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Elevations in Serum Creatinine with Tenofovir-Based HIV Pre-exposure Prophylaxis: A Meta-Analysis of Randomized Placebo-Controlled Trials

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Pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate (TDF), alone or in fixed-dose combination with emtricitabine (FTC/TDF), decreases the risk of sexual transmission of HIV.[1-5] In HIV-infected individuals, there is a small risk of acute kidney injury and proximal tubulopathy,[6-8] and cumulative TDF exposure has been associated with decreased glomerular filtration rate (eGFR).[9,10] In clinical trials of healthy HIV-uninfected adults receiving TDF-containing PrEP, there was no statistically significant increase in renal adverse events; however, the trials were not powered to detect rare safety events.[2-5,11-16] Secondary analyses of three large PrEP trials demonstrated small but statistically significant declines in eGFR or calculated creatinine clearance (CrCl) in participants assigned to active PrEP.[17-19] We performed a systematic review and meta-analysis of randomized, placebo-controlled trials to assess the risk of renal adverse events in healthy subjects receiving TDF-containing PrEP.

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This meta-analysis was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[20] Detailed methods are provided in the Supplementary Appendix. We included randomized clinical trials evaluating daily TDF-based PrEP, alone or in combination with FTC. All studies used a graded elevation in serum creatinine as the primary measure of renal adverse events. Most studies used the National Institutes of Health Division of AIDS (DAIDS) toxicity table;[21] several studies modified the DAIDS definition (Supplementary Table 1). For the pooled analysis, we defined the endpoint as any Grade 1 or higher elevation in serum creatinine as reported by the study investigators. Analyses were based on the number of participants with at least one graded creatinine elevation, divided by the number at risk as defined by the study investigators. We also considered a modified intention to treat analysis including only HIV-negative participants who were dispensed at least one dose of study drug.

Data were analyzed using Stata 11 (Stata Corp LP) and RevMan 5 (The Cochrane Collaboration). We chose a conservative analytic approach using random effects due to differences in patient population, duration of PrEP exposure, loss-to-follow up and adherence, and frequency of creatinine assessment across studies. Results are expressed as the pooled odds ratio (OR); we re-expressed this result as number needed to harm to illustrate the magnitude of risk. Potential heterogeneity in the estimated effect of PrEP *versus* placebo was explored via random-effects meta-regression.

We identified 2657 potential articles, and 10 studies were eligible for inclusion (Supplementary Table 1 and Supplementary Figure 1). Analysis of publication quality is summarized in Supplementary Table 2. The included studies enrolled a total of 19,507 HIV-positive participants, including 17,220 participants randomized to daily oral PrEP (n=9913) *versus* placebo (n=7307). Eight studies followed participants for 12 months or longer, while two small studies followed participants for only 4 months. No individual study demonstrated a statistically significant difference in the odds of graded creatinine elevation between participants assigned to active PrEP *versus* placebo (Figure 1).

The majority of elevations were Grade 1 (1.1-1.3 x upper limit of normal, ULN) regardless of treatment assignment. Of the 352 participants assigned to daily active PrEP or placebo who experienced a graded creatinine elevation, only 23 experienced Grade 2 elevations (1.4-1.8 x ULN), including 16 assigned to PrEP and 7 to placebo. Eight participants experienced Grade 3 or 4 elevations (≥1.9 x ULN), 4 in each group; six of those participants were enrolled in a single study evaluating persons who inject drugs.[2]

Although we did not detect significant statistical heterogeneity across trials (I^2=0%, P= 0.51), we chose a conservative approach using random effects due to relevant differences between the studies. In meta-analysis, participants assigned to daily TDF-based PrEP *versus* placebo had a modestly increased risk of Grade 1 or higher creatinine events (pooled OR=1.36, 95% CI 1.09-1.71; Figure 1). The absolute risk increase was small (pooled risk increase 0.6%; 95% CI 0.1-1.2%), with a number needed to harm=167. In sensitivity analysis, excluding the study with the highest weight and highest number of events[14] reduced our statistical power, but resulted in a similar pooled estimate (pooled OR=1.40, 95% CI 1.05-1.88). Standardizing the number at risk across all studies to include only

participants who were HIV-negative at baseline and who were dispensed at least one dose of study drug also resulted in similar results (pooled OR=1.37, 95% CI 1.09-1.71). Finally, the results were similar using a fixed effects model (pooled OR=1.38, 95% CI 1.121-1.72).

We found no evidence of publication bias (Supplementary Figures 3 and 4). In meta-regression, there was no statistically significant heterogeneity across the studies due to variability in age, sex, follow-up time, or self-reported adherence (Supplementary Table 3).

In this meta-analysis of randomized trials, assignment to TDF-based PrEP was associated with a modest increase in the risk of graded creatinine events in HIV-negative individuals. Nonetheless, the absolute risk increase was small (number needed to harm 167), and the majority of events in these carefully monitored clinical trial participants were mild. Our findings are consistent with the results of secondary analyses reported by three trials of TDF-based PrEP, which demonstrated small but statistically significant declines in eGFR or CrCl in participants assigned to active PrEP.[17-19] The clinical significance of the declines in kidney function is unclear, as most were mild and self-limited or resolved after stopping PrEP.[17] Our findings expand on those studies by confirming that the small but significant effects observed in those studies are representative of the available renal safety data for daily oral PrEP.

In clinical practice, PrEP recipients may not be monitored as closely, and PrEP may be given to individuals with other risk factors for kidney disease, who were excluded from the clinical trials. Data on the risk of renal adverse events during implementation of PrEP will be important. In the interim, the decision to prescribe PrEP should weigh the small risk of kidney injury against the risk of HIV infection in a given individual. In a meta-analysis of PrEP efficacy including 6 of the 10 trials included in our analysis, the absolute risk reduction for HIV infection was 2.04% overall (number needed to treat 49).[22] The number needed to treat is even smaller among those at highest risk for HIV acquisition,[23,24] supporting a favorable risk: benefit ratio when PrEP is used by healthy individuals at substantial risk of acquiring HIV infection.

An important limitation of this analysis is the reliance on serum creatinine as the only indicator of kidney function. We were unable to evaluate the effect of PrEP on proximal tubulopathy, as comprehensive evaluation of proximal tubular function has been performed in only a small subset of PrEP trial participants to date.[17] Although serum phosphorus was routinely measured as a surrogate marker of proximal tubular function, the clinical relevance of mild hypophosphatemia is unclear because of the influence of dietary intake, intra-individual variability in results, and the overlap of DAIDS toxicity criteria with normal reference values for serum phosphorus. There are also differences in the serum creatinine assays used across studies, but these differences should have minimal impact on intra-individual variation in creatinine.[25]

All meta-analyses are subject to limitations of the original studies. Although not statistically significant, there was a high degree of heterogeneity between the studies with respect to patient population, duration of PrEP exposure, and frequency of creatinine assessment. These differences may explain some of the variability in event rates. Although self-reported

study drug adherence was high in all studies, pharmacological evidence of adherence ranged from 30% to 80% across studies.[3,5,13,14,16] Low adherence in some studies may have attenuated the risk of renal adverse events. Because objective measures of adherence were only available for a subgroup of participants, the current analysis is based on intention to treat. Finally, studies varied in defining the population at risk; pooled results were similar in a modified intention to treat analysis including only HIV-negative participants dispensed at least one dose of study drug.

Our results were similar using random effects and fixed effect models. Regardless of the model used, individual studies are assigned a weight inversely proportional to the within-study variance, such that the study with the most precise estimate of effect size is assigned the highest weight. The assignment of weights does not consider other relevant factors such as duration of exposure or adherence to study drug. Follow-up time and self-reported adherence did not contribute to significant heterogeneity in meta-regression, and removal of the study with the highest weight and lowest adherence[14] yielded similar results.

These results demonstrate a small increase in the relative and absolute risk of kidney injury with daily oral PrEP, which is outweighed by the more substantial reduction in risk of HIV infection in situations where PrEP is indicated. Experience with PrEP in individuals with traditional risk factors for kidney disease is limited, as individuals with hypertension, diabetes mellitus, or concomitant nephrotoxic medications were excluded. More frequent monitoring of kidney function is warranted in these groups until more data are available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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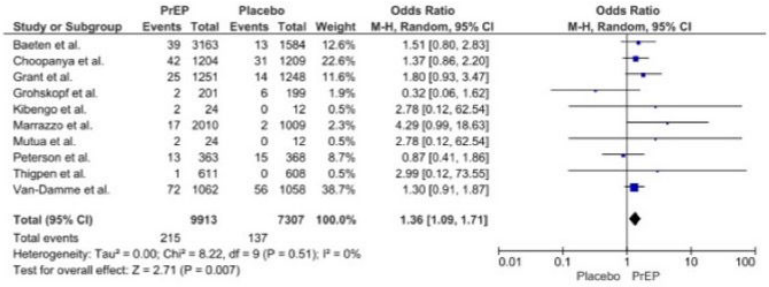

Figure 1.
Daily oral PrEP and graded creatinine events: forest plot