How safe is PrEP?

An analysis of the safety of TDF(/FTC) as PrEP

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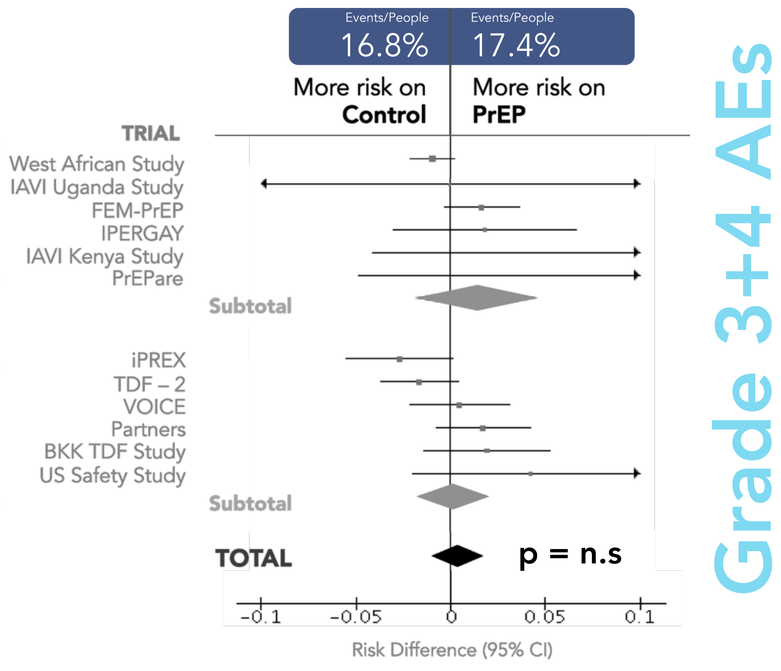
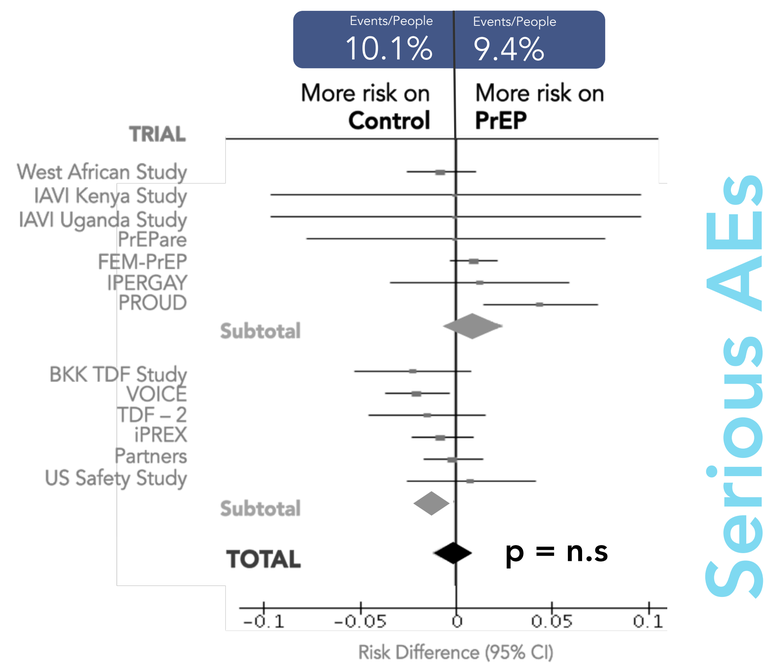
BACKGROUND: Tenofovir/Emtricitabine (TDF/FTC) used as pre-exposure prophylaxis (PrEP) has proven benefits in preventing HIV infection. Widespread use of TDF/FTC can only be justified if the preventative benefits outweigh potential risks of adverse events. A previous meta-analysis of TDF/FTC compared to alternative Tenofovir Alafenamide (TAF/FTC) for treatment found no significant difference in safety endpoints when used unboosted. More evidence around the safety of TDF/FTC is needed to address concerns and inform widespread use.

METHODS: A systematic review identified 13 randomised controlled 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).

Figure 1: Flow chart showing the process of searching, screening and reviewing papers to come to a final inclusion list and data extraction and processing.



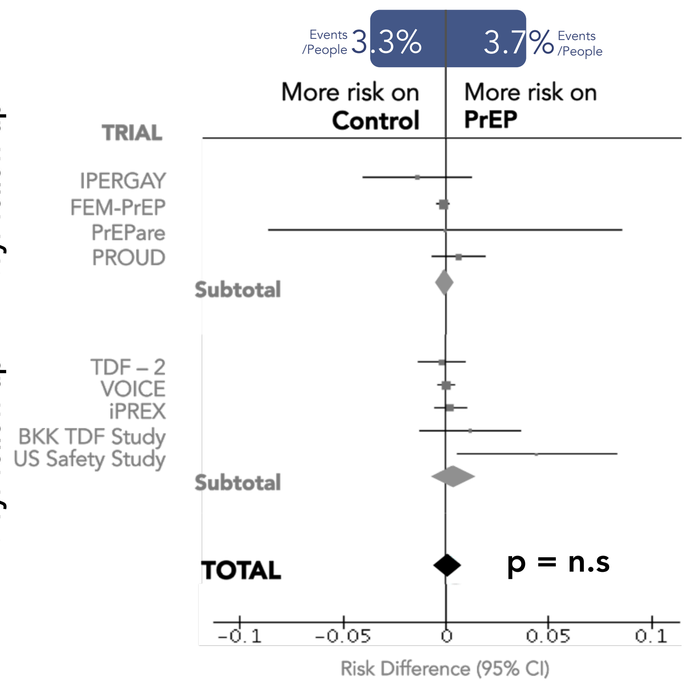
Grade 3+4 AEs



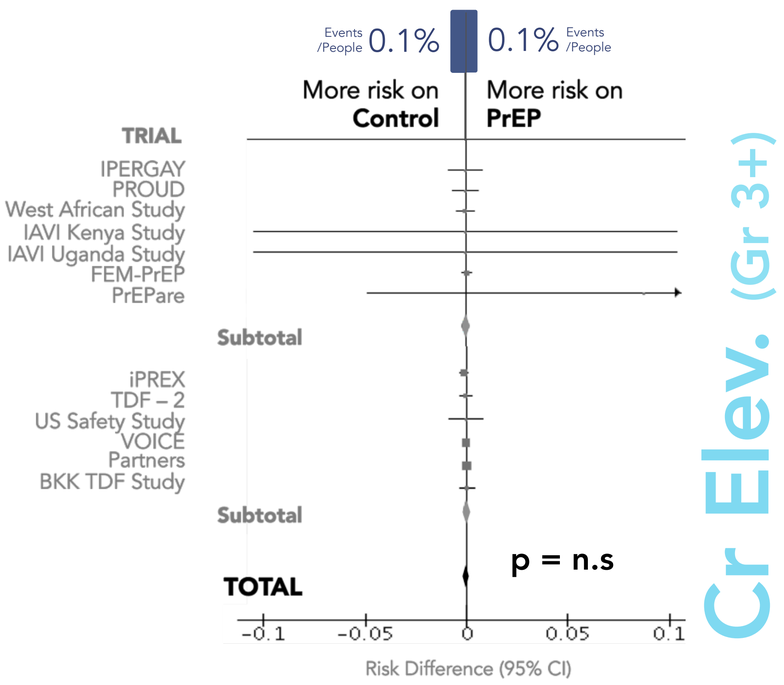
Serious AEs

RESULTS: The 13 randomised trials included 15,678 participants in relevant treatment and control arms. Three studies assessed TDF use only. There was no risk difference in the number of participants with grade 3+4 adverse events between the treatment and control arms (p=0.53). There was no risk difference for serious adverse events (p=0.80). There was also no risk difference in bone fractures (p=0.50) or grade 3+ creatinine elevations (p=0.68). However, creatinine elevations of all grades (1-4) showed a borderline statistically significant increase in risk of events on PrEP (p=0.04).

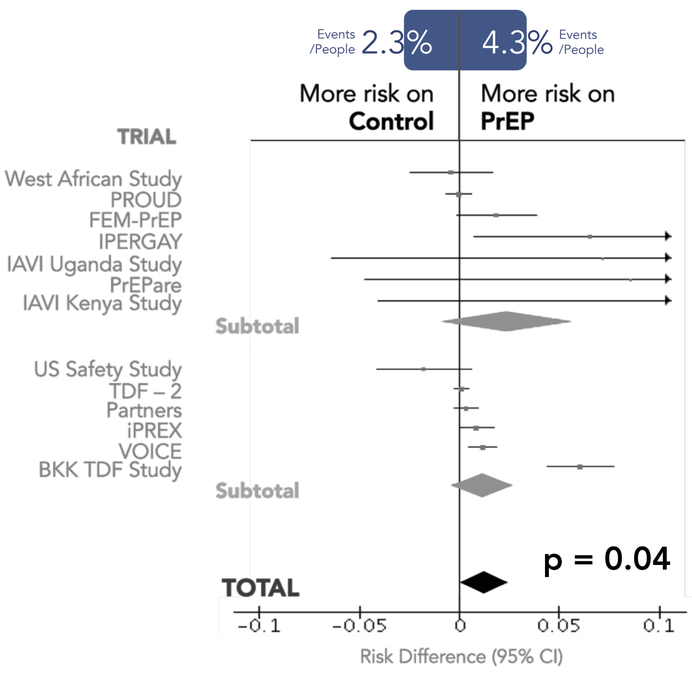
	PrEP Events/ People	Control Events/ People	Risk Difference (95% CI)	Significance
Grade 3/4 AE	1306/ 7504	1259/ 7502	0% (-1% to 2%)	**p = 0.53**
Serious Adverse Events	740/ 7843	795/ 7835	0% (-1% to 1%)	**p = 0.80**
Bone Fractures	217/ 5789	189/ 5795	0% (0% to 1%)	**p = 0.50**
Grade 3+ Creatinine Elevations	8/ 7843	4/ 7835	0% (0% to 0%)	**p = 0.68**
All Creatinine Elevations	336/ 7843	178/ 7835	2% (0% to 3%)	**p = 0.04**



Fractures



Cr Elev. (Gr 3+)



Cr Elev. (Gr 1-4)

Figures: Meta-analyses of five adverse event end points; Risk difference of adverse event occurrence on PrEP versus control. Trials are stratified into subgroups by length of trial follow up (</>1year average).

KEY MESSAGE: **There is no evidence that TDF/FTC causes increased risk of severe adverse events when used as PrEP**

This favorable safety profile may justify widespread provision to millions worldwide.

CONCLUSIONS: In this meta-analysis of 13 RCTs 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) and control. Whilst there is a borderline significance in risk of renal events overall, there was no significant difference in risk of severe renal or bone adverse outcomes. This favourable safety profile would support more widespread use of TDF/FTC as PrEP in populations worldwide.