.[23] Both in the trial and in routine practice after switching, patients are followed up at week 12, 24, and every 24 weeks thereafter at minimum. Data were collected in the time-window according to the FDA-snapshot. The prospective BACTAF-study was approved by the Dutch Competent Authority and the Institutional Review Board of the Erasmus MC Rotterdam (NL55668.078.16) and registered at www.clinicaltrials.gov number NCT02957864. The study was done in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided verbal and written informed consent before study procedures. The retrospective BACTAF-R study was approved by the Institutional Review Board of the Erasmus MC Rotterdam as well. All patients in Dutch Hospitals were enrolled in the ATHENA cohort and had consented to have their data used for research purposes, and the Belgian local ethics committee approved the use of anonymized data.

Sample size and statistical analysis

With the hypothesis that eGFR-recovery is similar in patients on ABC and TAF and will be observed in 70% one year after switch**,** the inclusion of 215 patients is needed to exclude that the upper 90% C.I. of the HR of eGFR-recovery (as defined above) is higher than 1.5 with a study power 80% and alfa 0.05. For all endpoints, comparisons between ABC and TAF were done at baseline, week 24 and week 48. Baseline characteristics are described as numbers with percentages (N, (%)), means with standard-deviations (SD), or medians with interquartile ranges (IQR). A multivariate binary logistic regression model was performed to determine independent factors associated with eGFR-recovery at week 48. Factors included in this model are: eGFR-decline during TDF, pre-treatment and end of therapy CD4 T-lymphocytes, eGFR at TDF-discontinuation, and TDF-duration. Analyses between and within groups were performed using unpaired and paired T-tests, Mann Witney U and Wilcoxon Rank Sum tests, and Chi square tests.

RESULTS

Of 9752 HIV-infected individuals in the participating centers, 2062 underwent a switch from TDF to TAF- or ABC-containing cART, and were screened for eligibility for the BACTAF-study between September 10, 2016 and November 14, 2017. 250 were included, including 131 who switched to TAF and 119 to ABC (figure 1). Of them, 35 were switched in the context of the prospective BACTAF trial (17 randomized to TAF and 18 to ABC). Patients were mostly middle-aged Dutch men having sex with men (Table 1). No significant differences were appreciable in baseline characteristics between those included in the clinical trial and those from the retrospective cohort. The median year of HIV diagnosis was 2007 (TAF) and 2005 (ABC) and their median initiation year of TDF-containing cART was 2009 and was

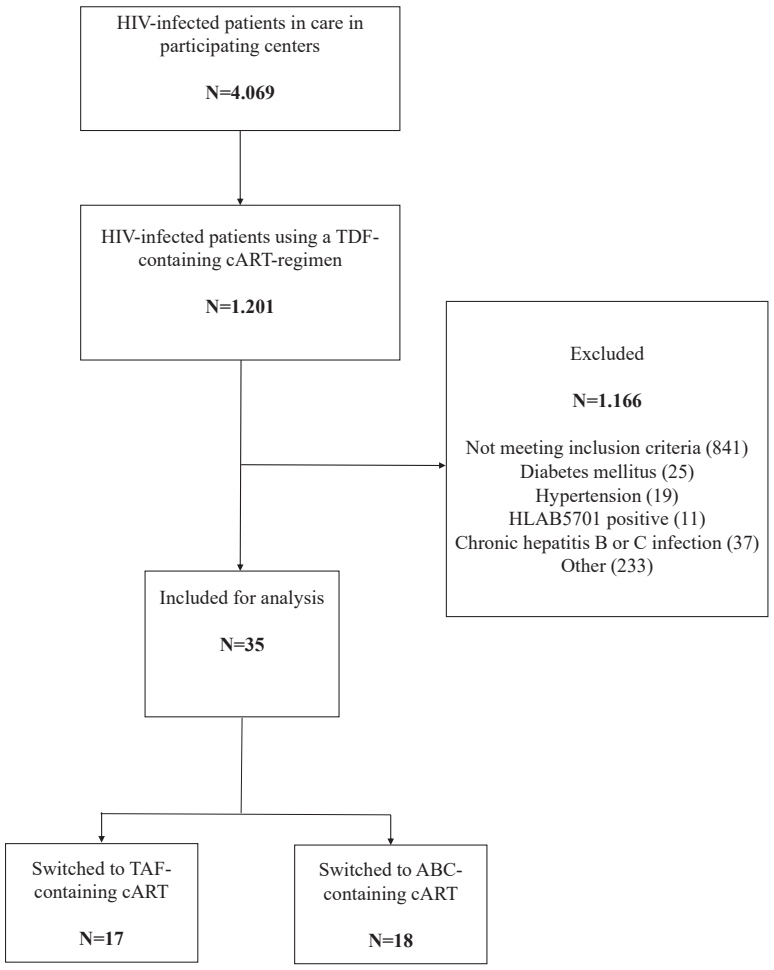

Figure 1. Patient disposition in the BACTAF-study.

predominantly NNRTI-based. During a median of 8 (TAF) and 6 (ABC) years of TDF-use, the eGFR declined by 29.0 (SD 22.0) mL/min and 27.5 (SD 25.8) mL/min respectively. At the moment of TDF-discontinuation, the mean eGFR was 67.9 (SD 14.8) for ABC versus 72.9 ml/min (SD: 15.0) for TAF (95%CI: -8.7 - -1.3, p=0.01).

	TAF (N=131)	**ABC (N=119)**	**P-value**
Male sex, N (%)	113 (86.3)	97 (81.5)	0.31
Age, mean (SD)	48 (11)	49 (11)	0.35
Region of origin, N (%)			0.24
Netherlands	87 (66.4)	76 (63.9)	
Europe	14 (10.7)	19 (16.0)	
Africa	17 (13.0)	8 (6.7)	
South America and Caribbean	9 (6.9)	10 (8.4)	
Other	4 (3.0)	6 (5.0)	
Mode of transmission, N (%)			0.37
MSM	89 (67.9)	78 (65.5)	
HSX	26 (19.9)	26 (21.9)	
Unknown	13 (9.9)	7 (5.9)	
Other	3 (2.3)	8 (6.7)	
Year of HIV-diagnosis, median (IQR)	2007 (2002-2010)	2005 (2001-2009)	0.08
HIV RNA zenith, Log_{10} c/mL, median (IQR)	1.0E5 (6.1E4-3.4E5)	1.0E5 (5.1E4-3.2E5)	0.79
CD4 T-lymphocyte nadir, cells/mm^3, median (IQR)	220 (98-323)	230 (128-314)	0.81
Year of TDF initiation, median (IQR)	2009 (2007-2012)	2009 (2006-2010)	0.14
Year of TDF discontinuation, median (IQR)	2017 (2016-2017)	2015 (2013-2016)	<0.001
Third agent before TDF discontinuation, N (%)			<0.001
NNRTI	63 (48.1)	45 (37.8)	
PI	7 (5.3)	25 (21.0)	
INI	61 (46.6)	49 (41.2)	
RPV	38 (29.0)	24 (20.2)	
PI/b	18 (13.7)	39 (32.8)	
ATV/r	*4 (3.1)*	*24 (20.2)*	
LPV/r	*2 (1.5)*	*5 (4.2)*	
DRV/r or c	*12 (9.2)*	*10 (8.4)*	
EVG/c	26 (19.9)	4 (3.4)	
DTG	11 (8.4)	6 (5.0)	
Other	38 (29.0)	46 (38.7)	
HIV-RNA <50 c/mL at TDF-discontinuation, N (%)	131 (100)	119 (100)	*
CD4 T-lymphocyte count at TDF-discontinuation, cells/mm^3, median (IQR)	660 (407-875)	607 (500-850)	0.70
eGFR-decline during TDF-use, ml/min, mean (SD)	29.0 (22.0)	27.5 (25.8)	0.60

eGFR-slope during TDF-use, mL/min/year, median (IQR)	-4.4 (-7.0 - -3.4)	-6.1 (-10.5 - -3.9)	0.01
eGFR at TDF-discontinuation, mean (SD)	72.9 (15.0)	67.9 (14.8)	0.01
Serum lipids, mean (SD)			
TC, mmol/L	4.9 (0.9)	5.4 (1.0)	0.01
HDL-C, mmol/L	1.3 (0.4)	1.4 (0.4)	0.15
LDL-C, mmol/L	3.0 (0.8)	3.4 (0.9)	0.02
TG, mmol/L	1.67 (1.23)	1.42 (0.62)	0.18
TC:HDL-ratio	3.9 (1.3)	4.0 (1.0)	0.75

Table 1. Baseline characteristics of participants of the BACTAF-study. TAF=tenofovir alafenamide fumarate, ABC=abacavir, SD=standard deviation, MSM=men having sex with men, HSX=heterosexual, IQR=inter quartile range, TDF=tenofovir disoproxil fumarate, RPV=rilpivirine, PI/b=boosted protease inhibitor, EVG/c=cobicistat boosted elvitegravir, DTG=dolutegravir, * no p-value calculated, eGFR=estimated glomerular filtration rate (according to CKD-EPI), TC=total cholesterol, HDL-C=high-density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, TG=triglycerides, TC:HDl-ratio=total cholesterol to HDL ratio.

During follow up, 25 patients discontinued their ABC or TAF containing regimen for a multitude of reasons (e.g. treatment related adverse events (n=17), participation in a cART switch trial, virological failure, moving outside the Netherlands etc.). Ten of these patients failed to reach the week 24 endpoint and 12 the week 48 endpoint. Since this is an interim analysis, another 28 patients have not yet reached week 24 and 78 patients lacked week 48 data. HIV-RNA remained suppressed in at least 95% of patients. Data on the recovery of eGFR were available in 211 patients at week 24 and 183 patients at week 48. At week 48, a 50% or better recovery of the eGFR decline, which had been observed during TDF use, was observed in 51 of the 183 patients (27.9%). Recovery was observed to a similar extent in patients that switched to TAF (21/81 or 25.9%)) or ABC (30/102 or 29.4%) with a difference of 3.5%, 95%CI: -9.7 – 16.7; p=0.60). At week 24, 40/211 (19.0%) of the overall population had 50% eGFR-recovery. A 25% or better recovery at week 24 was observed in 36.5% of TAF users and 44.9% of ABC users. These numbers were 65.4% (TAF) and 59.2% (ABC) respectively at week 48 (Figure 2).

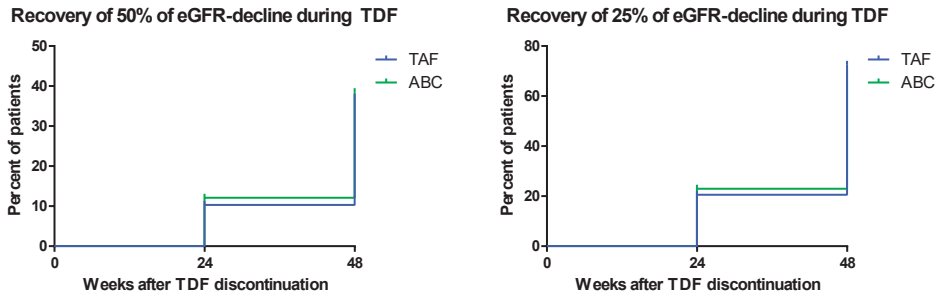

Figure 2. Kaplan Meier curve showing rates of recovery of eGFR to 50% and 25% of the decrease during TDF-use in patients who switched from TDF to TAF- or ABC-containing cART.

None of these differences were statistically significant (p>0.1 for all). None of the following factors were independently associated with eGFR-recovery in the logistic regression model; eGFR-decline during TDF, pre-treatment and end of therapy CD4 T-lymphocytes, eGFR at TDF-discontinuation, and TDF-duration (all p>0.1). After TDF-discontinuation, the mean eGFR-increase in patients on TAF and ABC was 6.5 and 8.1 mL/min at week 24 and 8.4 and 6.4 mL/min at week 48 and these increases were statistically significant (p<0.001). The increases were comparable between the ABC and TAF groups at all timepoints. The changes in fasting serum lipids after TDF-discontinuation are shown in Table 2, and they were available in 51 patients at week 24 and 44 patients at week 48. In both groups, all lipid markers increased slightly during 48 weeks, except from TC:HDL-ratio in patients on ABC (-0.01). In patients on TAF, TC:HDL-ratio increased with 0.3, which was significantly larger than the change in patients on ABC (-0.1, p=0.04). Within the group of patients using TAF, the TC, LDL, TC:HDL-ratio, and TG all increased significantly compared to baseline, whereas no significant changes compared to baseline occurred in the serum lipid markers of patients who switched to ABC.

	TAF	ABC	p-value
Change at week 24 from baseline, mean (SD)			
Total cholesterol	+0.2 (0.9)	+0.3 (0.9)	0.82
HDL-C	+0.0 (0.3)	+0.1 (0.3)	0.05
LDL-C	+0.1 (0.7)	+0.1 (0.8)	0.98
Triglycerides	+0.19 (1.77)	+0.41 (1.62)	0.60
TC:HDL-ratio	+0.5 (1.4)	-0.1 (0.7)	0.05
Change at week 48 from baseline, mean (SD)			
Total cholesterol	+0.5 (0.7)	+0.3 (0.7)	0.19
HDL-C	+0.0 (0.2)	+0.2 (0.4)	0.18
LDL-C	+0.5 (0.7)	+0.1 (0.5)	0.13
Triglycerides	+0.61 (0.83)	+0.30 (0.71)	0.16
TC:HDL-ratio	+0.3 (0.7)	-0.1 (0.7)	0.04

Table 2. Changes in fasting serum lipid markers in patients who switched from TDF to TAF or ABC. SD=standard deviation, HDL-C=high-density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, TC:HDL-ratio=total cholesterol to high-density lipoprotein cholesterol ratio, reported p-values are between group-values.

In the subset of patients who were included in the randomized BACTAF-study, the complete set of all seven PTD-markers were available in 26 and 21 patients at week 24 and 48 (Table 3). In these patients, the median UPCR was 12.6 at baseline and decreased with 3.1 (IQR 0.8 - 9.3) mg/mmol at week 48. In the 14 patients with an increased UPCR at baseline, data at weeks 24 and 48 were available in 12 and 7. In 11/12 at week 24 and in 3/7 at week 48, UPCR remained increased. UAPR further decreased in patients with an increased UPCR. Median

serum phosphate remained comparable after TDF-discontinuation, leading to a decrease in the proportion of patients with hypophosphatemia from 32.3% at baseline to 14.3% at week 48. The proportion of patients with an abnormal FePO4 was 48.4% at baseline and 47.6% at week 48. Serum uric acid increased with mean (SD) 0.02 (0.04) and 0.03 (0.05) mmol/L at weeks 24 and 48, the proportion of patients with hypouricemia decreased slightly, and the proportion of patients with an abnormal FeUA was 9.7% at baseline and 4.8% at week 48. Of the 21 patients with data over 48 weeks, the proportion of PTD did not change: 10 had ≥ 2 PTD markers at baseline, 8 patients at week 24 (of whom 5 had PTD at baseline), and 9 patients at week 48 (of whom 5 had PTD at baseline).

	Week 0 N=31	**Week 24 N=26**	**Week 48 N=21**
Serum phosphate, median (Q1,Q3)	0.88 (0.78,1.04)	+0.01 (-0.15,0.11)	+0.04 (-0.11,0.17)
Serum phosphate < 0.8 mmol/L, N (%)	*10 (32.3)*	*7 (26.9)*	*3 (14.3)*
Serum uric acid, mean (SD)	0.28 (0.08)	+0.02 (0.04)	+0.03 (0.05)
Serum uric acid < 0.20 (m) or < 0.15 (f), N (%)	*3 (9.7)*	*2 (7.7)*	*2 (9.5)*
UPCR, median (Q1,Q3)	12.6 (7.6,21.6)	-1.5 (-3.1,2.9)	-3.1 (-9.3,0.8)
UPCR increased, N (%)	*14 (45.2)*	*13 (50.0)*	*6 (28.6)*
UAPR, median (Q1,Q3)*	0.11 (0.05,0.15)	-0.05 (-0.06,0.00)	-0.06 (-0.11,0.00)
UAPR decreased, N (%)	*11 (78.6)*	*8 (61.5)*	*5 (83.3)*
FePO4, median % (Q1,Q3)	17.8 (12.8,23.8)	-1.0 (-5.7,3.6)	-1.8 (-2.6,4.6)
FePO4 increased, N (%)	*15 (48.4)*	*12 (46.2)*	*10 (47.6)*
FeUA, median (Q1,Q3)	9.67 (7.2,12.1)	-1.2 (-3.5,0.9)	-0.9 (-3.1,1.3)
FeUA increased, N (%)	*3 (9.7)*	*0 (0.0)*	*1 (4.8)*
Normoglycaemic glucosuria, N (%)	*3 (9.7)*	*1 (3.8)*	*1 (4.8)*
≥ 2 markers of PTD, N (%)	*18 (58.1)*	*12 (46.2)*	*9 (42.9)*

Table 3. Markers of proximal tubular dysfunction (PTD) in a subset of patients. SD standard deviation, UPCR=urine protein to creatinine ratio, UAPR=urine albumin to protein ratio, * only patients with increased UPCR included, FePO4=fractional excretion of phosphate, FeUA=fractional excretion of uric acid.

Significantly more patients on ABC discontinued ABC for an AE (n=16) than patients on TAF discontinuing TAF for an AE (n=2), p<0.001. Reasons for ABC discontinuation in these 16 patients were rash (N=2), neuropsychiatric (N=2), diarrhea (N=3), nausea (N=5) and other (N=5). TAF was discontinued in 2 (thrombopenia, rash).

DISCUSSION

In the BACTAF study, we aim to compare recovery of eGFR after a switch from TDF to a TAF or ABC-containing cART in patients in which an accelerated eGFR-decline was observed during their treatment with TDF-containing cART. Although the anticipated recovery rates of

70% that we based on previous research on this topic were not reached, our results suggest that 48 weeks after the discontinuation of TDF a comparable recovery (expressed in mL/min) of glomerular filtration was observed in patients switched to ABC or TAF. In fact, more often a stabilization rather than recovery of eGFR was observed after TDF-discontinuation. Our results suggest that both ABC and TAF can be used when TDF needs to be discontinued for renal toxicity.

The stabilization rather than recovery of the estimated glomerular function was an unexpected observation in light of previous reported cohorts.[6–13] However, this finding makes it likely that in part of the patients the use of TDF resulted in an irreversible decrease in glomerular filtration rate and thus without any future perspective of recovery. Our recovery-rates differ from those in a large cohort study, in which recovery rates up to 62% after 7 years of TDF-discontinuation were shown. Baseline characteristics were comparable, except from more non-black people being included in our study, more patients being on an INSTI-containing cART-regimen at the time the TDF was switched to ABC or TAF, and less on PI- or NNRTI-containing cART. However, a crucial difference between our study design and the previously published cohort studies is that in previous studies patients who discontinued TDF for any reason were included, so they were not necessarily suffering from a TDF-associated eGFR-decline. Besides, recovery was defined as an eGFR within 5% of the eGFR at the moment of TDF-initiation (or within 5% of the expected eGFR at TDF-discontinuation when TDF-use was preceded by a decline in eGFR). This may not be a realistic expectation if patients had been on TDF for many years, given the fact that natural aging results in eGFR-loss as well.[7] In a randomized clinical trial including 242 patients with renal impairment defined as eGFR between 30-69 mL/min, patients switched from cART containing any NRTI-backbone to TAF, combined with FTC, EVG, and COBI. Comparable results of eGFR-improvement were found in this study, with no clinically relevant change in eGFR in patients discontinuing TDF after 48 weeks. However, proteinuria markers significantly improved in patients discontinuing TDF, which was not the case for patients discontinuing a non-TDF containing regimen. People in this study were older, were more often using a PI before switch, a substantial part had comorbidities like diabetes mellitus or hypertension, and their eGFR at TDF-discontinuation was lower than in our population. Importantly, the duration of TDF-use was not mentioned.[24] It is therefore not surprising that no recovery in the eGFR was observed because reasons other than TDF toxicity were more likely to be the cause of the eGFR decline during the years of TDF use. In other studies, some factors are mentioned to be associated with incomplete recovery. Therefore, we performed a multivariable logistic regression model, but none of the included factors were independently associated with recovery.[7–9]

Regarding recovery of PTD, the presence of PTD markers remained common after TDF-discontinuation. Also, UPCR was more favorable than expected at baseline but seemed to

ameliorate further after TDF discontinuation. This is in line with other phase III studies on renal consequences of a switch from TDF- to TAF-containing cART in which an improvement of UPCR was observed after 48 weeks.[24–26] The changes in serum lipids in patients using TAF are comparable with findings in other studies on TDF-discontinuation.[27,28] However, the stabilization of lipids in patients switching to ABC is remarkable. This might be due to the higher (although not statistically significant) baseline lipids in these patients and a regression to the mean during 48 weeks of follow-up. Importantly, we are reporting data on a relatively healthy population (as patients with underlying diseases that may damage the kidneys were excluded) and this limits its generalizability to more vulnerable populations.

A statistically significant higher number of patients on ABC discontinued study drug for AEs compared to patients using TAF. The ABC-related discontinuations were mainly driven by gastrointestinal AEs, but also skin and neuropsychiatric AEs. These are all well-known side effects of ABC. In contrast, the discontinuation-rate of TAF is low, which suggests that TAF is better tolerated than ABC.

Some important limitations of our study should be mentioned. First, the results of this interim analysis might change with longer follow up. However, we do not expect clinical relevant changes since the effect was consistent in the patients from the trial and the cohort. Furthermore, no outcomes after 72 and 96 weeks are studied. Reassuringly, others have shown that the eGFR-recovery after TDF-discontinuation is predominantly established in the first 24 to 48 weeks, although we should also acknowledge that further eGFR-recovery has also been observed after this time point up to 5 years.[7–13] Second, the accuracy of eGFR as marker of actual creatinine clearance (and renal function) decreases when eGFR is above 60 mL/min. With the application of our inclusion criteria in relatively healthy people, we might have overestimated the extent of renal dysfunction in our patients, which might contribute to the low recovery rates. In future, the hypothesis could be tested that eGFR-recovery depends on the inclusion criteria on eGFR-decline which are used. Also, the optimal definition of eGFR-recovery is unknown, which contributes to the varying results in previous studies which all used different definitions of renal recovery. Remarkably, other studies defined eGFR-recovery more strictly than we did, not always taking the natural course of eGFR-decline into account, and show comparable or higher recovery rates compared to our data after one to five years after TDF-discontinuation.[7–13] This is difficult to explain because, in contrast to previous studies, we excluded all patients who had other underlying diseases that may also lead to eGFRdecline. Therefore, if anything we would have expected a better recovery rate in our study compared with previous studies. Data on PTD, proteinuria and lipids were based on incomplete data, with unavailable follow-up in a substantial number of patients. Therefore, those findings should be interpreted with caution. An important strength of our study is that, in contrast to previous studies, our study used stricter definitions of TDF related renal

dysfunction and was more stringent in excluding patients with other likely causes of renal dysfunction. This might at least partly explain the difference between previous studies and the current observed eGFR-recovery rates. Second, this is the first study comparing renal safety of two first-line recommended antiretroviral NRTIs backbones replacing TDF. In addition, our study is the largest to date on this subject.

At this moment, as a result of the eligibility criteria, the results are particularly applicable to relatively healthy white middle-aged males with good drug-adherence. Future analyses should be performed to define patients with the highest chance of recovery, which may also contribute to extension of recovery-definitions for those subgroups (for example younger versus older people). Also, it is not known whether women, non-Caucasian people, elderly and adolescents can also safely use TAF and ABC interchangeably in terms of eGFR-recovery, and whether TAF is non-inferior to ABC in patients with (cardiovascular) comorbidities. This should be subject of further study. Furthermore, a time-to-recovery analysis on complete follow-up data would provide interesting insights on independent factors associated with eGFR-recovery after TDF-discontinuation.

In conclusion, the results of this study strongly suggest that renal outcomes of a switch to TAF are non-inferior to ABC in patients with a TDF-associated eGFR-decline. Furthermore, a switch to ABC more often led to the discontinuation of this drug for AEs. Therefore, TAF is an important new treatment option for patients with TDF related renal dysfunction.

REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0.
2. European AIDS Clinical Society. European guidelines for treatment of HIV-positive adults. Available at http://www.eacsociety.org/files/guidelines_9.0-english.pdf.
3. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;**69**:375–382.
4. Cooper RD, Wiebe N, Smith, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010;**51**:496–505.
5. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. *AIDS Res Hum Retroviruses* 2009;**25**:387–394.
6. Romo FT, Aziz M, Livak B et al. Renal Function Recovery and HIV Viral Suppression Following Tenofovir Discontinuation for Renal Impairment. *J AIDS Clin Res* 2014;**5**:pii379.
7. Jose S, Hamzah L, Campbell LJ et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. *J Infect Dis* 2014;**210**:363–373.
8. Wever K. van Agtmael MA, Carr A. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. *J Acquir Immune Defic Syndr* 2010;**55**:78–81.
9. Bonjoch A, Echeverria P, Perez-Alvarez N et al. High rate of reversibility of renal damage in a cohort of HIV-infected patients receiving tenofovir-containing antiretroviral therapy. *Antiviral Res* 2012;**96**:65–69.
10. Bonjoch A, Echeverria P, Perez-Alvarez N et al. Prospective study to assess progression of renal markers after interruption of tenofovir due to nephrotoxicity. *Biomed Res Int* 2016;**2016**:4380845.
11. Cha A, Besignano-Long AR, Rothberger N, Shah B. Reversibility of renal dysfunction after discontinuation of tenofovir. *J Am Pharm Assoc* 2016;**56**:280–283.
12. Young J, Wang Q, Fux CA et al. The rate of recovery in renal function when patients with HIV infection discontinue treatment with tenofovir. *HIV Med* 2014;**15**:505–510.
13. Yoshino M, Yagura H, Kushida H et al. Assessing recovery of renal function after tenofovir disoproxil discontinuation. *J Infect Chemother* 2012;**18**:169–174.
14. Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Inter., Suppl.* 2013;**3**:1–150.
15. Mallal S, Phillips E, Carosi G et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;**358**:568–579.
16. D:A:D Study Group, Sabin CA, Worm SW et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008;**371**:1417–1426.
17. Markowitz M, Zolopa A, Squires K et al. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV-infected adults. *J Antimicrob Chemother* 2014;**69**:1262–1369.
18. Gallant JE, Daar ES, Raffi F et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV* 2016;**3**:e158–e165.

19. Moyle GJ, Stellbrink HJ, Compston J et al. 96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naïve, HIV-1-infected adults: ASSERT study. *Antivir Ther* 2013;**18**:905–913.
20. Sax PE, Wohl D, Yin MT et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015;**385**:2606–2615.
21. Stanford University HIV Drug Resistance Database. Available on https://hivdb.stanford.edu/hivseq/by-mutations/.
22. Lucas GM, Ross MJ, Stock PG et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV medicine association of the infectious diseases society of America. *Clin Infect Dis* 2014;**59**:296–e138.
23. Maggi P, Montinaro V, Mussini C et al. Novel antiretroviral drugs and renal function monitoring of HIV patients. *AIDS Rev* 2014;**16**:144–151.
24. Pozniak A, Arribas JR, Gathe J et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label phase 3 study. *J Acquir Immune Defic Syndr* 2016;**71**:530–537
25. Raffi F, Orkin C, Clarke A et al. Brief report: long-term (96-week) efficacy and safety after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in HIV-infected, virologically suppressed adults. *J Acquir Immune Defic Syndr* 2017;**75**:226–231.
26. Post FA, Tebas P, Clarke A et al. Brief report: switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected adults with renal impairment: 96-week results from a single-arm, multicenter, open-label phase 3 study. *J Acquir Immune Defic Syndr* 2017;**74**:180–184.
27. Arae H, Tateyama M, Nakamura H et al. Evaluation of the lipid concentrations after switching from antiretroviral drug tenofovir disoproxil fumarate/emtricitabine to abacavir sulfate/lamivudine in virologically-suppressed human immunodeficiency virus-infected patients. *Intern Med* 2016;**55**:3435–3440.
28. Arribas JR, Thompson M, Sax PE et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *J Acquir Immune Defic Syndr* 2017;**75**:211– 218.