Tenofovir alafenamide vs. tenofovir disoproxil fumarate: an updated meta-analysis of 14 894 patients across 14 trials

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Background: Both tenofovir disoproxil fumarate (TDF)/emtricitabine and tenofovir alafenamide (TAF)/emtricitabine demonstrate excellent efficacy and safety overall, but concerns remain over specific changes in markers of bone and renal function. Lower plasma tenofovir concentrations are seen with TAF and in unboosted regimens. We assess TAF vs. TDF safety with and without booster coformulation.

Methods: A previous systematic review was updated with recent clinical trials. TAF vs. TDF efficacy and safety were compared in boosted and unboosted subgroups. Efficacy was measured by viral suppression. Key safety endpoints included all adverse events, serious adverse events, Grades 3–4 adverse events and adverse event discontinuation. Further specific renal and bone markers were also assessed.

Results: A total of 14 clinical trials comparing TDF and TAF regimens were identified. A significant difference ($P = 0.0004$) in efficacy was shown in the boosted subgroup in favour of TAF, but no difference was seen in the unboosted subgroup. There were no significant differences between TAF and TDF for any of the key safety endpoints analysed. No differences were seen for the bone markers analysed. No difference was found for renal tubular events. There was a difference in risk for discontinuation due to renal adverse events when boosted ($P = 0.03$), but none when unboosted.

Conclusion: Across all main safety endpoints, no differences between TAF and TDF are seen. Boosted TDF regimens were associated with lesser comparative efficacy than boosted TAF and a higher risk of renal event discontinuation. However, modern antiretroviral regimens are more commonly unboosted. This study finds no difference in efficacy or safety in unboosted TAF vs. TDF.

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Background

Tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) is a well established and widely used dual-nucleoside antiretroviral therapy (ART) backbone, with proven efficacy and applications in treatment and prevention of HIV and hepatitis B.

While TDF/FTC formulations demonstrate excellent tolerability overall, the two most often quoted drawbacks

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are the potential for nephrotoxicity and decreased bone mineral density [1–4]. A more recently developed prodrug formulation of tenofovir, containing tenofovir alafenamide (TAF), leads to higher intracellular concentrations, but lower plasma concentrations of tenofovir when compared with TDF [5–7]. This pharmacokinetic attribute had been theorized to be protective against adverse effects, with the reduced serum concentration resulting in lesser exposure of the kidneys and bone [2]. This led to the prediction that TAF might confer similar clinical efficacy to TDF, whilst offering a marginally favourable safety profile overall [1,2,8–10].

Therapeutic antiretroviral regimens are recommended to supplement the dual nucleoside analogue reverse transcriptase inhibitors backbone with a third agent, either a nonnucleoside reverse transcriptase inhibitor, or integrase or protease inhibitor. Certain third agents, such as ritonavir or cobicistat act as pharmacokinetic boosters, increasing the maximum concentration (C_{max}) and absorption of tenofovir when coadministered with TDF. When these boosting agents are used, TAF doses are adjusted from 25 to 10 mg daily [11], whereas 300 mg TDF doses are not similarly adjusted [5,12–14]. It is possible that this pharmacokinetic enhancement, but inconsistent dose adjustment, results in lesser tolerability of TDF compared with TAF regimens overall.

In modern antiretroviral regimens, TAF and TDF are mainly used unboosted, such as alongside emtricitabine, efavirenz, dolutegravir and bictegravir, due to the greater risk of drug interactions and poor gastrointestinal tolerability [15]. Therefore, comparison between TAF and TDF when used in unboosted regimens is most relevant to modern treatment for HIV. Given the need for lifelong ART, increasingly used in the context of comorbidities and copharmacy [16–19], it is vital that there be a range of feasible safe, tolerable and long-term efficacious regimens to choose from and a comprehensive, up-to-date and reliable evidence basis behind this.

A previous systematic review sought to compare the efficacy and safety of TAF vs. TDF, in boosted and unboosted regimens and found no difference in most key safety endpoints, and where differences existed in bone and renal adverse events this was only seen for boosted TDF regimens [20]. Since this previous review there has been ongoing research in this area, with prolonged follow-up of several existing studies as well as newer relevant studies being newly published. Furthermore, since the publication of the original review, TDF has become increasingly affordable in higher income countries, due to the expiry of patent periods [21–24], whereas TAF can be obtained more cheaply in lower income countries due to voluntary licences and pharmaceutical deals [25,26]. Variable cost-effectiveness of these regimens in different settings, alongside the lack of synthesis of more recent safety evidence, has led to ongoing concern and debate over the merits of the two regimens.

Objectives

Given the inconsistency of evidence and continued debate, we sought to undertake an updated summary of all existing comparisons of the efficacy and safety of the two drugs, to inform policy and clinical practice.

Methods

We conducted a review of the comparative efficacy and safety of tenofovir disoproxil fumarate (TDF) vs. tenofovir alafenamide (TAF). This is an update of a previous review conducted comparing TAF and TDF [20]. The original review was carried out in accordance with the Cochrane framework for systematic reviews and following Preferred Reporting Items for Systematic review and Meta Analysis (PRISMA) guidelines [9,27,28]. The original review search, across Pubmed, Embase and ClinicalTrials.gov, is described previously [20]. Predefined selection criteria required randomized-controlled trials (RCTs) directly comparing TDF vs. TAF-based regimens, over at least 24 weeks, to qualify for inclusion. Observational and dose-ranging studies were excluded [9]. This original search was supplemented with all available more recently published relevant trials, as well as by exploration of the grey literature and Clinicaltrials.gov.

Data on key efficacy and safety outcomes were extracted from the included studies. The key outcome measure for efficacy was the number of patients achieving HIV RNA less than 50 copies/ml (log copies/ml). The efficacy results were analysed only for the studies of TAF vs. TDF in HIV-infected people, excluding efficacy in different viral infections such as hepatitis.

For the safety analysis, the risk of overall adverse events was assessed in terms of all Grades 1–4 adverse events (Gr1–4AE) and Grades 3–4 adverse events (Gr3–4AE), serious adverse events (SAE), Grade 3 or 4 laboratory abnormalities and deaths (any cause). Gr3 + 4AE are those classified as severe or life threatening, either by preset grading systems or clinical judgement, as specified in the trial protocol. Further analysis of specific bone and renal adverse events was also undertaken. Effects on bone were assessed, using study discontinuations due to bone toxicity, and bone fracture events as a clinically relevant marker of loss of bone mineral density. Markers of renal toxicity were 'renal adverse events' and 'discontinuations due to renal adverse event'. Renal adverse events were defined as any adverse events reported by study investigators as being indicative of or related to renal dysfunction. Cumulative incidence rates of all renal event types were gathered.

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Further information, including total sample sizes, follow-up time and control comparison was also extracted. Safety data were extracted as absolute number of events occurring, rather than numbers of people affected, as this allowed for the most consistency across trials. Similarly, total event numbers, rather than those deemed treatment related, were extracted and comparison between arms used as an unbiased measure of relationship to treatment. Where one publication reported data from more than one trial combined, these were treated as one study on meta-analysis. Where studies had more than one treatment arm using a TDF or TAF containing regimen, the two arms containing the same non-TDF/TAF were used for comparison. Sensitivity analyses were run to explore the effects of any major inconsistencies in reporting or trial types and population and the resultant pooled estimates.

Meta-analyses were carried out, directly comparing adverse event data for TDF against TAF in each trial, across all specified key safety outcomes. Review Manager Software Version 5.3 (Cochrane Collaboration, London, UK) was used for all analyses. Across studies, where variability in outcome reporting was found, finalized published data was preferred over data found on clinicaltrials.gov. The clinical diversity in TAF and TDF regimens and patient populations warranted the use of random-effects models. As the outcomes were dichotomous numbers of adverse events recorded in each study arm, the effect estimate was calculated as risk difference, following Mantel–Haenszel methods [28]. Predefined subanalyses explored the differences in outcomes between studies with boosted TDF arms vs. those using unboosted TDF.

Results

The original review has been previously described [20] but briefly; the original literature search identified a total of 253 records. After inclusion and exclusion criteria were applied, 11 eligible RCTs comparing TDF with TAF were identified [29–41]. Reasons for exclusion include incorrect trial design [32] and short trial duration [42]. These 11 studies in the initial review were then supplemented with three additional recently published trials (ADVANCE, AMBER, DISCOVER), accounting for 6814 new patients across 11 262 patient-years of follow-up (PYFU). New, longer term follow-up data from three previously included studies was also added to the updated analysis, adding an additional 1515 PYFU.

Details of all 14 studies included in this analysis are shown in Table 1. Eleven of the studies enrolled participants with HIV-1 infection, two enrolled people with chronic

Table 1. Summary table displaying details of all trials included in the meta-analysis.

Study	Disease	Study type	Phase	Interventions	Study length (weeks)	Boosted or unboosted	Number of participants	
							TAF	TDF
Advance	HIV-1	Naïve	3	DTF/FTC/TAF 25 mg vs. DTG/FTC/TDF	48	Unboosted	351	351
GS-US-366-1160	HIV-1	Switch	3b	FTC/RPV/TAF 25 mg vs. EFV/FTC/TDF	48	Unboosted	438	437
GS-US-366-1216	HIV-1	Switch	3b	FTC/RPV/TAF 25 mg vs. FTC/RPV/TDF	48	Unboosted	316	314
GS-US-311-1089	HIV-1	Switch	3	FTC/TAF 25 mg or 10 mg + 3rd agent vs. FTC/TDF + 3rd agent	96	Mixed	333	330
Emerald	HIV-1	Switch	3	DRV/COBI/FTC/TAF 10 mg vs. boosted PI + FTC/TDF	48	Boosted	763	378
GS-US-292-0109	HIV-1	Switch	3	EVG/COBI/FTC/TAF 10 mg or 25 mg vs. TDF regimen	48	Mixed	959	477
GS-US-292-0104	HIV-1	Naïve	3	EVG/COBI/FTC/TAF 10 mg vs. EVG/COBI/FTC/TDF	144	Boosted	438	434
GS-US-292-0111	HIV-1	Naïve	3	EVG/COBI/FTC/TAF 10 mg vs. EVG/COBI/FTC/TDF	144	Boosted	435	437
Amber	HIV-1	Naïve	3	DRV/COBI/FTC/TAF 10 mg vs. DRV/COBI/FTC/TDF	48	Boosted	362	363
Discover	HIV uninfected	Prevention	3	TAF 25 mg vs. TDF 300 mg	96	Unboosted	2694	2693
GS-US-292-0102	HIV-1	Naïve	2	EVG/COBI/FTC/TAF 10 mg vs. EVG/COBI/FTC/TDF	48	Boosted	112	58
GS-US-299-0102	HIV-1	Naïve	2	DRV/COBI/FTC/TAF 10 mg vs. DRV/COBI/FTC/TDF	48	Boosted	103	50
GS-US-320-0108	HBeAg-negative chronic HBV	Mixed	3	TAF 25 mg vs. TDF 300 mg	96	Unboosted	266	129
GS-US-320-0110	HBeAg-negative chronic HBV	Mixed	3	TAF 25 mg vs. TDF 300 mg	96	Unboosted	581	292

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hepatitis B infection, and one further trial population was HIV-uninfected adults in a study on preventive pre-exposure prophylaxis (PrEP) usage. Two trials were phase II, and 12 were phase III. Follow-up periods ranged from 48 to 144 weeks, with the longest 144 week follow-up trials only carried out using boosted regimens. Participants in TAF and TDF trial arms has overall similar baseline characteristics across studies. While event number reporting was used wherever possible, ADVANCE required use of person numbers data rather than event numbers. Sensitivity analyses confirmed that this had no effect on the overall result significances.

Overall, the 14 studies report data from 14 894 patients, accounting for a total of 23 723 PYFU. 6743 patients receiving TDF and 8151 receiving TAF. A total of 6032 patients were participant in the eight trials assessing boosted regimens, vs. 8862 patients in the six trials of unboosted regimens.

Baseline demographics

The baseline demographics of participants were variable between trial populations in this analysis, but on average participants had a mean age of 39.4 years. Ethnically, 60.7% of trial participants were White, 26.4% were Black and 15.1% were Asian. Only 16.7% of trial participants were women. The same underrepresentation of women and black and minority ethnic (BME) populations is seen in boosted trials as compared with unboosted. The average BMI across trials was 25.3. The average $CD4^+$ cell count at baseline was 501 cells/μl. As a marker of baseline renal function, average creatinine clearance of participants at the beginning of studies was 109.6 ml/min, and this average creatinine clearance level at baseline was similar between trials assessing boosted and unboosted TDF (see Appendix 1, http://links.lww.com/QAD/B849).

Efficacy outcomes

The efficacy analysis included data from nine studies. Data from five studies were excluded, of which two were phase II, two were carried out on populations with hepatitis rather than HIV, and one assessed PrEP for HIV prevention in uninfected study participants.

Figure 1 shows the percentage of patients with HIV RNA suppression less than 50 copies/ml, by treatment arm, the end of each studies predefined efficacy reporting timeframe.

On analysis (Appendix 1, http://links.lww.com/QAD/B849) of the differences between boosted and unboosted subgroups, a statistically significant difference between was found ($P = 0.01$). When comparing boosted TDF vs. TAF, there was an increased rate of viral suppression on TAF as opposed to TDF with a statistically significant ($P = 0.0004$) 2% difference [confidence interval (CI) 1–4%] between the

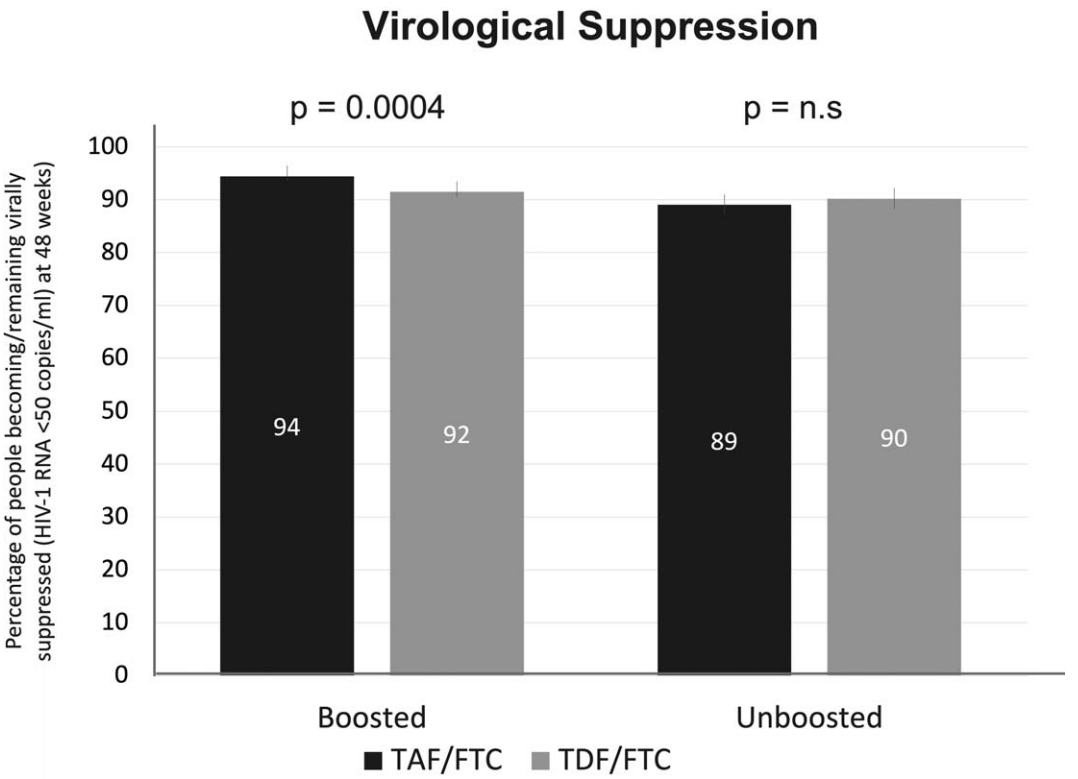

Fig. 1. Bar chart displaying the comparative efficacy of tenofovir alafenamide vs. tenofovir disoproxil fumarate in all trials, and then stratified into boosted and unboosted regimens.

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study arms (meta-analysis Appendix 1, http://links.lww.com/QAD/B849). However, no statistical difference was seen in HIV RNA suppression rates between unboosted TAF and TDF ($P = 0.40$).

These findings are based on both treatment naïve and switch studies, which may effect suppression results. However, there were similar proportions of naive and switch studies within each subgroup, with one naive and two switch in the unboosted group, and three naïve and three switch in the boosted group.

Safety outcomes

Clinical adverse events

There were no significant differences between TAF and TDF for measures of Gr1–4AE or Gr3–4AE, SAE, Grades 3–4 laboratory abnormalities (Gr3–4LAE) or deaths, with no differences apparent between boosted and unboosted subgroups. Summary graphs of the main safety outcomes, displaying the proportion of adverse events occurring across all trial participants, both in boosted and unboosted trials, are shown in Fig. 2.

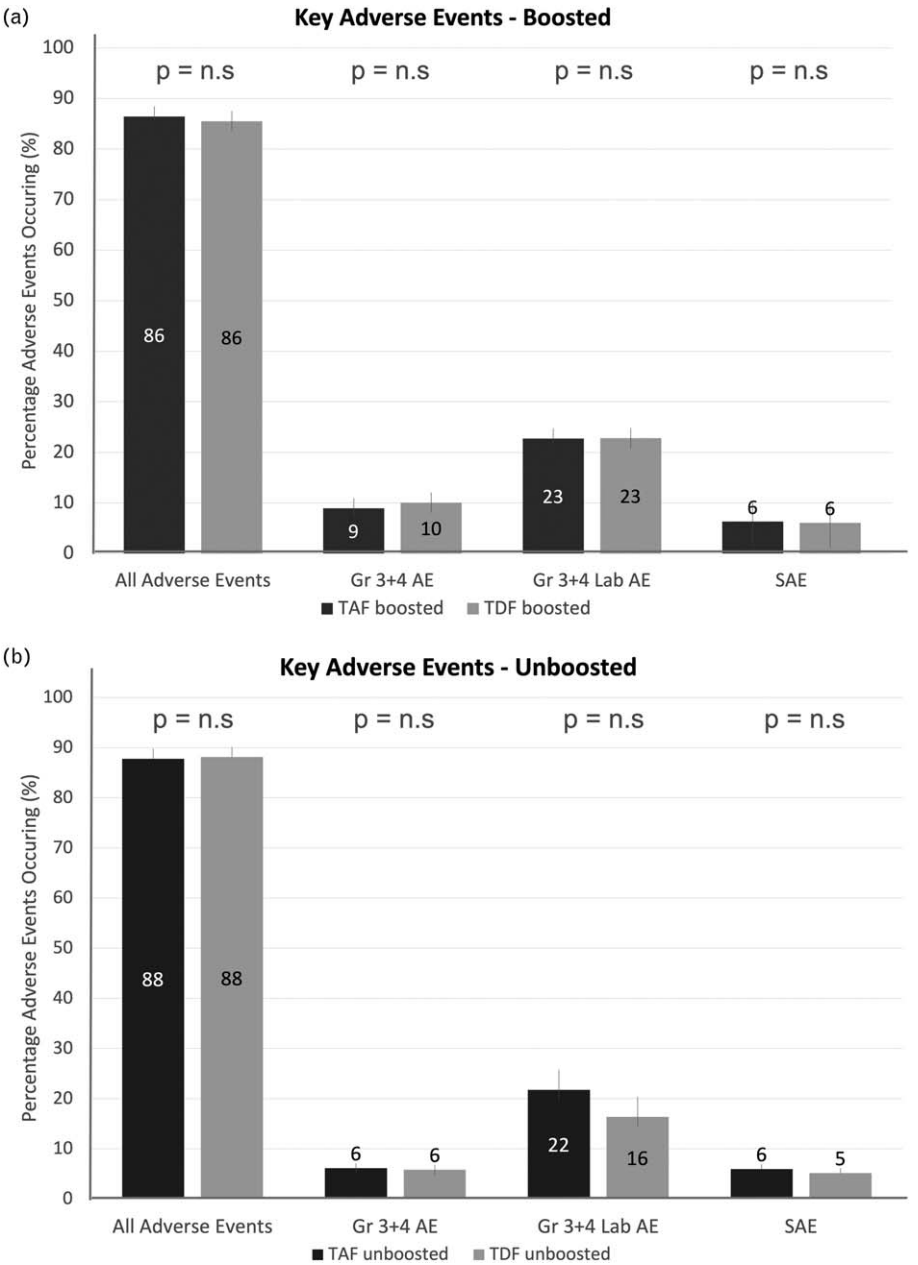

Fig. 2. Bar charts showing all main safety endpoints (Grade 1–4, Grade 3/4, serious adverse events, etc) in TAF vs TDF. Proportion of adverse events occurring was calculated as the number of events occurring as a proportion of total trial participants who could have experienced the event, expressed as a percentage for comparability. (a) Boosted trials. (b) Unboosted trials.

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On meta-analysis of all Gr1–4AE (Appendix 2, http://links.lww.com/QAD/B849), no significant ($P = 0.24$) risk difference between trial arms was demonstrated overall, estimated as 1% (95% CI = 0–2%). Heterogeneity between studies was very low ($I^2 = 0\%$). On subgroup analysis there were no further significances found for either boosted or unboosted study subgroups.

On meta-analysis of Gr3–4AE (Appendix 3, http://links.lww.com/QAD/B849), no significant ($P = 0.93$) difference between trial arms was seen, with an estimated risk difference of 0% (95% CI = −1–1%) and on subgroup analysis no further significances were demonstrated.

There were a greater proportion of Gr3–4LAE adverse events seen on TAF (22%) than TDF (20%). In unboosted trials this difference is greater, with TAF = 22% and TDF = 16%. However, on meta-analysis of Gr3–4LAE (Appendix 4, http://links.lww.com/QAD/B849) none of these differences demonstrate statistical significance ($P = 0.65$).

A greater proportion of SAE occurred on TAF than TDF, particularly in the unboosted arm, where TAF = 6% SAF and TDF = 5%. However again, on meta-analysis (appendix 5, http://links.lww.com/QAD/B849), these differences were not statistically significant ($P = 0.59$), with no further significances within subgroups.

On analysis of discontinuations due to adverse events, similar proportions of discontinuations were seen between trial arms. On meta-analysis (Appendix 6, http://links.lww.com/QAD/B849) there was a 0% risk difference (95% CI = −1–0%) ($P = 0.66$).

Finally, a total of 13 deaths occurred from any cause across all 14 studies, six in study participants taking TAF and seven in participants on TDF. There was no significant risk difference shown (risk difference = 0%, 95% CI = 0–0%), ($P = 0.67$) (Appendix 7, http://links.lww.com/QAD/B849).

Bone parameters

No significant differences were found between TAF and TDF across the bone parameters assessed, fractures and relevant discontinuations. Only one discontinuation due to bone-related, study drug associated adverse events was reported through all 14 trials. On meta-analysis (Appendix 8, http://links.lww.com/QAD/B849) this was calculated as a 0% (95% CI = 0–0%) risk difference ($P = 0.86$). Dual-energy X-ray absorptiometry (DEXA) scans were performed during most of the studies included in this analysis, and therefore study discontinuations due to bone toxicity, although rare, reflect concerning new incidences of fast reduction in bone mineral density or osteoporosis.

A total of 77 bone fractures of any cause occurred across all patients, with 43 occurring in those taking TAF and 34 in those taking TDF. On meta-analysis of bone fractures of all causes (Appendix 9, http://links.lww.com/QAD/B849), the risk of bone fractures was the same for TAF vs. TDF regimens (risk difference = 0%, 95% CI = 0–0%, $P = 0.45$) with no significant differences between boosted and unboosted subgroups. No fracture reported across the trials in this analysis was deemed to be a fragility or osteoporotic fracture.

Renal parameters

For renal outcomes, no difference was demonstrated in actual renal tubular events occurring between TAF and TDF or between overall number of discontinuations due to renal adverse events. However, a small but significantly ($P = 0.03$) greater number of discontinuations due to renal adverse events occurred in the boosted regimen subgroup, but this difference was not seen in the unboosted subgroup (Appendix 10, http://links.lww.com/QAD/B849).

Regarding renal tubular adverse events, there were only three of these events across study participants. There was no statistically significant differences and the overall risk difference was 0% (see Appendix 11, http://links.lww.com/QAD/B849).

Discussion

The current meta-analysis of 14 trials, including data from 14 894 patients, compared treatment formulations of TAF against TDF. This included 23 723 PYFU, with 6743 patients receiving TDF and 8151 receiving TAF. A total of 6032 patients were participant in the eight trials assessing boosted regimens, vs. 8862 patients in the six trials of unboosted regimens. This provides an extra 12 777 person years of follow-up, from three new studies and three continued follow-up studies, onto the original analysis (Table 2) [20].

In this analysis, rates of HIV RNA suppression were 2% higher for TAF versus TDF when used in combination with pharmacokinetic boosters. When used unboosted, there were no significant differences in HIV RNA suppression between TAF and TDF. However, there were no major differences in safety between TAF and TDF, including all Grade 1–4, Grade 3–4 and SAE, with no differences apparent between boosted and unboosted subgroups. These results are in keeping with previous findings, which demonstrated the same overall similarity in efficacy and safety between TAF and TDF, with the only significant differences in safety shown being specifically on boosted TDF regimens [20]. These new results, accounting for a larger total patient population, demonstrate this same trend in small differences as seen

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Table 2. Summary table of all findings.

Formulation	Outcome measure	TAF/FTC Events/Total	TAF/FTC %	TDF/FTC Events/Total	TDF/FTC %	Effect estimate – risk diff. (CI)	*P* value
Boosted	Viral suppression	3101/3283	94	2210/2415	92	2% (1–4%)	0.0004
	All adverse events	3023/3498	86	2157/2523	86	1% (−1–3%)	n.s
	Gr 3 + 4 AE	313/3498	9	254/2523	10	−1% (−2–1%)	n.s
	Gr 3 + 4 Lab AE	516/2270	23	395/1732	23	0% (−5–4%)	n.s
	SAE	221/3498	6	154/2523	6	0% (−1–1%)	n.s
	Deaths	2/3283	0	3/2415	0	0% (0–0%)	n.s
	Bone fractures	22/3498	1	16/2523	1	0% (0–0%)	n.s
	Renal tubule AE	0/3498	0	3/2523	0	0% (0–0%)	n.s
	DC A/E	44/3386	1	50/2465	2	−1% (−2–0%)	n.s
	D/C bone	0/2529	0	0/1606	0	0% (0–0%)	n.s
	D/C renal	3/3395	0	12/2473	0	0% (−1–0%)	0.03
Unboosted	Viral suppression	984/1105	89	994/1102	90	−1% (−3–1%)	n.s
	All adverse events	4094/4665	88	3724/4227	88	1% (−1–3%)	n.s
	Gr 3 + 4 AE	286/4665	6	246/4227	6	0% (−2–2%)	n.s
	Gr 3 + 4 Lab AE	429/1971	22	251/1534	16	2% (−3–6%)	n.s
	SAE	278/4665	6	218/4227	5	1% (−1–2%)	n.s
	Deaths	4/4665	0	4/4227	0	0% (0–0%)	n.s
	Bone fractures	21/1971	1	18/1534	1	0% (−1–0%)	n.s
	Renal tubule AE	0/1620	0	0/1183	0	0% (0–0%)	n.s
	D/C AE	64/4665	1	64/4227	2	0% (0–0%)	n.s
	D/C bone	1/1971	0	0/1534	0	0% (0–0%)	n.s
	D/C renal	3/4665	0	6/4227	0	0% (0–0%)	n.s

Viral suppression = HIV-1 RNA less than 50 copies/ml at 48 weeks. AE, adverse events; CI, confidence interval; D/C, discontinuations; Gr, grade; SAE, serious adverse events.

previously between efficacy, as well as bone and renal markers, on comparison of boosted TDF and TAF, but these differences are diluted in the new analysis.

Where differences between TAF and TDF can be demonstrated, in efficacy and discontinuations due to adverse events, this is only in boosted regimens. Viral suppression rate statistically favours TAF over TDF in the boosted groups, however the absolute difference is small (94% suppression vs. 92% suppression) and therefore unlikely to be clinically significant. The treatment failure endpoints were mainly from discontinuation of randomized treatment while the HIV RNA levels remained suppressed and we did not see evidence for differences in virological failure between TAF and TDF in this analysis. In particular, no differences are observed across any endpoint measured in unboosted regimens. In modern antiretroviral regimens, TAF and TDF are mainly used unboosted, such as alongside emtricitabine, efavirenz, dolutegravir and bictegravir, due to the greater risk of drug interactions and poor gastrointestinal tolerability [15]. Therefore, comparison between TAF and TDF when used in unboosted regimens is most relevant to modern treatment for HIV.

These results must be considered with appropriate context in mind. First, we find evidence to support the idea that, whilst TAF may offer some small advantages in renal safety profile in boosted regimens, this difference has not been seen in unboosted regimens, such as those used in PrEP. Second, while incremental improvements in specific renal safety are welcome advances, when implementing ART in a world scale the comparative costs and viability of widespread use must be taken into account. If TAF offers no, or limited, improvements in incidence of one specific type of study event, when boosted, this is unlikely to justify the disregard of proven, affordable and established safe TDF regimens. Certainly, where no difference is seen in safety when unboosted, these results so have no bearing on decisions to use unboosted TDF-containing PrEP regimens in efforts to reduce rates of HIV incidence. TDF for PrEP remains a safe, affordable and realistic option in providing protection to those at risk of HIV worldwide.

A recent pooled analysis sought to compare the renal safety of TAF with TDF [4], finding differences in proximal renal tubular and discontinuations for adverse events. Their pooled analysis of raw data provides useful information, including data from smaller, noncontrolled trials. Our larger analysis compares high-quality RCTs in head-to-head meta-analysis, across a broader range of clinically relevant outcomes, stratified for boosted vs. unboosted regimens. Specifically, for renal outcomes, we assessed the same outcomes across larger patient numbers and found no difference between reported numbers of renal tubular events on TAF vs. TDF, and a difference in renal discontinuations only on boosted TDF.

Limitations

We acknowledge that this review is limited to the existing pool of reported data from published trials. In particular,

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reporting of adverse events may rely on investigator clinical judgement, which could result in underestimation of some events. Reporting bias can also result in overestimation of certain expected events, although the potential for bias is reduced by blinding. We also acknowledge that we did not have access to individual level data and therefore could not calculate or adjust specific event rates accordingly, and so have instead used dichotomous event comparisons overall.

As with all reviews using clinical trial data, the participants selected for inclusion in the trials may have been healthier than the general population of people living with HIV. The baseline demographics of participants of the trials included in this analysis may not be representative of the clinical populations to whom these results will be applied. Participants were relatively young (average 39.4 years) and there was also underrepresentation of women and nonwhite populations. Given the young trial participants with few comorbidities, a follow-up even of 144 weeks in a study may not be enough time to observe major clinical adverse event's.

Furthermore, this review does not consider wider safety endpoints, such as the potential cardiovascular effects seen on TAF vs. TDF. Previous studies have found that TDF may offer benefits such as lesser weight gain [29] and improved lipid profiles [43–45]. Further analysis comparing the effects of common ART regimens on cardiovascular health is warranted.

Strengths

Data in this analysis account for 14 trials, including data from 14 894 patients and 23 723 PYFU. This is the largest single analysis comparing TAF directly to TDF, across the most comprehensive range of safety outcomes yet published. All trials included are high-quality, RCTs, providing robust evidence which we have now synthesized in this review. Furthermore, this analysis provides insight into the potential effects of booster agents, commonly used in ART regimens, on comparative efficacy and safety profiles.

Applications and implications

The current review demonstrates high levels of efficacy in viral suppression for regimens containing both TAF and TDF. Furthermore, no overall significant difference was seen in safety, across all core endpoints, between TAF and TDF, albeit in a relatively young trial participant population, with good baseline renal function. This has implications not only in HIV treatment but also in prevention, with TDF formulations for HIV PrEP having proven success in uptake and adherence worldwide [46–49], calling into question the need for TAF-based formations given the established tolerability of TDF [50]. These findings assuage pervasive concerns around the safety of TDF and can reassure clinicians and policy makers that TDF is a safe, well tolerated and affordable antiretroviral component to consider.

Conclusion

The current meta-analysis of 14 trials, including data from 14 894 patients and 23 723 PYFU, found comparable efficacy and safety profiles of TAF and TDF overall. The findings of this analysis confirm that both TAF and TDF-based regimens are highly efficacious and have good overall safety profiles. Where incremental differences between TAF and TDF can be demonstrated in boosted regimens, this is not seen in unboosted regimens, which are the more commonly used in modern HIV treatment. When implementing ART on a world scale the comparative costs and viability of widespread use must be taken into account.

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Conflicts of interest

There are no conflicts of interest.

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