How safe is TDF/FTC as PrEP? A systematic review and meta-analysis of the risk of adverse events in 13 randomised trials of PrEP

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Abstract

Background: Tenofovir/emtricitabine (TDF/FTC) used as pre-exposure prophylaxis (PrEP) has proven benefits in preventing HIV infection. Widespread use of TDF/FTC can only be justified if the preventative benefits outweigh potential risks of adverse events. A previous meta-analysis of TDF/FTC compared to alternative tenofovir alafenamide (TAF)/FTC for treatment found no significant difference in safety endpoints when used without ritonavir or cobicistat, but more evidence around the safety of TDF/FTC is needed to address concerns and inform widespread use.

Methods: A systematic review identified 13 randomised trials of PrEP, using either TDF/FTC or TDF, versus placebo or no treatment: VOICE, PROUD, IPERGAY, FEM-PrEP, TDF-2, iPrEX, IAVI Kenya, IAVI Uganda, PrEPare, PARTNERS, US Safety study, Bangkok TDF study, W African TDF study. The number of participants with grade 3/4 adverse events or serious adverse events (SAEs) was compared between treatment and control in the meta-analysis. Further analyses of specific renal and bone markers were also undertaken, with fractures as a marker of bone effects and creatinine elevations as a surrogate marker for renal impairment. Analyses were stratified by study duration (</>1 year of follow up).

Results: The 13 randomised trials included 15,678 participants in relevant treatment and control arms. Three studies assessed TDF use only. The number of participants with grade 3/4 adverse events was 1306/7504 (17.4%) on treatment versus 1259/7502 (16.8%) on control (difference=0%, 95% confidence interval [CI] −1% to +2%). The number of participants with SAEs was 740/7843 (9.4%) on treatment versus 795/7835 (10.1%) on no treatment (difference=0%, 95% CI −1% to +1%). The number of participants with creatinine elevations was 8/7843 on treatment versus 4/7835 on control (difference=0%, 95% CI 0%–0%). The number of participants with bone fractures was 217/5789 on treatment versus 189/5795 on control (difference=0%, 95% CI 0% to 1%). There was no difference in outcome between studies with <1 versus >1 year of randomised treatment.

Conclusions: In this meta-analysis of 13 randomised clinical trials of PrEP in 15,678 participants, there was no significant difference in risk of grade 3/4 clinical adverse events or SAEs between TDF/FTC (or TDF) and control. Furthermore, there was no significant difference in risk of specific renal or bone adverse outcomes. The favourable safety profile of TDF/FTC would support more widespread use PrEP in populations with a lower risk of HIV infection.

Keywords: Pre-exposure prophylaxis (PrEP), Safety, HIV, tenofovir, emtricitabine, kidney, bone density, adverse events

Background

There were 1.8 million new HIV infections worldwide in 2016 [1]. Whilst improvements in treatment have lowered mortality rates, the same success has not been matched in prevention, resulting in more new HIV infections than deaths each year [1]. This mismatch results in a rising prevalence, with millions in need of lifelong treatment, which places a massive strain on health systems worldwide. This is not sustainable. Renewed efforts to improve prevention are vital to comprehensively address the challenge of HIV.

There are a variety of different potential preventative measures. Behavioural methods include promoting condom use and reducing sexual-risk behaviours. Structural interventions, such as treatment-as-prevention, have shown promise around the world [2–4]. Biomedical prevention is a recent addition to this arsenal, with one of the most effective current methods being oral pre-exposure prophylaxis (PrEP]. This is an antiretroviral, given to those at high risk of HIV infection in order to provide a pharmacological barrier to infection. All of these preventative measures should ideally be used in combination, but this review will focus on the use of oral PrEP for HIV prevention.

Oral PrEP, in the form of tenofovir disoproxil fumarate/emtricitabine(TDF/FTC), has been approved for use in many countries worldwide and is now recommended by the WHO, as part of an optimal package of HIV prevention measures [5]. It has been proven to be efficacious in specific risk groups, such as MSM [6–8], serodiscordant couples [9] and intravenous drug users (IVDU) but has shown lesser or no efficacy in trials in African women [10,11]. These variations in efficacy are thought to be largely a result of poor adherence [8,12]. When taken regularly in observational studies, PrEP has been shown to be highly efficacious [13], with little or no breakthrough infection occurring in adherent individuals [14,15].

PrEP is currently only reaching around 300,000 users worldwide [1], falling short of what would be required to prevent the 1.8 million new infections annually. Furthermore, the vast majority of PrEP usage occurs in high-income countries, rather than the sub-Saharan African countries that experience the greatest burden of HIV incidence [1].

There are multiple barriers to worldwide provision of PrEP to all eligible, at-risk populations [16]. One roadblock to widespread rollout is cost, with hugely variable costing, but there is evidence that PrEP can be cost effective in certain populations [17,18]

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depending on HIV incidence [19,20]. A second barrier is uptake and adherence [21], which can be damaged by patient concerns around side effects and costs [22,23]. Additionally, cultural stigma towards marginalized at-risk groups affects political appetite to provide PrEP to these populations [24,25]. However, there is evidence of demand for PrEP in at-risk populations worldwide [14,26,27].

A third barrier to the promotion of PrEP programmes worldwide is concern over the safety profile of the drug. Safety concerns affect patients, providers and policy makers' attitudes towards PrEP. The main concerns centre around reports of renal and bone toxicity, with reports of subclinical reductions in kidney function [28] and bone mineral density [29]. TDF/FTC is usually used in treatment alongside booster drugs; however, when unboosted, it has been found to confer no increased risks of serious adverse events. Newer drug alternatives, such as TAF, are being promoted as potentially safer alternatives to TDF/FTC as PrEP. However, a previous meta-analysis of TDF/FTC compared to alternative TAF/FTC for treatment found no significant difference in safety endpoints when used without the pharmacokinetic boosters ritonavir or cobicistat, which elevate tenofovir levels. More evidence around the safety of TDF/FTC, which is now widely available in a cheaper generic form, is needed to address concerns and inform prevention efforts.

The potential benefits of PrEP vary greatly between populations, depending on risk, which is determined by HIV incidence in that community. For example, in a population with HIV incidence of 5%, the number of people who would be needed to treat with PrEP to prevent one infection would be 23, assuming that PrEP prevents 86% of new HIV infections, as seen in the PROUD study [6]. Whereas, if the risk were only 1%, the number needed to treat would become 115. Risk varies across countries and between risk groups, tending to be highest in known risk groups such as MSM, which show a 3.3% pooled incidence worldwide based on recent incidence studies [31]. In higher risk populations, PrEP is likely to be beneficial overall. However, some risk threshold exists below which it is no longer overall beneficial to use PrEP. Given that wide-scale prevention would involve medicating millions of healthy people, any potential safety concerns are a major obstacle. The more concern exists over safety of PrEP, the more conservatively it should be given and therefore the higher this risk threshold should be set.

Further analysis and quantification of the potential harms of PrEP, within the context of the potential benefits, is needed to inform recommendations for worldwide PrEP use. The aims of this analysis are to assess the safety of oral PrEP, informing policy and clinical decision-making. The potential harms considered are more severe adverse events (grade 3+), reported in PrEP randomised controlled trials. These are more comparable to the threat of HIV than mild or moderate grade adverse events. The difference in risk of adverse events between PrEP and control in the randomised trials is used to analyse the potential for harm from PrEP. This can then be compared with the benefits of PrEP in lowering the risk of HIV infection.

Methods

This review was carried out in accordance with the guidance of the Cochrane framework for systematic reviews and followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA statement) [32].

A search was carried out on Ovid across four databases (Embase, Medline, HMIC and Global Health) for randomised controlled trials, evaluating oral HIV PrEP as an intervention, with the outcome of interest being safety data regarding numbers of adverse events. Full search terms used are summarised in Appendix 1.

No further date or language restrictions were applied. Searches were supplemented with exploration of the grey literature through online databases of abstracts from two major HIV focused conferences, the British HIV Association Annual Conference (BHIVA), the Conference on Retroviruses and Opportunistic Infections (CROI) and the International AIDS Society conference (IAS). Clinicaltrials.gov was also explored. Follow up from reference lists and consultation with experts in the field further enhanced the comprehensiveness of the search.

Predefined selection criteria are outlined in Appendix 2. Studies were required to be published in a peer-reviewed journal, or presented at a scientific conference. The review included clinical randomised controlled trials of oral PrEP formulations containing TDF, as an intervention against HIV. Key outcome measures were HIV infection and adverse events. Intervention comparison against control arms, of either placebo or deferred start to treatment, was also a criterion. No further restrictions were applied.

A full list of studies returned by the search was uploaded to reference management software and duplicates removed. Remaining titles and abstracts were screened by one reviewer and considered against the pre-specified eligibility criteria. Irrelevant or unsuitable studies were classified by reason for exclusion.

Within trial safety data, the key outcomes extracted were adverse events: classified as grade 3 or 4 AE or protocol-defined serious adverse events (SAE). Grade 3 or 4 adverse events are those classified as severe or life-threatening, based on either pre-set grading systems or clinical judgement, as set out in individual trial protocols. Further analyses of specific renal and bone markers were also undertaken, with fractures as a marker of loss of bone mineral density and blood creatinine elevations (Grade 3+) as a surrogate marker for renal impairment. Further information, including total sample sizes, population risk exposure, 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, standardisation required that all events, rather than selection for those deemed treatment related, were extracted and compared to placebo as a more reliable measure of relationship to treatment. Where multiple publications reported data from the same study over the same follow-up periods, data were combined.

A meta-analysis of the safety data was conducted using the Cochrane Collaboration's Review Management software (RevMan version 5.3). Clinical diversity in interventions (with mostly daily TDF/FTC regimens, but some TDF only and some intermittent dosing) and in patient populations (with multiple different risk groups) warranted used of the random effects model in pooling the studies. As the outcomes were dichotomous numbers of adverse events in each arm, risk difference was calculated using Mantel–Haenszel (M-H) methods.

Where studies had more than one treatment arm, the arm assessing the most commonly used intervention (daily TDF/FTC) was included in the meta-analysis, versus control. A sensitivity analysis was run to explore the effects of this exclusion on resultant pooled estimates.

Statistical heterogeneity was assessed by consideration of the I^2 statistic, with values of <30% being considered be low, 30–50%, moderate and >50% substantial. Predefined subanalysis explored heterogeneity by stratifying studies by average follow-up time

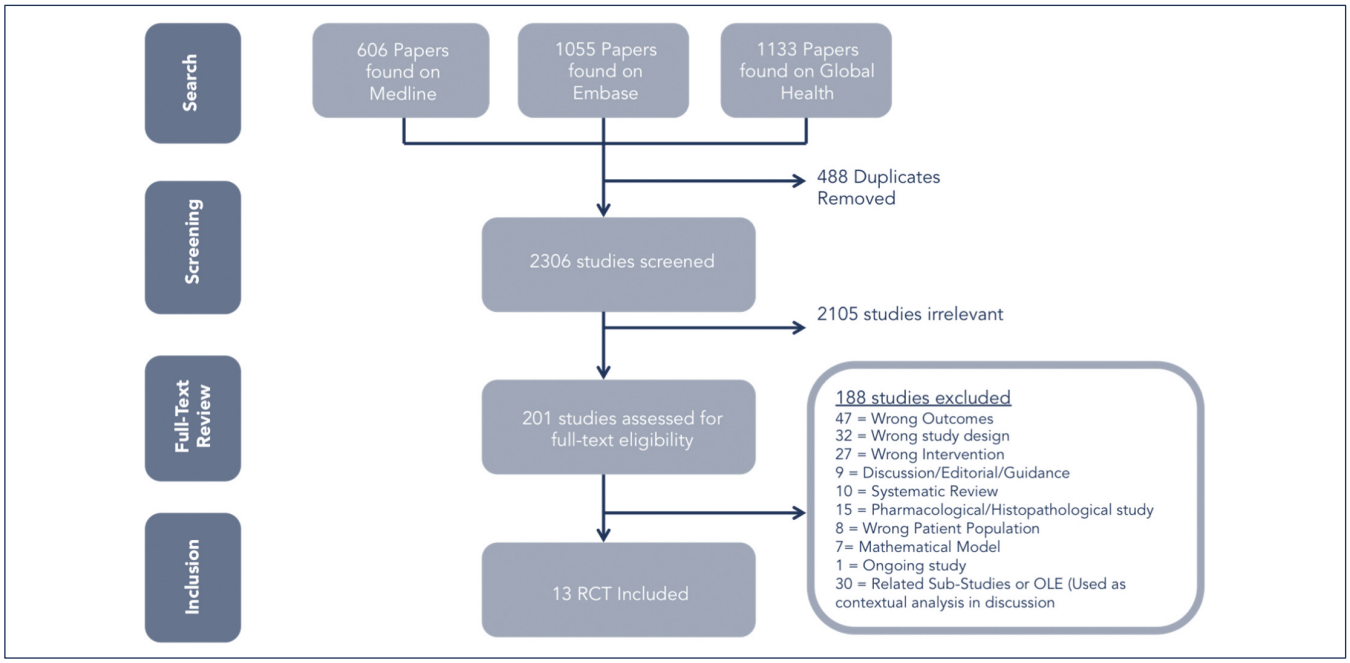

Figure 1. Flowchart denoting study selection process from identification to inclusion

(>/<1yr) and was also useful in ascertaining consistency in risk over time.

Results

Of 2306 initial citations screened, 13 eligible RCTs were identified (Figure 1). Extracted safety data of the occurrence of adverse events is displayed in Table 1. All 13 studies reported SAE, 12 reported grade 3 or 4 adverse events, nine reported fracture data and 13 reported creatinine elevation data. Six studies focused on MSM, three on women, two on serodiscordant couples, one on IVDU and one on adolescents. Trial follow-up times were variable (from 4 months to 5 years). Stratification by average length of follow-up, undertaken to determine consistency of underlying event rates, classified seven studies as short term (<1 year) and six as long term (>1 year) [9,10,38–41].

All 13 studies account for a total of 18,341 participants included in PrEP safety analysis, with 10,482 in treatment arms and 7859 in the control arms. Four of the studies [9,10,34,35] compare more than one treatment arm to control. Therefore, on meta-analysis, where relevant, data from only one treatment arm was included, to avoid double counting of the control comparison data, resulting in analysis of data from 15,678 participants across an estimated 22,250 person-years of follow up (PYFU). Daily TDF/FTC treatment was preferred, as this is the most common regimen. Three studies assessed TDF use only [36,38,41] and one assessed intermittent PrEP [7]. One study compared treatment against delayed treatment initiation, rather than placebo [42], and another included both immediate and delayed initiation in both treatment and placebo trial arms [38].

Due to inconsistencies in assessment and reporting, all events were included in the analysis, regardless of classification likelihood of relation to drug. Sensitivity analyses were undertaken to ascertain whether the decision to use numbers of events rather than numbers of people affected would change the significance of results and this was found to have no effect on the significance for any of the endpoints analysed. Sensitivity analysis was also performed to assess effect of sex, separating studies into those on female, male and mixed populations. It was found that sex did not change the significance of the results across all safety endpoints.

Meta-analysis of grade 3 or 4 adverse events (Figure 2) found no significant difference (P=0.53) between numbers of events in treatment versus control trial arms overall, with the pooled risk difference being 0.00 (95% confidence interval [CI]=-0.01–0.02). Heterogeneity between trials was substantial (I^2=55%). Subgroup analyses demonstrated no further statistically significant differences, and there was no statistical difference between subgroups, (I^2=0%, P=0.52), indicating a generally consistent rate of adverse events over time.

Similarly, on meta-analysis of SAE, no significant (P=0.80) risk difference between trial arms was demonstrated overall (Figure 3), estimated as 0.00 (95% CI –0.01 to 0.01). Heterogeneity between studies was substantial (I^2=53%). Short-term follow-up subgroup analysis demonstrated no significant difference in event numbers between trial arms (RD=0.01, 95% CI –0.01 to 0.03, P=0.19). However, in the long-term follow-up subanalysis, there was significantly (P=0.02) less risk in the treatment arm versus control, with a risk difference of –0.01 (95% CI –0.02–0.00).

There were 12 cases of grade 3+ serum creatinine elevation, used as a surrogate marker for renal impairment, occurring across the trials. On meta-analysis (Figure 4), there was no significant difference (P=0.68) between numbers of events in treatment versus control trial arms. The overall risk difference was 0.00 (95% CI –0.00 to 0.00). Statistical tests revealed no heterogeneity (I^2=0%). Subgroup analyses demonstrated no further statistically significant differences, and there was no statistical difference between subgroups, (I^2=0%, P=0.65), indicating a consistent rate of adverse events over time.

Given the low numbers of grade 3+ creatinine elevations occurring, a further analysis of creatinine elevations of all grades (1–4) was undertaken. A total of 514 creatinine elevations occurred (97.7% being grades 1–2). Grade 1 is defined as 1.1–1.3 times the upper limit of the normal range (ULN) and grade 2 is 1.1-1.8 x ULN, while grade 3+ is >1.9xULN. On meta-analysis (Figure 5), there was a borderline statistically significant overall risk difference (P=0.04) between numbers of events in treatment versus

Table 1. Safety data extracted from the 13 included RCTs comparing TDF(/FTC) with control

Study	Type of PrEP	Population	Location	(Average) Follow Up	Total (In Safety Analysis)	Grade 3/4 adverse events		Serious adverse events		Fractures		Creatinine (grade 3+)		Creatinine (all grades)	
						Events/people									
						PrEP	Control	PrEP	Control	PrEP	Control	PrEP	Control	PrEP	Control
VOICE [10]	TDF/Daily FTC	Women	SA, Uganda, Zimbabw	12-36 months	2012	140/1003	135/1009	43/1003	68/1009	3/1003	2/1009	0/1003	0/1009	16/1003	2/1009
US SAFETY STUDY [38]	TDF Daily	MSM	USA	24 months	400	36/201	26/199	20/201	8/199	15/201	5/199	0/201	0/199	2/201	6/199
TDF 2 [39]	TDF/Daily FTC	MSM + Women	Botswana	1.1-3.7 years	1219	21/611	32/608	68/611	79/608	7/611	8/608	0/611	0/608	1/611	0/608
PROUD [6]	TDF/Daily FTC	MSM	UK	1 year	544	– / –	– / –	23/275	6/269	3/275	1/269	0/275	0/269	0/275	0/269
Partners [9]	TDF/Daily FTC	SC	Kenya/Uganda	Up to 36 months	3163	377/1579	307/1584	115/1579	118/1584	– / –	– / –	1/1579	0/1584	20/1579	13/1584
iPREX [40]	TDF/Daily FTC	MSM + TW	Thailand, Brazil, Ecuador, Peru, SA, USA	1.2-2.8 years	2499	248/1251	285/1248	76/1251	87/1248	16/1251	12/1248	0/1251	1/1248	28/1251	15/1248
IPERGAY [33]	TDF/ on- FTC Demand	MSM	Frace and Canada	Med 9.3 months	400	19/199	15/201	20/199	17/201	3/199	6/201	0/199	0/201	35/199	20/201
FEM-PrEP [11]	TDF/Daily FTC	Women	Kenya, SA, Tanzania	52 weeks	2058	83/1025	64/1033	36/1025	24/1033	1/1025	2/1033	1/1025	0/1033	1/1025	0/1033
Bangkok Tenofovir Study [41]	TDF Daily	IVDU	Thailand	4 years	2413	414/1204	389/1209	340/1204	375/1209	169/1204	153/1209	4/1204	3/1209	4/1204	3/1209
PrEPare - ATN 082 [37]	TDF/Daily FTC	Adolescents	USA	24 weeks	39	4/20	1/19	0/20	0/19	0/20	0/19	0=2/20	0/19	2/20	0/19
IAVI Uganda Study [35]	TDF/Daily FTC	SC	Uganda	4 months	36	0/24	0/12	0/24	0/12	– / –	– / –	0/24	0/12	2/24	0/12
IAVI Kenya Study [34]	TDF/Daily FTC	MSM + FSW	Kenya	4 months	36	3/24	0/12	0/24	0/12	– / –	– / –	0/24	0/12	3/24	0/12
West African Safety Study [36]	TDF Daily	Women	Ghana, Cameroon, Nigeria	6 months	859	0/363	5/368	9/427	13/432	– / –	– / –	0/427	0/432	13/427	15/432
					TOTAL	1306/7504	1259/7502	740/7843	795/7835	**217/5789**	**189/5795**	**8/7843**	**4/7835**	**336/10482**	**178/10452**

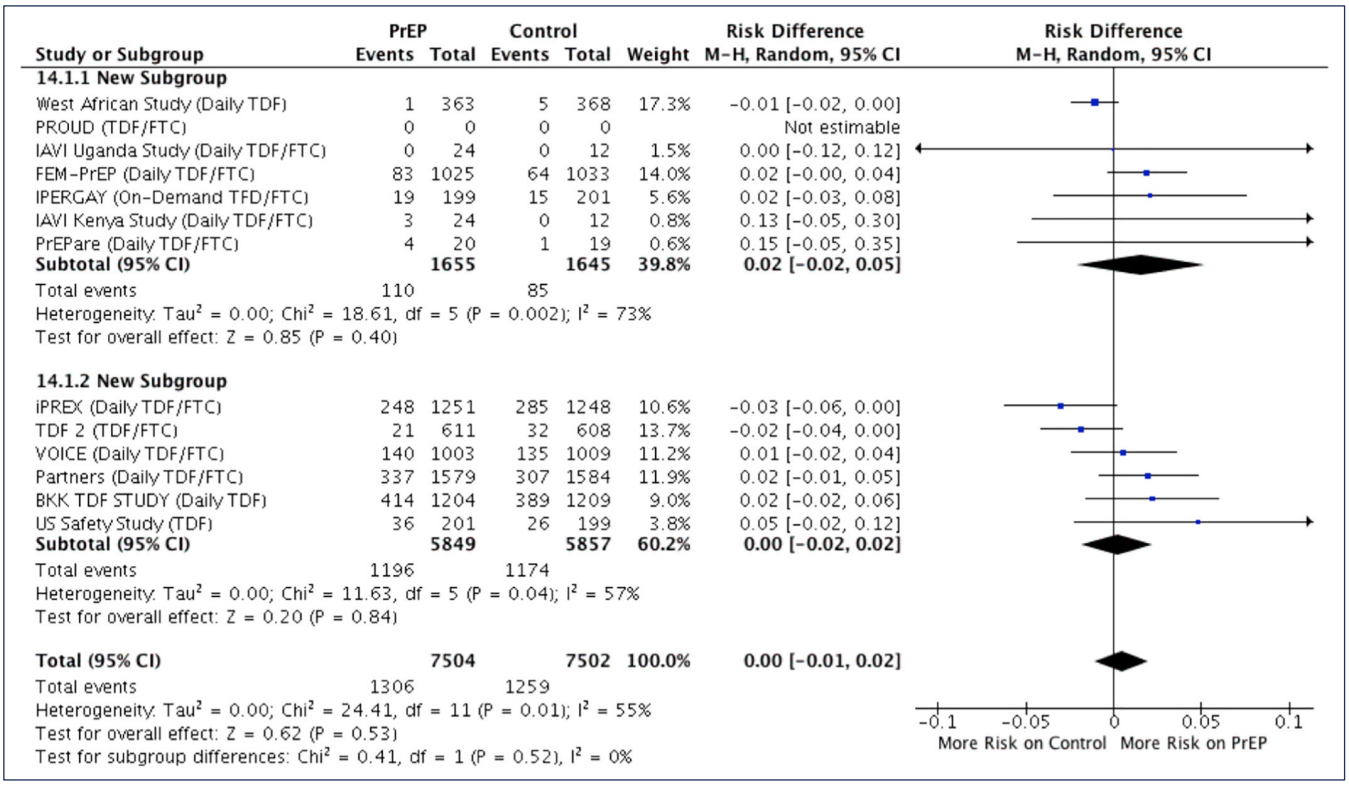

Figure 2. Display of safety data and forest plot of PrEP versus control for serious adverse events

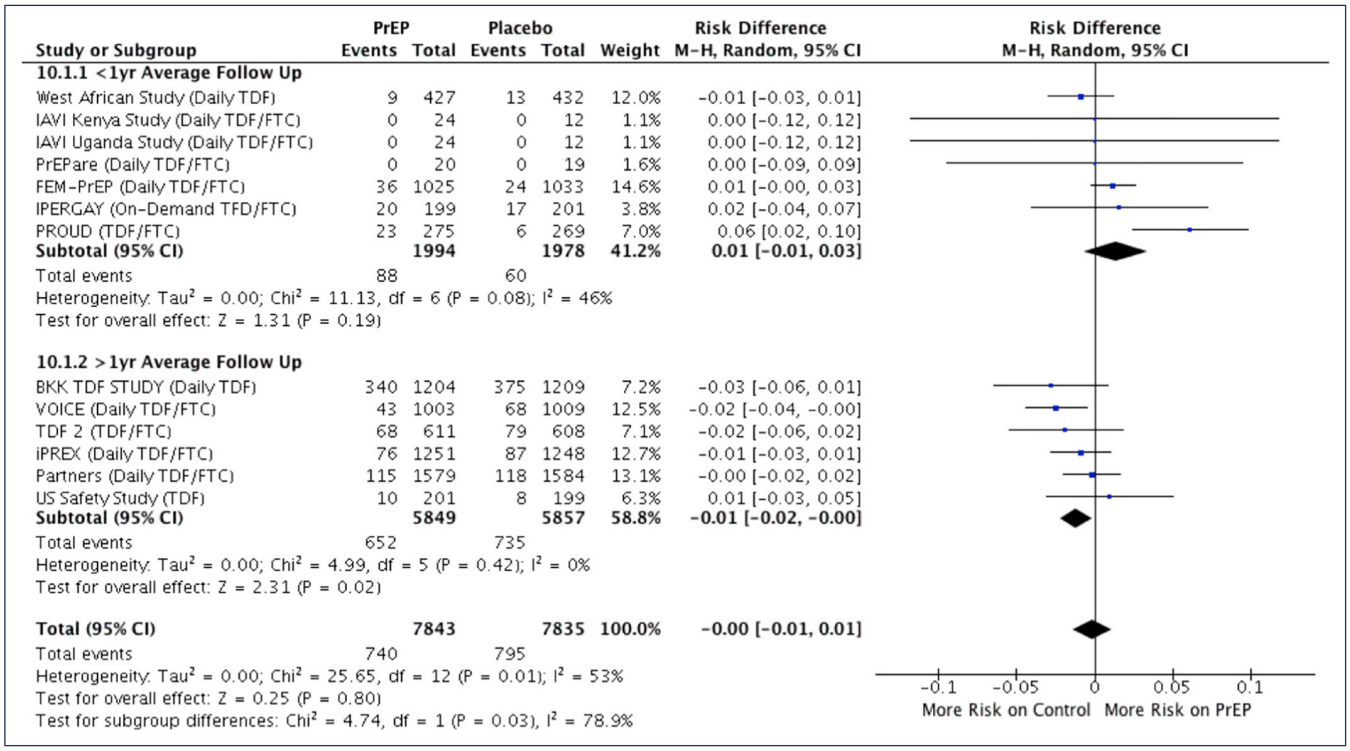

Figure 3. Display of safety data and forest plot of PrEP versus control for grade 3/4 adverse events

control arms. The overall risk difference was 0.02 (95% CI 0.00–0.03). Statistical tests revealed substantial heterogeneity (I^2=93%). Subgroup analyses demonstrated no further statistically significant differences, and there was no statistical difference between subgroups, (I^2=0%, *P*=0.48), indicating a consistent rate of adverse events over time.

Meta-analysis of fractures (Figure 6), used as an indicator of adverse bone effects, found no significant difference (*P*=0.50) between numbers of events in treatment (217/5789) versus control trial arms (189/5795) overall, with the pooled risk difference being 0.00 (95% CI –0.00 to 0.01). Heterogeneity was substantial (I^2=66%). Subgroup analyses demonstrated no further statistically significant differences, and there was no statistical difference between subgroups, (I^2=0%, *P*=0.32), indicating a consistent rate of adverse events over time.

A summary graph displaying the total number of events occurring as a proportion of the total number of study participants for each of these four endpoints is shown in Figure 7.

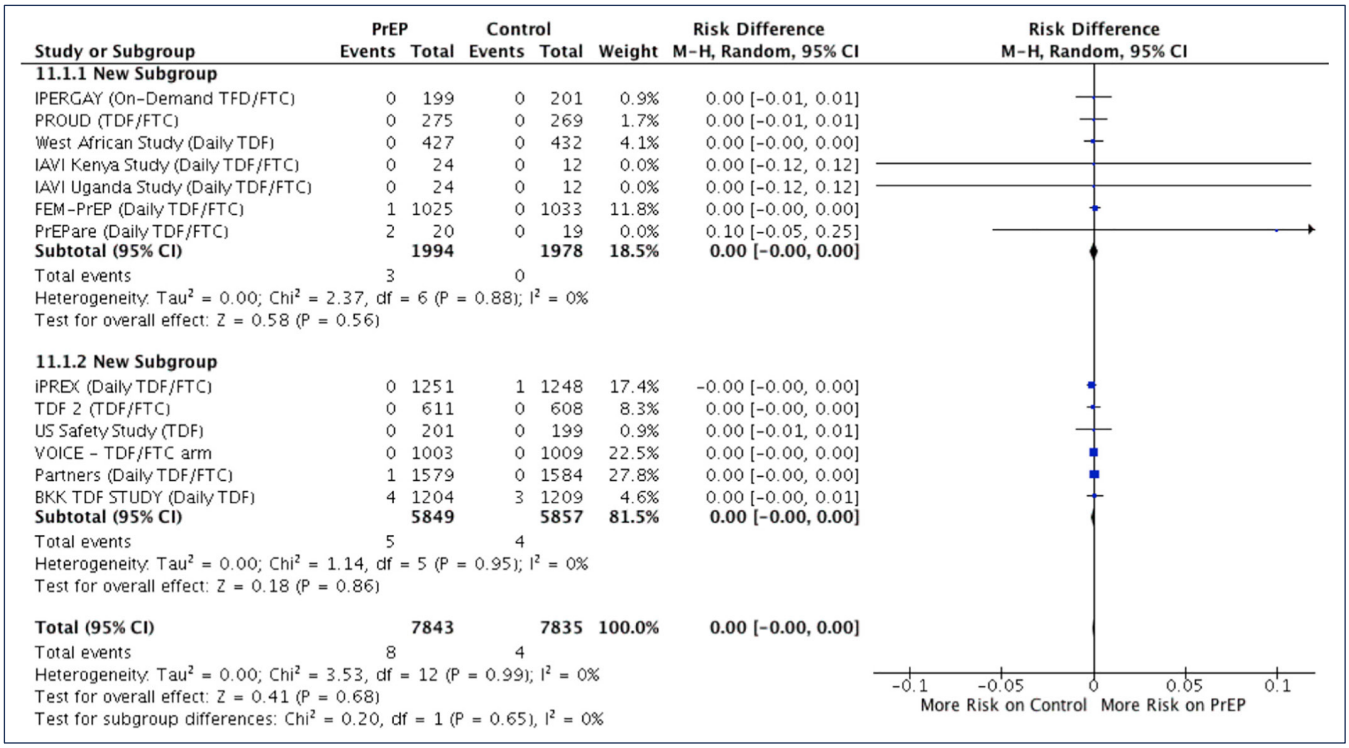

Figure 4. Display of safety data and forest plot of PrEP versus control for grade 3/4 creatinine elevations

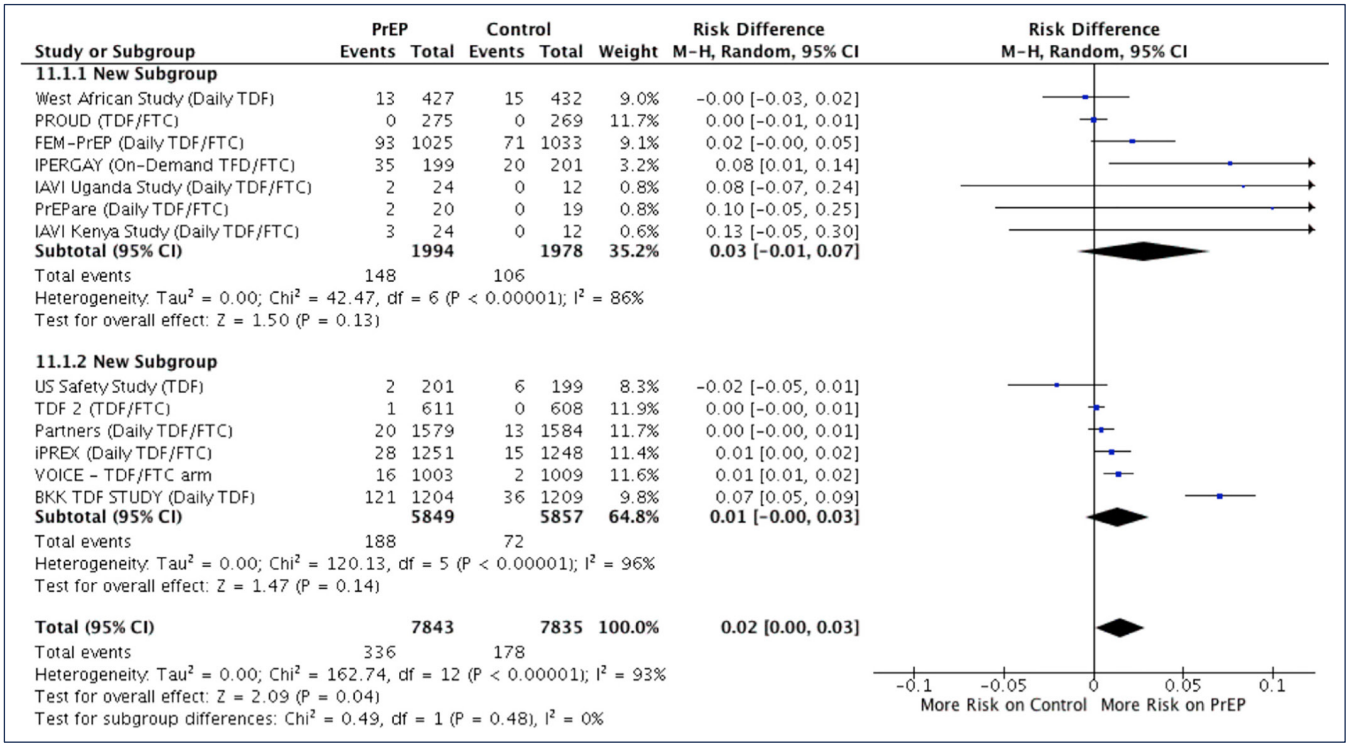

Figure 5. Display of safety data and forest plot of PrEP versus control for creatinine elevations of all grades (1-4)

Discussion

These meta-analyses of the safety data from 13 randomised clinical trials, in 15,678 participants, found no significant difference in the risk of various severe adverse event types in TDF/FTC (or TDF) and control. Notably, trials with longer-term (>1yr) average follow-up time reported a statistically significantly greater risk of SAE on placebo versus treatment itself; an interesting and counterintuitive finding. The favourable safety profile of TDF/FTC would support more widespread use of PrEP in populations with a lower risk of HIV infection.

Existing PrEP safety concerns centre around reports of subclinical decreases in renal function [43,44] and bone mineral density [28,45,46] in PrEP users. This review found a borderline statistically significant increase in numbers of creatinine elevations of all grades; however 97.7% of these were grade 1–2. The trials themselves classified these lower level events as fully reversible

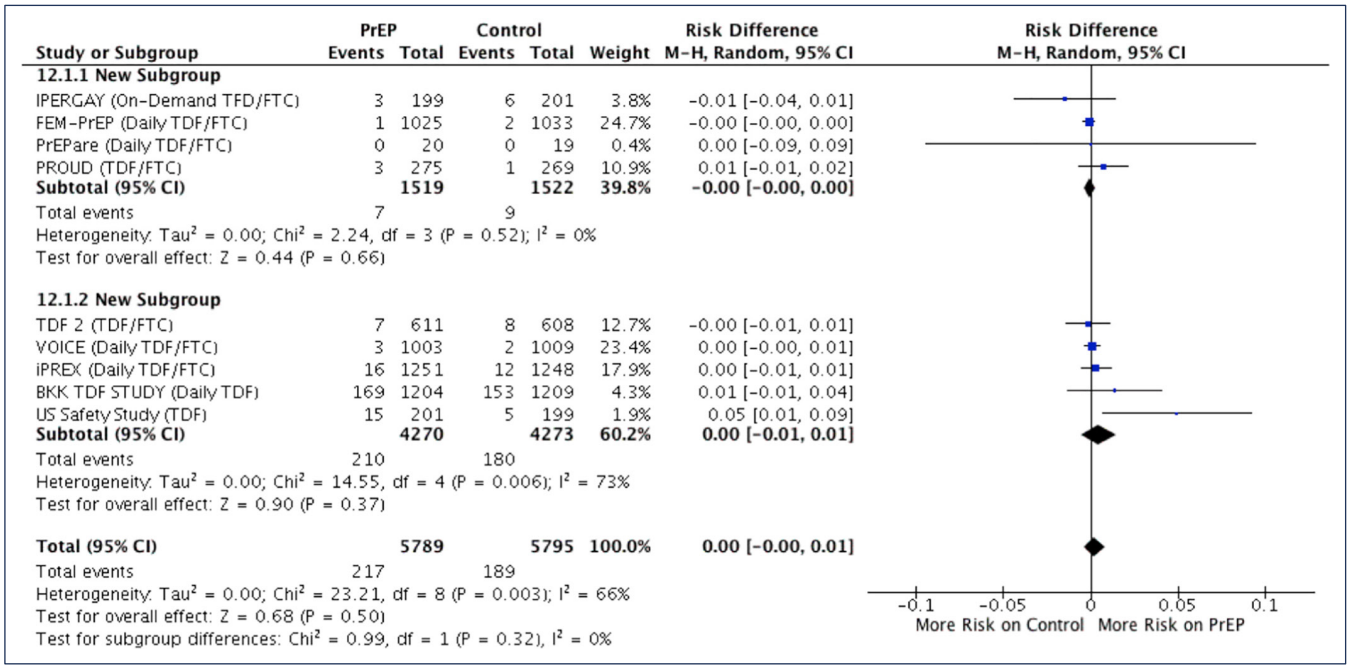

Figure 6. Display of safety data and forest plot of PrEP versus control for bone fractures

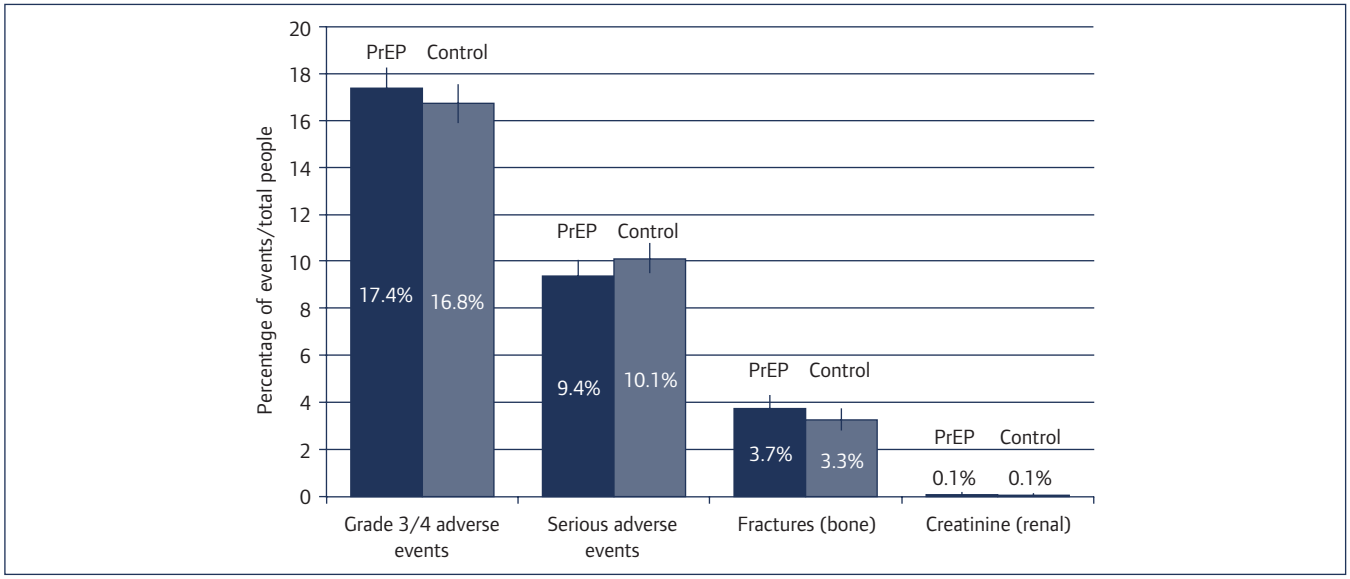

Figure 7. Graph summarising the differences in occurrence of all adverse event types, between PrEP and control arms (number of events per total number of people in that safety analysis)

and non-progressive in the long term and this is consistent with further reports of such events (as well as other adverse event types) in the wider literature. These adverse-event findings might also be overstated in the literature, due to confirmation biases, as awareness of these potential harms is high and therefore they are more carefully screened and checked for in any trial population.

Overall, our meta-analysis found no evidence to support severe (grade 3+) renal or bone damage caused by PrEP. Furthermore, we found no evidence of translation into relevant clinically visible endpoints, particularly bone fractures. Trial follow-up periods may have been inadequate to fully assess long-term effects so further research is warranted. However, there is a lack of current evidence of clinically relevant harms, so further exploration via baseline risk assessment and clinical monitoring [48,49] to appraise long-term effects would be appropriate.

PrEP has the potential to cause further harms, which were outside of the scope of this review. One such harm is the potential that use of dual therapy with the same nucleos(t)ide analogues used to treat HIV might lead to the emergence of drug resistance. This is a possibility and the limited evidence needs monitoring and exploration [50] Low adherence often raises resistance concerns, but the VOICES trial, which had low adherence, found very few cases of resistance to TDF or FTC amongst seroconverters [10]. A recent review of the evidence concluded that there is no significant excess risk of drug-resistant mutations in seroconverters on TDF/FTC [12].

Furthermore, there are fears that PrEP usage, in removing the threat of HIV, might encourage risk compensation behaviour and therefore increase other sexually transmitted infection (STI] rates. There is variable evidence on this topic, with RCTs and some observational studies generally finding no evidence [8,51–56], but other observational studies finding decreasing condom usage and increasing STI incidence over time [13,57,58]. A recent systematic review concluded that PrEP use does not lead to risk

compensation [12]. On analysis of the studies included in this review, 12 of the 13 reported either a trend towards lesser risk behaviours across trial periods, or no change to risk behaviours, within their participant populations. However, evidence from trial environments may not be wholly representative of wider population behaviours, as they select for motivated, health-aware individuals and often provide supportive behavioural interventions [52,59]. It is likely that these behavioural interventions may be a necessary addition to PrEP programmes to mitigate any risk compensation.

To further contextualise risk, if PrEP is not used, the HIV infections that occur in its absence would require lifelong treatment with antiretrovirals, associated with higher risks of adverse events [29,60] as well as HIV itself conferring a toxicity to liver and bone [61,62]. Therefore, any risk of PrEP harms could still be beneficial in comparison. There is also some evidence of some further benefits of PrEP, including a protective effect against HSV-2 acquisition [63] and evidence that PrEP users may benefit from a lowered cholesterol [30].

Strengths and limitations

This analysis followed PRISMA and Cochrane review guidelines throughout, screening a wide array of studies, as well as grey literature, for each review in order to ensure that all relevant articles had been retrieved. On assessment, all included studies were of a consistently high quality with a low risk of bias (Appendix 3).

External limitations in the relevant literature resulted in areas of scarcity of data, with not all relevant risk groups and world regions having been represented adequately and equally in PrEP trials to date. However, when looking at adverse events occurring in these trials, there does not appear to be any significant risk differences in different risk populations between studies [12], so perhaps the risk of adverse events can be reasonably assumed to be constant across populations. Trials have inherent limitations in that participants may have been excluded if they showed a higher baseline risk of renal or bone disease, biasing potential findings. An important limitation may be low adherence in several of the trials, which could dilute the rate of drug-related adverse events.

Statistical heterogeneity was present, but the studies were all RCTs of similar quality and low risk of bias, therefore this is unlikely to be the source of heterogeneity. Clinical heterogeneity is a more likely potential source. The included trials demonstrate significant variability in regimen, risk populations, age and duration, which we attempted to minimise, but it still remains a fundamental influencing factor. Furthermore, on funnel plot assessment, there does seem to be a possibility of publication bias across the literature in this area.

Trial follow-up periods may have been inadequate to fully assess long-term effects. However, our analysis showed comparatively fewer SAE during longer-term follow up, as well as consistency in other adverse-event rates over time, suggesting that event rates may tail off or remain constant and these trial periods are adequate to analyse safety risk. This analysis gathered evidence from all 13 relevant PrEP trials carried out to date, including an estimated 22,250 total PYFU safety data, so analysis should be sensitive enough to detect any adverse risks on TDF/FTC. Creatinine was used as a surrogate marker of renal impairment, as it was most consistently reported across trials. However, alternative indicators, such as glycosuria and proteinuria, may have been more appropriate to pick up early stage impairment, particularly in those trials with shorter follow-up periods.

The findings of this review focus on severe adverse events. As is the case with any medication, there may well be lower level adverse events caused by TDF/FTC, particularly gastrointestinal events, such as nausea. Whilst these may not be a concern to providers and policy makers as they are lesser than the threat of HIV, they may well be a concern to PrEP users and could adversely affect drug uptake and adherence.

Applications and implications

This review demonstrates no significant risk of severe side effects on TDF/FTC. This is applicable to policy makers, confirming worldwide PrEP potential, and clinicians, in assuaging PrEP safety concerns. It is also applicable to PrEP users themselves, making informed decisions regarding their own use of PrEP.

Alternative PrEP formulations in development include TAF/FTC and injectable cabotegravir [65,66]. Given these findings of no significant risks associated with the current, widely generically available TDF/FTC formulation, further safety improvements can only hope to be very subtle. Improvements in facilitating adherence, rather than focusing on safety profile, are likely to be more beneficial to overall PrEP impact.

PrEP has proven feasibility in uptake and adherence, evidenced by demonstration projects worldwide [14,67–70]. Real-world populations vary and differences in behaviours and adherence will influence PrEP effectiveness and HIV incidence, but we can conclude that TDF/FTC has a favourable overall safety profile. This means that the remaining limiting factors are cost-effectiveness barriers, as well as difficulties in encouraging PrEP uptake and adherence in real-world contexts. This all sits within a wider package of HIV prevention measures and a combination approach is necessary to collaboratively address the challenge of HIV incidence.

Conclusions

This review finds no evidence that oral TDF/FTC is associated with any increased risk of severe adverse events. On these grounds, lower risk thresholds for PrEP provision may be warranted, allowing wider provision of PrEP to at-risk populations.

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Appendix 1. Search terms

Intervention	Disease	OUTCOME
Pre-exposure prophylaxis/chemoprophylaxis/ Pre-Exposure Prophylaxis.mp PrEP.mp	HIV/ Human immunodeficiency virus/ Human Immunodeficiency Virus.mp. HIV.mp.	drug efficacy/ safety/ adverse drug reaction/ adverse outcome/ adverse event/ Treatment Outcome/ safety/ efficacy.mp. Safety.mp. adverse.mp. adverse event*.mp. adverse outcome*.mp.

Listed are free text search terms (.mp), as well as general subject headings (/) mapped to the search within each category. Subject headings were altered to be correct and applicable to each individual database and separate searches carried out in each database as appropriate.
Table display: terms within the same column are combined with OR. All terms between columns are combined with AND.

Appendix 2. Predefined inclusion and exclusion criteria

PrEP trials

Inclusion	Exclusion
• Randomised controlled trials, with a placebo or comparison arm • Published in a peer-reviewed journal • Clinical trials that assess safety of the treatment drug and report absolute numbers of adverse events occurring in both arms	• Non human trials • Earlier than Phase III • Trials of non-oral PrEP (e.g. microbicides) • Substudies looking at the wrong outcome (e.g. measures of adherence and dosing, and measures of qualitative wellbeing or commitment, etc)

Appendix 3: Risk of bias assessment, carried out using the Cochrane collaboration's risk of bias assessment tool