Is tenofovir disoproxil fumarate associated with weight loss?

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Background: Recent clinical trials have shown weight gain associated with newer antiretrovirals. It is unclear how the nucleoside reverse transcriptase inhibitor backbone affects weight. Recent evidence suggests greater weight gain with tenofovir alafenamide (TAF) compared with tenofovir disoproxil fumarate (TDF). However, it is not fully understood whether TDF contributes to weight suppression.

Methods: A systematic search of PubMed, Embase and clinicaltrials.gov was conducted to identify all randomized control trials comparing TDF/FTC or TDF to control in HIV-negative individuals. The primary endpoint included the number of events of 5% weight loss. Mantel–Haenszel test with random-effects modelling was used to calculate the odds ratio (OR) and 95% confidence intervals (95% CI). Further analyses of gastrointestinal (GI) adverse events were also undertaken.

Results: Seven PrEP trials: PARTNERS, VOICE, TDF-2, Bangkok PrEP, iPrEX, FEM-PrEP and HPTN 084 were included in the analysis of weight loss, with a total sample size of 19 359. One study (HPTN 084) compared TDF/FTC to cabotegravir (CAB). HIV-negative individuals taking TDF were more likely to experience weight loss compared with control [odds ratio (OR) 1.44; 95% CI 1.12–1.85; $P = 0.005$). Exposure to TDF was also linked to greater odds of vomiting (OR 1.81; 95% CI 1.20–2.73; $P < 0.005$). There were no increased odds of nausea, diarrhoea or loss of appetite.

Conclusion: There is evidence in HIV-negative individuals that TDF may be associated with weight loss. Further research should be carried out in HIV-positive individuals, and clinical trials of TDF/FTC should publish weight data to widen the evidence base.

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Introduction

Tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) is a well tolerated, and widely used combination used for preexposure prophylaxis (PrEP), hepatitis B virus (HBV) and as the nucleoside reverse transcriptase inhibitor (NRTI) backbone in HIV-1 antiretroviral therapy, as well as for treating hepatitis B. Lamivudine (3TC) is regarded as equivalent in terms of potency to FTC, and both are extremely well tolerated with no effect on weight changes.

The major downside to the TDF component is its effect on bone mineral density and renal toxicity, which has been observed in HIV-positive and HIV-negative individuals [1,2]. Its use has, therefore, been replaced by tenofovir alafenamide (TAF), in guidelines for HIV-1 [3]. The TAF/FTC combination has more recently been approved for PrEP [4], after being shown to be noninferior to TDF and because of less impact on bone density and renal tubular effects.

Despite this, a meta-analysis showed no safety differences in renal and bone markers when TDF was used in 'unboosted' regimens, when compared with TAF [5]. Generic TDF/FTC is now available and may be a more cost-effective option for treatment and prevention of

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HIV. TDF has more favourable metabolic effects compared with TAF, with TDF demonstrating lipid-suppressive effects in previous studies [6,7]. In HBV studies, treatment with TAF led to greater grade 3 and above hyperglycaemia and fasting low-density lipoproteins greater than 190 mg/dl vs. TDF [8,9]. In HIV-1 studies, switching from TDF to TAF has also been associated with weight and lipid changes [10–14]. It is unclear whether this is because of the removal of TDF suppressing weight gain or TAF directly contributing to weight. In the DISCOVER PrEP trial, TDF/FTC was associated with weight loss and declines in lipids compared with TAF/FTC [2]. Initiating TAF has also shown to increase weight to a greater extent than TDF, especially when combined with integrase inhibitors in HIV studies, and particularly in black women [15–17].

Obesity and weight gain is a growing public health concern for persons with HIV (PWH), particularly as they are predisposed to CVD [18]. Recent analyses show that weight changes could lead to an increased risk of myocardial infarction, diabetes and adverse birth outcomes [19,20]. Risk factors for weight gain include a baseline low $CD4^+$ count, high viral load, Black race and female sex [21,22]. Choice of ART also contributes, with integrase inhibitors increasing weight, and evidence of efavirenz lowering weight [21].

The objective of this analysis is to establish how TDF plays a role in weight changes, and if it contributes to weight loss. In this analysis, we will be analysing the data from PrEP studies. This will enable us to focus on the independent effect of TDF on weight compared with placebo, or to other control treatments, eliminating the return-to-health effect seen in HIV trials and the effect of other antiretrovirals on weight.

Methods

We performed a systematic search of MedLine, Embase, Global health database, conference proceedings and clinical trial registry clinicaltrials.gov, to identify all randomized trials comparing oral TDF/FTC or TDF as intervention to placebo for PrEP for HIV. The methodology of this search has been previously described [23]. We also conducted a separate search to identify randomized trials comparing TDF/FTC to TAF/FTC or Cabotegravir. We included studies, which reported adverse event data on 5% or grade 2/moderate severity weight loss or grade 1–4 gastrointestinal adverse events in this analysis.

We extracted the data on the safety outcomes from 10 included studies, VOICE, TDF-2, FEM-PrEP, BKK, PARTNERS, iPReX, IPERGAY, US Safety Study, HPTN 084 and HPTN 083 [24–33], comparing endpoints in the TDF arm versus the control arm. Where the data was not available publicly, authors were contacted to attempt to obtain some of the data. The primary safety outcome was weight loss. This was reported as '>5% weight loss' or 'grade 2 abnormal loss of weight.' Grade 2 weight loss is classified as more than 5% weight loss in the Division of AIDS grading of severity of adverse events [34]. Two studies had two arms containing TDF (TDF/FTC or TDF). For the meta-analysis, the adverse events in these two arms were added up.

We also conducted a separate analysis on the gastrointestinal safety data and extracted the safety data on the number of Grade 1–4 adverse events of nausea, vomiting, diarrhoea and loss of appetite.

The meta-analyses were performed on Review Manager Software Version 5.4 (Cochrane Collaboration, London, UK). The Mantel–Haenszel test with random-effects modelling was applied to calculate the odds ratio (OR) and 95% confidence intervals (95% CI). Statistical heterogeneity was assessed with the I^2 statistic. An I^2 value less than 30% was considered low; 30 to 50%, moderate and more than 50% substantial.

Results

We identified eight randomized trials comparing TDF/FTC or TDF to placebo [24–31] and two studies comparing TDF/FTC to cabotegravir [32,33], which reported the safety endpoints for this analysis: 5% weight loss and gastrointestinal adverse events, nausea, vomiting, diarrhoea and loss of appetite. Table 1 contains a summary of the studies included in this analysis.

Weight loss

Of these, seven studies ($n = 19\,359$) reported grade 2+ loss of weight or at least 5% weight loss as an endpoint. Taking oral TDF was associated with 44% greater odds of 5% weight loss, compared with placebo or cabotegravir (Fig. 1). This was statistically significant ($P = 0.005$). However, there was substantial heterogeneity in the results ($I^2 = 52\%$).

Gastrointestinal adverse effects

Nausea

Nausea was reported as an adverse events in eight of the studies comparing TDF to placebo. Meta-analysis found no significant association with exposure to TDF versus placebo ($P = 0.25$), with substantial heterogeneity ($I^2 = 87\%$) (Fig. 2.1).

Vomiting

Five studies assessing TDF to placebo reported vomiting as an adverse event. The odds of vomiting on exposure to TDF greater than on exposure to placebo (OR 1.81; 95%

Table 1. Summary of studies included in the analysis and safety data extracted.

				5% Weight loss		Nausea		Vomiting		Diarrhoea		Loss of appetite	
Study	Arms	Population	Location	TDF	Control	TDF	Control	TDF	Control	TDF	Control	TDF	Control
VOICE [24]	(TDF or TDF/FTC versus PBO)	Women	SA, Uganda, Zimbabwe	49/2010	17/1009	21/2010	15/1009	12/2010	9/1009	33/2010	21/1009	3/2010	2/1009
TDF-2 [25]	TDF/FTC versus PBO	MSM + women	Botswana	133/611	72/608	132/611	48/608	87/611	47/608	93/611	76/608	–	–
FEM-PrEP [26]	TDF/FTC versus PBO	Women	Kenya, SA, Tanzania	1/1025	0/1033	52/1025	33/1033	38/1025	12/1033	18/1025	21/1033	10/1025	4/1033
BKK [27]	TDF versus PBO	IVDU	Thailand	140/1204	135/1209	113/1204	71/1209	113/1204	71/1209	302/1204	312/1209	–	–
PARTNERS [28]	TDF or TDF/FTC versus PBO	SC	Kenya/Uganda	13/3163	6/1584	1/3163	0/1584	–	–	86/3163	39/1584	–	–
iPReX (39)	TDF/FTC versus PBO	MSM + TW	Thailand, Brazil, Ecaudor, Peru, SA, USA	34/1251	19/1248	22/1251	10/1248	–	–	49/1251	61/1248	–	–
IPERGAY [30]	TDF/FTC versus Placebo	MSM	France and Canada	–	–	16/199	48/201	3/199	0/201	8/199	6/201	–	–
US Safety Study [31]	TDF versus Placebo	MSM	USA	–	–	27/201	13/199	–	–	42/201	57/199		
HPTN 084 [32]	TDF/FTC versus CAB	Women	SSA	101/1610	78/1614	–	–	–	–	–			
HPTN 083 [33]	TDF/FTC versus CAB	MSM/TGW	Argentina, Brazil, Peru, US, SA, Thailand, Vietnam			–	–	–	–	158/2284	148/2282		
Total				471/11054 (4.3%)	327/8305 (3.9%)	384/9964 (3.9%)	238/7498 (3.2%)	253/5049 (5%)	139/4060 (3.4%)	631/9664 (6.5%)	593/7091 (8.4%)	13/3035 (0.4%)	6/2042 (0.3%)

TDF, tenofovir disoproxil fumarate.

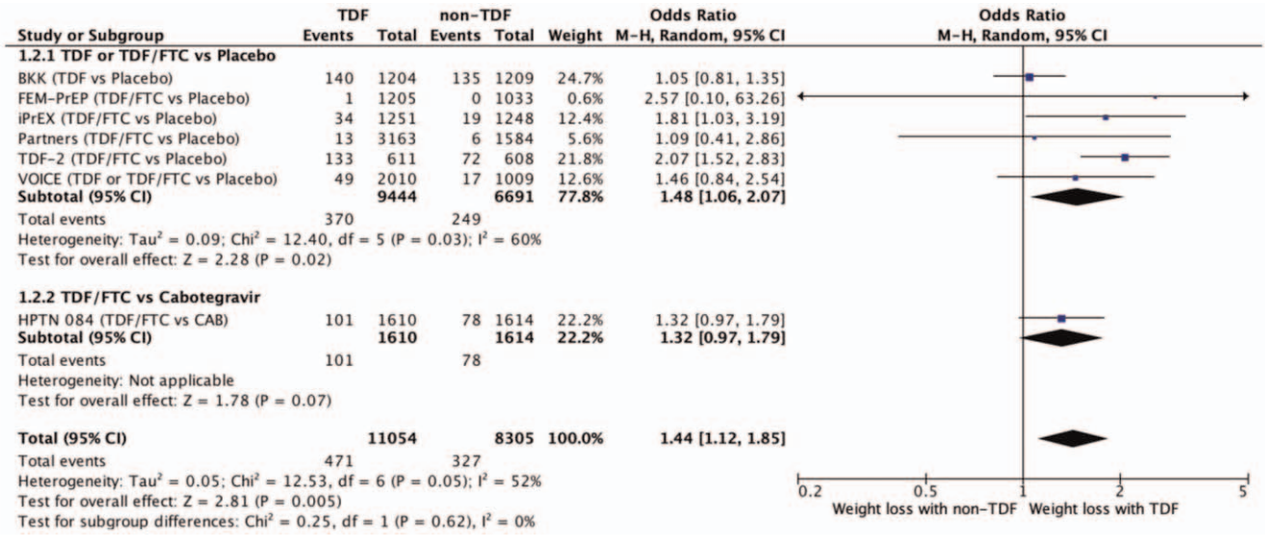

Fig. 1. Display of forest plot of preexposure prophylaxis versus control for weight loss.

CI 1.20 – 2.73; $P < 0.005$) (Figure 2.2). There was substantial heterogeneity ($I^2 = 58\%$).

Diarrhoea

The difference in number of events of reported diarrhoea was not statistically significant between TDF and placebo or cabotegravir ($P = 0.75$) (Fig. 2.3).

Loss of appetite

Two studies, VOICE and FEM-PrEP, reported loss of appetite as an adverse events. TDF/FTC was not statistically associated with a loss of appetite ($P = 0.36$) (Fig. 2.4).

When including only grade 2 and above adverse events, there was no difference between TDF/FTC and placebo (OR 1.29 95% CI 0.32–5.24 $P = 0.73$)

Discussion

This analysis shows that TDF may be associated with unintentional weight loss. Weight changes have been reported in some of the PrEP studies. In the DISCOVER (TAF/FTC versus TDF/FTC) [2] iPReX study (TDF/FTC versus placebo [29,35] and HPTN 083 (TDF/FTC versus cabotegravir [33] studies, transient weight loss was observed in the first 24 weeks in participants on the TDF/FTC arm. However, in all three studies, participants returned to their baseline weight and continued to gain weight at the same rate as the control arm. At week 48, the difference between TAF/FTC (+1.1 kg) and TDF/FTC (−0.1 kg) was statistically significant ($P < 0.001$). In both the HPTN 083 and HPTN 084 trials, weight changes in the cabotegravir arm compared with the TDF/FTC arm were statistically significant [32,33].

In the phase 2a study, HPTN 077, no weight difference was observed between cabotegravir and placebo (1.48 versus 1.57 kg/year, respectively) [36]. This suggests that cabotegravir may be weight neutral in HIV-negative individuals, and that the weight differences observed between cabotegravir and TDF/FTC in HPTN 083 and 084, could in fact be because of a weight-suppressive effect of TDF.

Our analysis also highlights that TDF may be associated with an increased risk of gastrointestinal adverse events, in particular, vomiting, compared with placebo, and may be a contributing factor to weight loss. In the ADVANCE HIV study, there was a difference in GI adverse events between the TAF/FTC+dolutegravir (DTG) and TDF/FTC+DTG arm (24.8 versus 28.2%, respectively). However, when participants reporting these side effects were excluded from the analysis, TAF/FTC+DTG group had significantly greater weight gain compared with those taking TDF/FTC+DTG [15]. By contrast, in the DISCOVER study, there was no difference in gastrointestinal adverse events between the groups taking TDF/FTC and those taking TAF/FTC [2].

The effect of TDF on lipid suppression may also be a contributing factor to weight loss. This effect has been observed in the PrEP DISCOVER (TAF versus TDF) and iPrEX (TDF placebo) studies [2,35].

Future studies should report grade 1 events, as well as grade 2–4. To assist in understanding the contribution to this weight difference. One of the limitations of this study, was the lack of consistency in the reporting of gastrointestinal adverse events. Some studies reported a breakdown of the

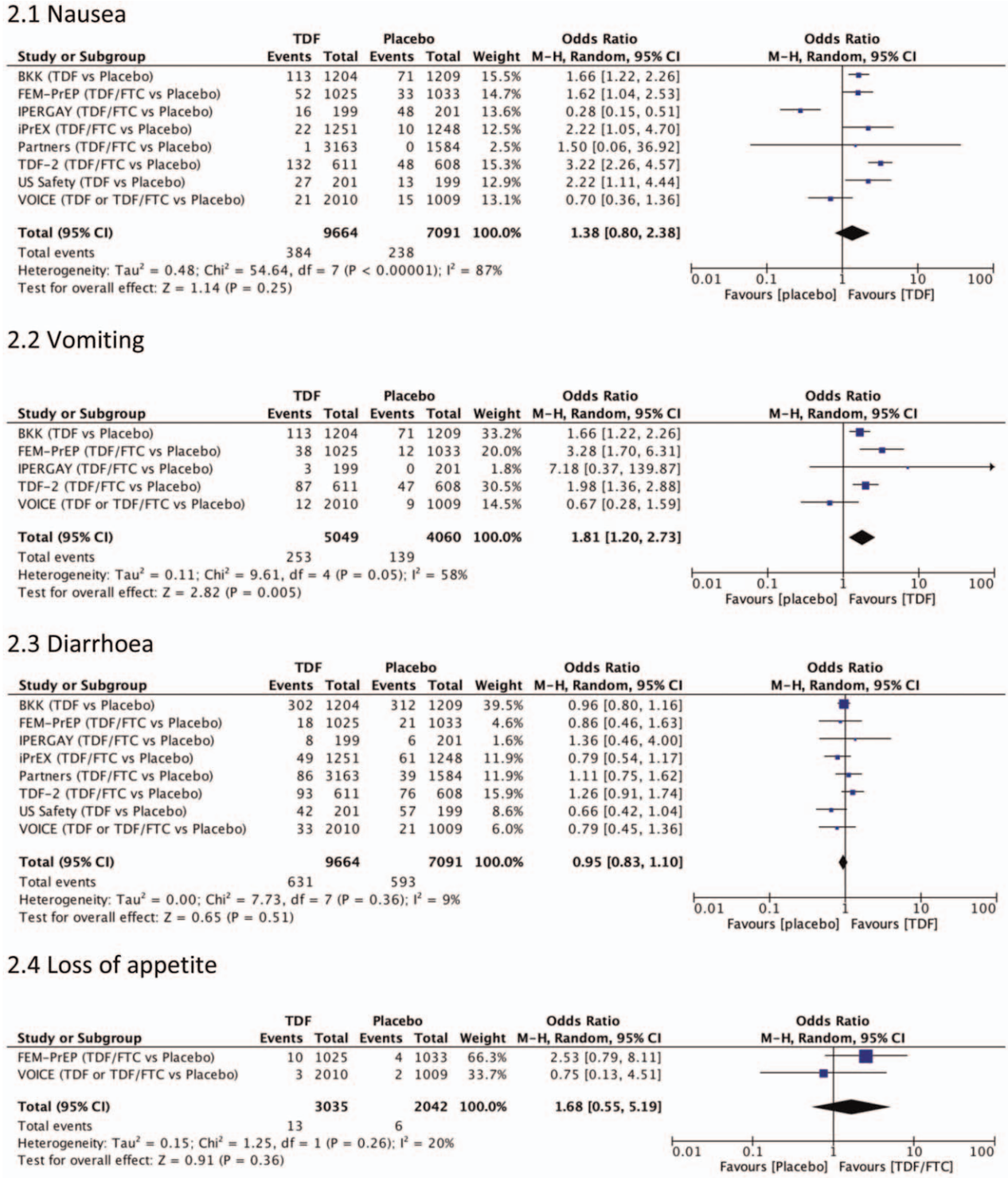

Fig. 2. Display of forest plot of preexposure prophylaxis versus control for gastrointestinal adverse events.

adverse events by grade, other stated that the adverse events were grade 2+. However, some studies did not state, which grade the adverse events were, and so we were unable to stratify by grade in our analysis. Substantial clinical heterogeneity was also present in our analysis.

Furthermore, a lack of representation of all ethnic groups or the female gender in these trials could provide an external limitation to this analysis. In HIV studies, identified risk factors for weight gain include being black, female and having a high baseline BMI [21]. Differences

in weight changes could be greater if all groups were equally represented in this analysis, or if these factors were controlled for in this analysis.

More research is required to understand the mechanism of TDF and weight loss, and whether this may have clinical implications. It is also unclear whether these observed changes are transient or persist long-term. Longer term data is required to ascertain stronger evidence. However, considering the results of this analysis, the use of TDF should be preferred in patients who are at a risk of weight gain as it could have unintended benefits for certain groups who may go on to develop metabolic syndrome and obesity-linked non-communicable disease secondary to weight gain. Clinically, patients taking TDF as part of their therapy for PrEP, HIV or HBV should have their weight closely monitored. Future clinical trials should report gastrointestinal and metabolic adverse events, and weight data.

In conclusion, TDF is associated with a higher risk of 5% weight loss in HIV-negative individuals taking pre-exposure prophylaxis therapy. This could be attributed to some gastrointestinal side effects associated with TDF therapy. More research and reporting of weight data is required to widen the evidence base and to establish clinical significance.

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S.S. and V.P. performed the meta-analysis. All authors have reviewed and approved of the submitted manuscript.

Conflicts of interest

There are no conflicts of interest.

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