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Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials

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Objective: Compared with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) has been associated with improvement in markers of renal dysfunction in individual randomized trials; however, the comparative incidence of clinically significant renal events remains unclear.

Design: We used a pooled data approach to increase the person-years of drug exposure analysed, maximizing our ability to detect differences in clinically significant outcomes.

Methods: We pooled clinical renal safety data across 26 treatment-naive and antiretroviral switch studies to compare the incidence of proximal renal tubulopathy and discontinuation due to renal adverse events between participants taking TAF-containing regimens vs. those taking TDF-containing regimens. We performed secondary analyses from seven large randomized studies (two treatment-naive and five switch studies) to compare incidence of renal adverse events, treatment-emergent proteinuria, changes in serum creatinine, creatinine clearance, and urinary biomarkers (albumin, beta-2-microglobulin, and retinol binding protein-to-creatinine ratios).

Results: Our integrated analysis included 9322 adults and children with HIV ($n = 6360$ TAF, $n = 2962$ TDF) with exposure of 12 519 person-years to TAF and 5947 to TDF. There were no cases of proximal renal tubulopathy in participants receiving TAF vs. 10 cases in those receiving TDF ($P < 0.001$), and fewer individuals on TAF (3/6360) vs. TDF (14/2962) ($P < 0.001$) discontinued due to a renal adverse event. Participants initiating

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TAF-based vs. TDF-based regimens had more favourable changes in renal biomarkers through 96 weeks of therapy.

Conclusion: These pooled data from 26 studies, with over 12 500 person-years of follow-up in children and adults, support the comparative renal safety of TAF over TDF.

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Keywords: adverse drug event, drug safety biomarkers, HAART, HIV, proximal renal tubular dysfunction, renal fanconi syndrome, tenofovir disoproxil fumarate

Introduction

Tenofovir (TFV) disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor that is highly efficacious and generally well tolerated. However, TDF is associated with renal adverse events, including proximal renal tubulopathy (PRT), which occurs in less than 1% of individuals [1,2]. TFV alafenamide (TAF), a TFV prodrug, is associated with a mean 91% lower plasma TFV exposure compared with TDF [3]. As higher plasma TFV levels have been associated with nephrotoxicity [4,5], reduced circulating TFV levels are hypothesized to result in fewer renal adverse events. In phases 2 and 3 clinical trials of both treatment-naive and virologically suppressed adults and children [3,6–35], TAF-containing regimens have demonstrated high efficacy and favorable changes in renal biomarkers including creatinine clearance (CrCl), total and tubular proteinuria, and albuminuria compared with a variety of unboosted and ritonavir (RTV)-boosted or cobicistat (COBI)-boosted TDF-containing regimens. It has been more challenging to determine whether the favourable biomarker profile of TAF translates into improved renal clinical outcomes, due to the low rates of renal events in individual trials, although the 144 week follow-up of the pooled pivotal trials for elvitegravir (EVG)/COBI/emtricitabine (FTC)/TAF had zero cases of PRT and zero renal discontinuations compared with four cases of PRT and 12 renal discontinuations in the EVG/COBI/FTC/TDF group [8]. To better understand the renal clinical outcomes in TAF vs. TDF-containing HIV regimens, we conducted a large integrated analysis of people living with HIV (PLH) from 26 TAF clinical trials. These trials included cumulative exposures of 12 519 person-years to TAF and 5947 person-years to TDF, thereby providing increased statistical power to evaluate the comparative impact on renal adverse events and renal function over time.

Methods

Study design and participants

We included 26 phases 2 and 3 multicenter, multinational, clinical studies of TAF-containing regimens in PLH including adults, adolescents, and children (aged ≥6 years) who were either ART-naive or virologically suppressed on a stable ART regimens containing TDF. These studies were conducted between 28 December 2011 and 4 December 2017. Study design and inclusion criteria, including minimum renal function, of each trial are described in Appendix Table 1, http://links.lww.com/QAD/B470. Of the 26 studies, 14 were double blinded and randomized, six were open label and randomized, and six were single arm. All trials were undertaken in accordance with the Declaration of Helsinki and approved by central or site-specific review boards or ethics committees. All participants or their legal guardians (if minors) provided written, informed consent.

Procedures

Postbaseline study visits were conducted at weeks 4, 8, 12, 24, 36, and 48 and every 12 weeks thereafter until week 96. Renal laboratory tests included serum creatinine (SCr), CrCl by Cockcroft–Gault, treatment-emergent proteinuria by dipstick, urine albumin-to-creatinine ratio (UACR), and tubular proteinuria [urine retinol binding protein-to-creatinine ratio (RBP : Cr) and β2-microglobulin-to-creatinine ratio (β2M : Cr)] (Covance Laboratories, Indianapolis, Indiana, USA).

Renal safety was assessed by recording of adverse events, which were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1–19.1) (Appendix Table 2, http://links.lww.com/QAD/B470).

Analysis of primary renal safety outcomes

The primary renal safety outcomes were incidence of PRT events, and study drug renal discontinuation events. For primary outcomes analysis, we pooled all participants from the 26 available trials who received at least one dose of study drug (safety analysis set). We derived safety measures data using all data collected on or after study drug was first given up to either the data cut date for participants still on study drug or up to 30 days after the last dose of study drug for participants who permanently discontinued treatment early. We summarized baseline demographics and characteristics of the included participants with descriptive statistics.

We defined 'renal discontinuation events' as investigator-reported discontinuation events for which the attributable MedDRA code exists in selected renal preferred terms from the 'renal and urinary disorders' System Organ Class (Appendix Table 2, http://links.lww.com/QAD/B470). Similarly, PRT cases were defined as investigator-reported adverse events indicative of tubular disorders, including reported terms of PRT and Fanconi syndrome (preferred terms are provided in Appendix Table 3, http://links.lww.com/QAD/B470), regardless of study drug relatedness. The cumulative incidence rates of investigator-reported cases of PRT and renal adverse events leading to study drug discontinuation were calculated as the number of events divided by the total numbers of participants pooled from the 26 trials treated with TAF-containing or TDF-containing regimens, respectively. The differences in the cumulative incidence rates between treatment groups were compared using Fisher's exact test. To minimize type I error resulting from multiple hypothesis testing, we performed primary endpoint analysis in a predetermined sequence, only proceeding to the second endpoint (renal discontinuation events) if the first endpoint (PRT events) analysis demonstrated statistical significance with $\alpha = 0.05$.

Analysis of secondary renal outcomes

We assessed secondary renal outcomes including treatment-emergent renal adverse events, SCr, CrCl, treatment-emergent gross proteinuria (by dipstick), UACR, and tubular proteinuria (urine RBP : Cr and β2M : Cr). Treatment-emergent proteinuria was defined as 1+ or greater proteinuria by dipstick on any occasion during trial follow-up, regardless of persistence. Urine protein-to-creatinine ratio was monitored during the trials, but a change in assay methodology occurring partway through several trials resulted in data unsuitable for integrated analysis. For the analysis of these secondary renal outcomes, we selected a subset of trials that satisfied the following predetermined criteria: randomized design; TAF and TDF arms; and at least 48 weeks of follow-up. Based on these criteria, a total of seven trials were selected, including two treatment-naive studies and five virologically suppressed studies (referred to as switch studies) (Fig. 1). To facilitate accurate assessment of CrCl changes in study participants, we excluded participants who switched from an ART regimen lacking a known creatinine transport inhibitor to a regimen containing a known creatinine transport inhibitor (rilpivirine, dolutegravir, bictegravir, COBI, or RTV) [36–41]. This approach allowed us to reduce confounding caused by SCr increases attributable to initiation of a creatinine transport inhibitor.

Study Population	Study no.	Study design	N	Treatment
TN adults (n=7)	292-0102	DB, R	170	E/C/F/TAF vs E/C/F/TDF
	141-1475	DB, R	98	BIC+F/TAF vs DTG+F/TAF
	380-1490	DB, R	645	B/F/TAF vs DTG+F/TAF
	299-0102	DB, R	153	DRV/COBI/FTC/TAF vs DRV+COBI+FTC/TDF
	380-1489	DB, R	629	B/F/TAF vs ABC/DTG/3TC
	292-0104	DB, R	867	E/C/F/TAF vs E/C/F/TDF
	292-0111	DB, R	866	E/C/F/TAF vs E/C/F/TDF
VS adults (n=12)	366-1160	DB, R	875	EFV/FTC/TDF vs FTC/RPV/TAF
	366-1216	DB, R	630	FTC/RPV/TAF vs FTC/RPV/TDF
	311-1089	DB, R	663	F/TAF+3rd agent vs F/TDF+3rd agent
	292-0109	OL, R	1436	E/C/F/TAF vs TDF-containing regimens
	380-1878	OL, R	577	B/F/TAF vs boosted PI-regimens
	380-1844	DB, R	563	B/F/TAF vs ABC/DTG/3TC
	311-1717	DB, R	556	F/TAF+3rd agent vs ABC/3TC+3rd agent
	292-1823	OL, R	274	E/C/F/TAF vs ABC/3TC+3rd agent
	366-1992	OL, R	148	E/C/F/TAF vs R/F//TAF
	380-1961	OL, R	470	B/F/TAF vs E/C/F/TAF, E/C/F/TDF or ATV+RTV+F/TDF
	236-0128	OL, R	212	E/C/F/TAF vs ATV/r + FTC/TDF
	292-1824	Single arm	37	E/C/F/TAF
TN & VS adults (n=1)	292-1249	Single arm	77	E/C/F/TAF
TE adults (n=2)	292-0117	DB, R	37	TAF+failing regimen vs placebo+failing regimen
	292-0119	OL, R	133	E/C/F/TAF+DRV vs pre-existing regimen
TN & VS children (n=1)	292-0106	Single arm	102	E/C/F/TAF
VS adolescents (n=1)	292-1515	Single arm	60	E/C/F/TAF
TN & VS children & adolescents (n=2)	311-1269	Single arm	28	F/TAF
	380-1474	Single arm	24	B/F/TAF

Primary outcomes
(N=26 trials, 9,322 participants)
1) PRT events
2) Discontinuations due to renal AEs

Secondary outcomes
(N=7 trials; n=2 naïve [1733 participants], n=5 suppressed [4092 participants])
1) Treatment-emergent renal AEs
2) SCr (mg/dL)
3) CrCl (mL/min)
4) Treatment-emergent proteinuria (dipstick)
5) UACR
6) Tubular proteinuria (urine RBP:Cr and β2M:Cr)

Fig. 1. Characteristics of studies included in the integrated analysis. Treatment-naive studies included in the secondary analysis are highlighted in blue, virologically suppressed people living with HIV studies are highlighted in green. 3TC, lamivudine; ATV, atazanavir; AE, adverse event; B, BIC, bictegravir; C, COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; DB, double blind; E, elvitegravir; FTC, emtricitabine; OL, open label; PI, protease inhibitor; R, randomized; R, RPV, rilpivirine; RTV, ritonavir; STR, single tablet regimen; TE, treatment-experienced; TN, treatment-naive; VS, virologically suppressed.

Using these data, we evaluated the incidence rates of treatment-emergent renal adverse events (Appendix Table 2, http://links.lww.com/QAD/B470) and of proteinuria by dipstick. We also summarized change from baseline in SCr and CrCl and percentage change from baseline in UACR, RBP : Cr, and β2M : Cr. We used logistic regression models to compare the differences in incidence rates between treatment groups and linear regression and rank analysis of covariance (adjusted for baseline demographics and disease characteristics selected from step-wise procedure) for change and percentage change from baseline in renal parameters, respectively.

To control for type I error in the testing of multiple secondary renal outcomes hypotheses, we employed the following testing strategies. First, the primary comparisons of PRT and renal discontinuation events in all 26 studies were analyzed using a predefined sequence as described above. Subsequently, hypothesis testing for secondary outcomes was performed using the Holm–Bonferroni method; *P* values reported in the text are Holm–Bonferroni adjusted [42,43]. We used SAS Software Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) for all analyses. All studies were conducted according to protocol without substantial deviations

Results

We included a collective 9322 individuals across 26 studies (Appendix Table 1, http://links.lww.com/QAD/B470). Participants either initiated or switched to regimens containing TAF ($n = 6360$) or initiated or continued on regimens containing TDF ($n = 2962$) (Table 1). Baseline median age was 42 years, 21% were women, and 27% were of black race. Pooled data included exposure of 12 519 person-years to TAF and 5947 person-years to TDF.

Primary analyses

Incidence of proximal renal tubulopathy events

In the dataset including all 26 studies, 14 of which were double blinded, there were no cases of PRT or Fanconi syndrome reported in the TAF group (Fig. 2). Ten cases of PRT, including Fanconi syndrome, were reported by site investigators for the TDF group (0.34% of participants, $P < 0.001$ vs. TAF). Of the PRT cases, nine of 10 were investigator reported as study drug related, nine of 10 occurred during blinded therapy, and eight of 10 resulted in study drug discontinuation. Appendix Fig. 1, http://links.lww.com/QAD/B470 shows the specific ART regimens, duration of study drug exposure relative to onset of PRT and relatedness to study drug as determined by the site investigator. The timing of PRT development was variable but often occurred well into therapy, including three of 10 cases developing in participants who were virologically suppressed on TDF for at least 6 months at the time of enrolment (Appendix Fig. 1, http://links.lww.com/QAD/B470).

Discontinuations due to renal adverse events

In the dataset including all 26 studies, three of 6360 individuals (0.05%) who received TAF discontinued study drug due to renal adverse events compared with 14 of 2962 (0.47%) participants in the TDF group ($P < 0.001$) (Fig. 2). Of the 14 participants in the TDF group, four were in open-label studies and the remainder were in double-blinded studies; 12 of 14 discontinuations were reported as study drug-related. All three participants in the TAF group were enrolled in open-label studies, and no discontinuations were reported as study-drug related. Appendix Fig. 2, http://links.lww.com/QAD/B470 shows the specific ART regimens, duration of study drug exposure relative to onset of the renal adverse event, as well as relatedness to the study drug as determined by the investigator. Appendix Table 4, http://links.lww.com/QAD/B470 provides clinical narratives describing the renal discontinuation events.

Table 1. Baseline demographic and clinical characteristics.

Characteristic		TAF, $N = 6360$	TDF, $N = 2962$	Total, $N = 9322$
Age (years)		41 (7, 80)	42 (18, 79)	42 (7, 80)
Sex	Male	4966 (78%)	2436 (82%)	7402 (79%)
	Female	1394 (22%)	526 (18%)	1920 (21%)
Race	White	3796 (60%)	1884 (64%)	5680 (61%)
	Black	1799 (28%)	739 (25%)	2538 (27%)
	Asian	373 (6%)	181 (6%)	554 (6%)
	Other	376 (6%)	153 (5%)	529 (6%)
	Declined to respond	16 (<1%)	5 (<1%)	21 (<1%)
Ethnicity	Hispanic or Latino	1188 (19%)	537 (18%)	1725 (19%)
Treatment status	Naive	2191 (34%)	975 (33%)	3166 (34%)
	Experienced	4169 (66%)	1987 (67%)	6156 (66%)
CrCl (ml/min)		108.8 (91.2, 129.6)	107.7 (90.9, 128.4)	108.6 (91.1, 129.3)

Data are median (IQR) or *n* (%), except for age, which is median (range). CrCl, creatinine clearance; IQR, interquartile range; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

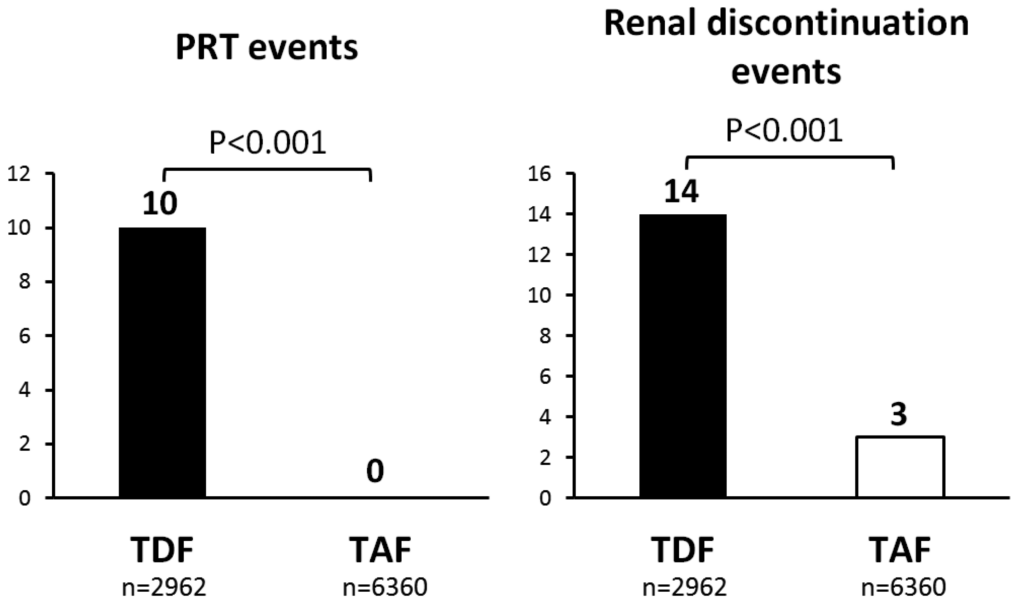

Fig. 2. Cases of proximal renal tubulopathy and renal adverse events leading to study drug discontinuation across 26 clinical studies. The incidence of proximal renal tubulopathy and renal discontinuation events were determined using pooled data from 26 studies as described in the Methods section. Differences between treatment groups compared using Fisher exact test.

Secondary analyses

We next sought to compare secondary renal outcomes between TAF-based and TDF-based regimens both in the settings of treatment-naive ART initiation and regimen switch in virologically suppressed PLH. To this end, we identified two ART-naive studies and five switch studies that were randomized, included both TAF and TDF arms, and included at least 48 weeks of follow-up (Fig. 1).

Total of all renal adverse events in antiretroviral therapy-naive people living with HIV

Based on pooled data from two randomized, double-blinded studies of treatment-naive PLH, clinical renal adverse events through week 96 were reported significantly less frequently in the TAF group than in the TDF group [47/866 (5.4%) vs. 74/867 (8.5%), $P = 0.042$].

Changes in renal laboratory parameters and biomarkers in antiretroviral therapy-naive people living with HIV

In treatment-naive PLH, median change from baseline at weeks 48 and 96 in SCr was significantly lower in the TAF group compared with TDF group [difference in least squares mean (LSM) −0.03 mg/dl, $P \leq 0.001$ at week 96] (Fig. 3a). Similarly, we noted that median CrCl had declined less in the TAF group compared with the TDF group (difference in LSM 6.0 ml/min, $P \leq 0.001$ for week 96) (Fig. 3b).

In treatment-naive PLH, we observed that treatment-emergent proteinuria at week 96 (defined as 1+ or greater proteinuria by dipstick on any occasion) was reported for fewer people in the TAF group compared with those in the TDF group [307/862; (36%) vs. 354/865 (41%); $P = 0.034$].

Treatment-naive PLH initiating TAF-based regimens had greater decreases or smaller increases from baseline through week 96 in median urinary biomarkers (UACR, RBP : Cr, β2M : Cr) compared with TDF (Fig. 4). At week 96, median UACR decreased by 5.2% with TAF vs. an increase of 4.9% with TDF ($P \leq 0.001$) (Fig. 4a). Median RBP : Cr increased by 13.8% with TAF compared with an increase of 74.2% on TDF ($P \leq 0.001$) (Fig. 4b). Median β2M : Cr declined by 32.1% with TAF compared with an increase of 33.5% on TDF ($P \leq 0.001$) (Fig. 4c).

Total of all renal adverse events in virologically suppressed people living with HIV

We evaluated pooled data from five randomized studies (two open-label, three blinded) of virologically suppressed PLH who switched from TDF-containing to TAF-containing regimens or continued their baseline TDF-based regimen. We observed no difference in the rate of reported clinical renal adverse events in these switch studies [114/2291 (5%) vs. 89/1801 (5%), $P = 1.00$].

Changes in renal biomarkers in virologically suppressed people living with HIV

For virologically suppressed PLH, there was a greater reduction in median SCr from baseline in the TAF group compared with the TDF group (difference in LSM −0.03 mg/dl, $P \leq 0.001$ for week 96) (Fig. 3a). Median

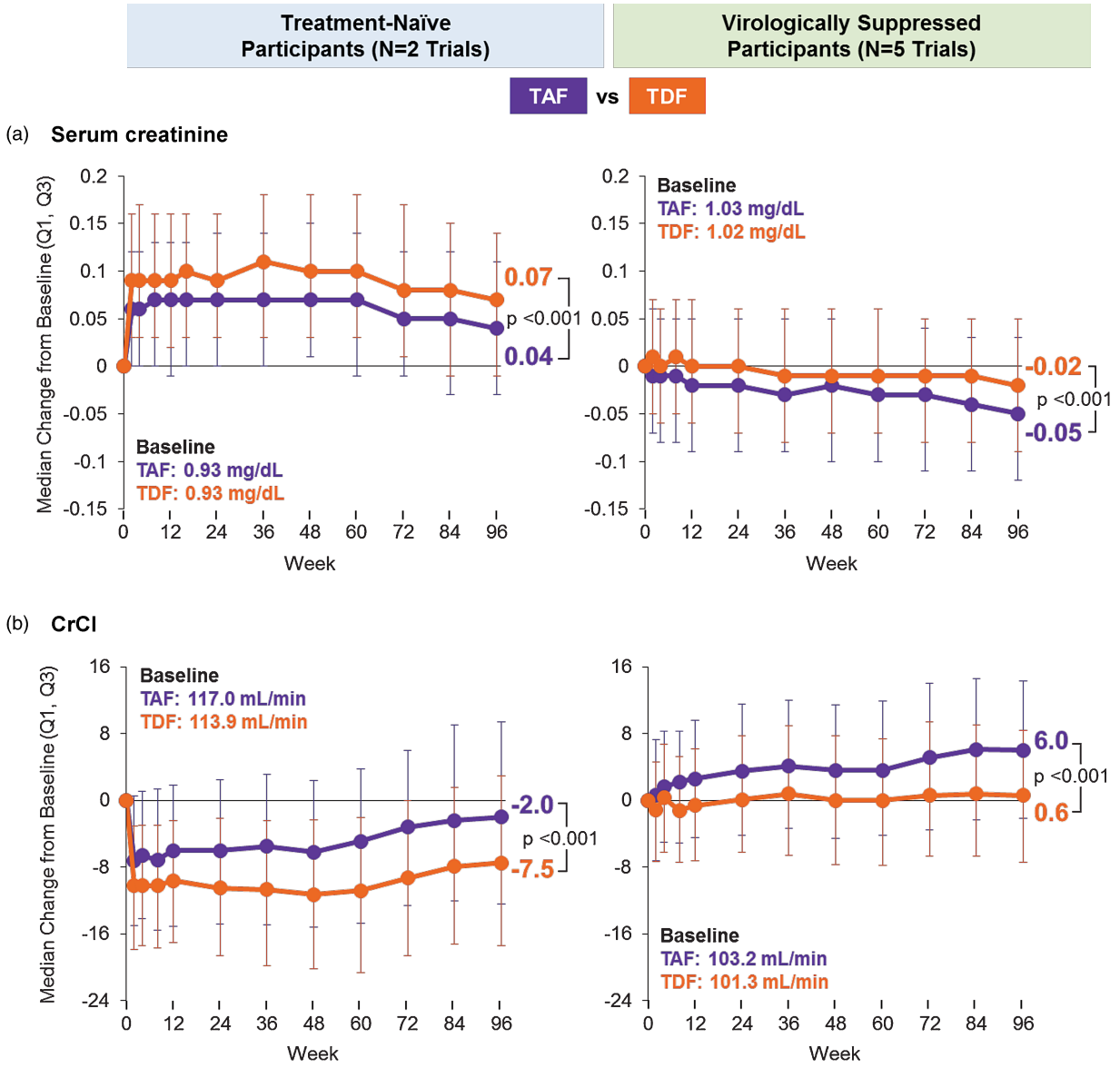

Fig. 3. Longitudinal changes in renal laboratory parameters. Serum creatinine (a) and creatinine clearance (b) were determined longitudinally as described in the Methods section, and are depicted as median change from baseline (purple = tenofovir alafenamide, orange = tenofovir disoproxil fumarate). In each panel, the first plot depicts pooled data from two treatment-naive studies, and the second plot depicts data from five virologically suppressed studies. Differences between treatment groups in changes from baseline were compared using linear regression (baseline demographics and disease characteristics selected from step-wise procedure adjusted).

CrCl increased in the TAF group while no change was seen in the TDF group (difference in LSM 5.2 ml/min, $P \leq 0.001$ for week 96) (Fig. 3b).

In virologically suppressed PLH, we observed that treatment-emergent proteinuria at week 96 (defined as 1+ or greater proteinuria by dipstick on any occasion) was reported for fewer people in the TAF group compared with those in the TDF group [636/2287 (28%) vs. 561/1794 (31%); $P = 0.04$].

In virologically suppressed participants switching from TDF to TAF, TAF-based regimens had greater decreases or smaller increases from baseline through week 96 in median renal biomarkers (UACR, RBP : Cr, β2M : Cr) compared with TDF (Fig. 4). Median UACR decreased by 5.4% on TAF and increased by 27.0% on TDF ($P \leq 0.001$) (Fig. 4a). Median RBP : Cr decreased by 2.3% on TAF and increased 61.2% on TDF ($P \leq 0.001$) (Fig. 4b). Median β2M : Cr decreased by 25.8% with TAF and increased by 53.0% on TDF ($P \leq 0.001$) (Fig. 4c).

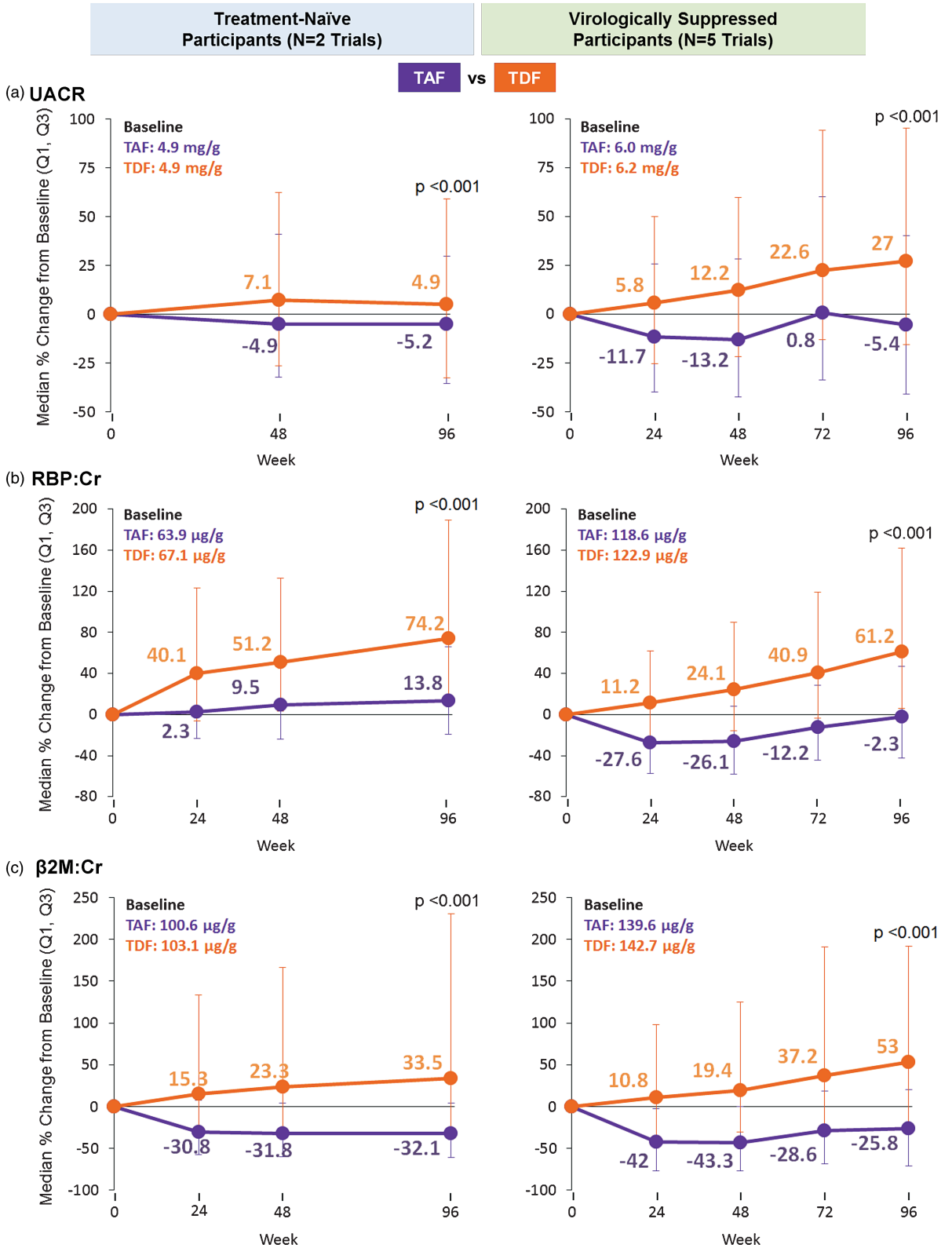

Fig. 4. Longitudinal changes in renal biomarkers. Urine albumin to creatinine ratio (a), retinol binding protein-to-creatinine ratio (b), and β2-microglobulin-to-creatinine ratio (c) were determined longitudinally as described in the Methods section and are depicted as median percentage change from baseline (purple = tenofovir alafenamide, orange = tenofovir disoproxil fumarate). In each panel, the first plot depicts pooled data from two treatment-naive studies, and the second plot depicts data from five virologically suppressed studies. Differences between treatment groups in changes from baseline were compared using linear regression (baseline demographics and disease characteristics selected from step-wise procedure adjusted).

Discussion

Previous studies have demonstrated more favourable renal biomarker profiles in TAF-containing regimens compared with TDF-containing regimens; however, the sample sizes of individual trials and the overall low rate of clinically significant renal adverse events in these trials limited the ability to detect differences in the rates of these events with the exception of the pooled pivotal EVG trials. In the present analysis, we integrated data from 26 individual trials and were able to demonstrate the renal safety of TAF over TDF across a broad range of PLH, including those who were treatment naive and those who were virologically suppressed at switch. After 12 519 person-years of exposure to TAF, there were no cases of PRT or Fanconi syndrome (identified objectively and independently by the primary investigator caring for the participant) and significantly fewer discontinuations due to renal adverse events in the TAF group compared with the TDF group. Notably, only three (0.02%) renal discontinuation events were reported in participants on TAF; none of these were reported as study drug-related by the investigators, and all had plausible alternative causes.

In treatment-naive participants, we observed fewer overall renal adverse events in participants taking TAF-containing regimens compared with those taking TDF-containing regimens. No difference in overall renal adverse events was observed in participants enrolled in switch studies; this may be explained by the fact that participants in those studies were already maintained on TDF at the time of enrolment, and thus self-selected as less likely to develop renal adverse events.

By using an integrated analysis, we were able to demonstrate favourable changes in renal biomarkers in participants taking TAF-containing regiments compared with those taking TDF, both in treatment-naive and treatment-experienced patients who switched to TAF-containing regimens. Our findings demonstrate favourable changes in CrCl as well as in proximal tubule function (RBP and β2M ratios). We also observed a lower incidence of treatment-emergent proteinuria in participants taking TAF-containing regimens. The observed incidences of proteinuria were high, but notably these are cumulative incidences over 96 weeks of follow-up, and are consistent with previously reported incidences of proteinuria in PLH [44]. These biomarker findings in combination with the clinical outcomes suggest that TAF does not induce proximal tubule dysfunction.

The mechanism for the improved renal safety profile of TAF is likely related to the approximately 90% lower plasma levels of TFV seen in participants receiving TAF compared with those receiving TDF. This mechanism is supported by the reported association between declines in renal tubular function and higher TFV plasma concentrations [45–47].

Conversely, the use of boosting agents such as RTV and COBI increase TFV exposure, and accordingly the use of boosting agents has been associated with an increased risk of renal adverse events [2,48]. A recent meta-analysis sought to compare the renal safety profiles of TDF-containing regimens in the presence and absence of boosting agents, and suggested that unboosted TDF could have a similar renal safety profile as TAF [48]. However, the aforementioned meta-analysis is limited by a relatively small number of participants and short duration of follow-up. In the findings presented here, nine out of 10 PRT cases occurred in participants receiving boosted regimens; however, one severe case of PRT occurred in a participant receiving TDF without a boosting agent. Our data support the principle that boosting agents increase the risk of TFV-associated renal adverse events; however, our ability to make robust conclusions about the renal safety of unboosted TDF is limited by the comparatively small number of participants taking such regimens (of 9322 total participants, 2962 were on TDF, and of those 1101 were on TDF without a boosting agent). Although the question of renal safety of TDF in unboosted regimens warrants more evaluation, the available data indicate that TAF can be safely used with boosted as well as unboosted third agents with a very low incidence of clinically significant renal events.

We note several limitations to our analyses. It is challenging to diagnose PRT, and no commonly accepted single diagnostic exists in the clinic to confirm PRT. As such, we utilized investigator-reported events to document PRT, which may have underestimated the number of PRT cases. A reporting bias is possible given the use of investigator reported events, but is unlikely to have affected our findings as most of the included trials were double-blinded, and the majority of reported renal discontinuation events and PRT cases were reported during blinded trial phases. Our clinical trial participants may have been healthier than the general population of PLH due to the presence of inclusion and exclusion criteria in the trials, although TAF was found to safe in patients with impaired renal function (CrCl 30–70 ml/min, many of whom with diabetes mellitus, hypertension, and proteinuria), with no reported cases of PRT and overall stable renal function through 96 weeks of follow-up [49]. We also acknowledge that we did not have individual level data on the duration of prior TDF therapy in our trials and therefore could not adjust the rates accordingly.

Despite these limitations, the integrated analysis presented here is based on the large cumulative exposure in person-years to TAF, both in antiretroviral naïve and virally suppressed populations. Furthermore, the pooled data used for analysis includes a demographically diverse population with a wide age range, a large number of women, and diverse ethnic background. It is also notable that a proportion of participants had relatively low CrCl,

with variable CrCl eligibility cut-offs of 30, 50, or 70 ml/min in the trials included in this analysis (Appendix Table 1, http://links.lww.com/QAD/B470). The clinical trial data are supported by experience from the postapproval use in PLH in which currently there has been no renal safety signal with 1.1 million cumulative person-years exposure to TAF.

In conclusion, the pooled data from 26 clinical studies, representing over 12 500 patient-years of follow-up in children and adults on TAF, suggests that the favourable renal biomarker profile observed with TAF vs. TDF in the individual trials translates into a lower rate of clinically significant renal events. These data support a comparative renal safety advantage of TAF over TDF in a broad range of PLH.

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Conflicts of interest

S.K.G. reports having received consultancy/advisory fees from Gilead Sciences, GSK-ViiV, and BMS and travel support to current study results at conferences from Gilead Sciences. F.A.P. reports grants to King's College Hospital NHS Foundation Trust from ViiV Healthcare and Gilead Sciences, and personal fees from Gilead Sciences, Janssen-Cilag, GlaxoSmithKline/ViiV Healthcare, and Merck. J.R.A. has received advisory fees, speaker fees, and grant support from ViiV Healthcare, Janssen, Gilead, Merck Sharp & Dohme, and Alexa. J.J.E.J. is an ad-hoc consultant to Gilead Sciences, Merck, Janssen, and ViiV Healthcare. D.A.W. participated in advisory boards convened by Gilead Sciences and Janssen Therapeutics. Merck and Co., Gilead Sciences, and GlaxoSmithKline have provided the University of North Carolina with funding for his research. A.E.C. reports receiving consultancy fees from ViiV Healthcare and Gilead Sciences; conference travel sponsorship from ViiV; and conference attendance sponsorship from Gilead. P.E.S. is a Scientific Advisory Board member for Gilead, GlaxoSmithKline/ViiV Healthcare, Merck, and Janssen; and has received grant support to his institution from BMS, Gilead, Merck, and GSK/ViiV. H.-J.S. reports honoraria for presentations or scientific advice from Gilead Sciences, Janssen, AbbVie, BMS, Merck, and Teva, and trial documentation fees for clinical trials from ViiV Healthcare, GlaxoSmithKline, and Janssen. S.E. has received honoraria for lectures or advisory boards and his institution has received research grants from ViiV, Gilead, MSD, AbbVie, BMS, and Janssen. A.L.P. has received honoraria for lectures or advisory boards, and his institution has received research grants from ViiV, Gilead, MSD, and Janssen. D.P. reports research grants and honoraria for participation in advisories or conferences from ViiV Healthcare, Pfizer, BMS, Gilead Sciences, Janssen, and Merck. L.W. has received support for attending conferences and/or honoraria for lectures or advisory boards from Gilead, ViiV, MSD, AbbVie, and Janssen. C.O. has received research grants, personal fees, and nonfinancial support for lectureships and serving on advisory boards from Gilead, Merck Sharp & Dohme, Bristol-Myers Squibb, ViiV Healthcare, Abbvie, and Janssen. J.K.R. has received grant or research support from Gilead Sciences; served as a consultant or advisor to Abbott, AbbVie, Bionor, Gilead Sciences, Hexal, Janssen, Merck, and ViiV Healthcare; and was a speaker at educational events for AbbVie, Gilead Sciences, Janssen, and Merck. E.N. has received speaker honoraria or consulting fees from ViiV Healthcare, Merck, Janssen Cilag, BMS, Gilead Sciences, and AbbVie. R.A.E. has received grants from Gilead Sciences, ViiV Healthcare, and Merck & Co. C.C., H.M., D.B., D.S., and M.D. are employees of Gilead and hold stock interest in the company. All other authors report no conflicts of interest.

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