Supplementary Appendix

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Detailed Methods

This meta-analysis was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. We performed a computerized search to identify relevant published studies (January 2000 to March15, 2015). MEDLINE, the Cochrane Library, relevant scientific conferences (Conference on Retroviruses and Opportunistic Infections, Infectious Diseases Society of America ID Week, Interscience Conference of Antimicrobial Agents and Chemotherapy, STD Prevention Conference, and HIV Research for Prevention), and ClinicalTrials.gov and EMBASE databases were searched using medical subject heading (MeSH) terms and keywords. The search was not limited to English language or publication type, and references of each article were evaluated for relevant studies. MeSH terms and keywords were: “tenofovir”, “prophylaxis”, “prevention and control”, “pre-exposure prophylaxis”, “HIV”, “human immunodeficiency virus”. We included randomized clinical trials evaluating daily TDF-based PrEP, alone or in combination with FTC. Only daily oral use of PrEP was studied; study arms assigned to intermittent oral therapy or topical application were excluded. Four reviewers (RY, GN, IK, and AB) performed independent study selection in duplicate; CW evaluated and reviewed the selected studies independently and arbitrated disagreements. The final decision regarding inclusion of each study was made by consensus.

All studies used a graded elevation in serum creatinine as the primary measure of renal adverse events. Most studies used the definition recommended in the National Institutes of Health Division of AIDS (DAIDS) toxicity table, which defines Grade 1 elevation as a

creatinine ≥ 1.1 x upper limit of normal (ULN). Several studies modified the DAIDS definition to include increases from baseline creatinine and/or decline in CrCl below 50mL/min, and one study only reported creatinine events that were confirmed on a repeat blood draw (Table 1). For the purposes of 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 who experienced at least one graded creatinine elevation, divided by the number at risk. For consistency and to maintain the randomized comparison in studies that were terminated early, we truncated follow-up at the time of the primary efficacy analysis for each study and included events as reported in the primary publications; authors of studies (N=3) with incomplete data were contacted. Studies varied in how they defined the population at risk for safety analyses, with some studies including all randomized participants and others including only participants who were confirmed to be HIV seronegative at baseline and who were dispensed at least one dose of study drug. For the primary analysis, we used the number at risk as defined by the study investigators. In a sensitivity analysis, we 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) statistical programs. I^2 test was used to study heterogeneity; regardless of the results we planned a conservative analytic approach using random effects due to

the heterogeneous patient populations, different durations of PrEP exposure, differences in loss-to-follow up and adherence rates, and variable frequency of creatinine assessment across studies. Rather than assuming that the true effect size is the same across all studies ("fixed effect"), the random effects model assumes a distribution of effect sizes that varies across studies. In sensitivity analysis, we considered the impact of using a fixed effect model. The results were presented using forest plots and expressed as the pooled odds ratio (OR); we also re-expressed this result as the pooled risk increase/ number needed to harm to illustrate the magnitude of risk. A delta value of 0.5 was added in case of a zero count. We performed Egger precision-weighted linear regression as a statistical test of publication bias. Potential heterogeneity in estimates of effect of PrEP *versus* placebo across studies was explored via random-effects meta-regression using the method of residual maximum likelihood (REML) to estimate the additive (between-study) component of variance tau^2. Proportion of between-study variance was explained with Knapp-Hartung modification.

Table 1: Characteristics of included studies

Citation	Year	Countries	N, HIV-	Age, years	Male, %	Study drug**	Follow up, Months ***	Risk group	Definition of event	Creatinine measurement frequency
Marrazzo *et al.*[16]	2015	South Africa, Uganda, Zimbabwe	5029	25*	0%	Daily PO TDF, PO FTC/TDF, 1% vaginal tenofovir gel	12-36	Sexually active women	DAIDS Toxicity Table	At enrollment, month 1, and every 3 months thereafter
Choopanya *et al.*[2]	2013	Thailand	2413	32*	80%	Daily PO TDF	12-84	Injecting drug users	ICD-10	At enrollment, months 1, 2, and 3, and every 3 months thereafter
Grohskopf *et al.*[12]	2013	United States	400	38^	100%	Daily PO TDF, immediate or delayed start	24	MSM	DAIDS Toxicity Table, Modified (1)	At enrollment and every 3 months thereafter
Kibengo *et al.*[13]	2013	Uganda	72	33*	50%	Daily PO FTC/TDF, Intermittent PO FTC/TDF	4	Serodiscordant couples	DAIDS Toxicity Table	Monthly
Mutua *et al.*[11]	2012	Kenya	72	26*	93%	Daily PO FTC/TDF, Intermittent PO FTC/TDF	4	MSM, female sex workers	DAIDS Toxicity Table	Monthly
Baeten *et al.*[4]	2012	Kenya, Uganda	4747	35^	62%	Daily PO TDF, PO FTC/TDF	23^	Serodiscordant heterosexual couples	DAIDS Toxicity Table, Modified(2)	At month 1 and every three months thereafter
Thigpen *et al.*[5]	2012	Botswana	1219	91% <30	54%	Daily PO FTC/TDF	13^	Sexually active adults	DAIDS Toxicity Table	Every three months
Van Damme *et al.*[14]	2012	Kenya, South Africa, Tanzania	2120	24*	0%	Daily PO FTC/TDF	12	Sexually active women	DAIDS Toxicity Table	At enrollment and Weeks 4, 12, 24, 36, and 52
Grant *et al.*[3]	2010	Peru, Brazil, Ecuador, Thailand, South Africa, United States	2499	28*	100%	Daily PO FTC/TDF	14^	MSM, transgender women who have sex with men	DAIDS Toxicity Table, Modified (3)	At enrollment, weeks 4, 8, 12, 16, and 24 and every 12 weeks thereafter
Peterson *et al.*[15]	2007	Ghana, Cameroon, Nigeria	936	24*	0%	Daily PO TDF	12	Sexually active women	Increase > 0.5 mg/dL	At months 1, 3, 6, 9, 12

*Mean; ^Median

**Only participants assigned to daily oral PrEP or placebo were included in the meta-analysis.

***Follow-up time was converted to months for comparison across studies, and is reported as planned or observed (median^) time.

MSM, men who have sex with men; ICD-10, International Classification of Diseases, 10th Revision, Thai version;[26]DAIDS Toxicity Table, DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004. Modifications included: (1) Grade 1 defined as ≥0.5 mg/dLabove baseline;(2) Grade 1 also included any creatinine ≥ 1.5x baseline. Grade 2 also included creatinine clearance <50 mL/min. Only creatinine events confirmed on repeat blood testing were reported; (3) Grade 1 also included any creatinine> 1.5 x baseline.

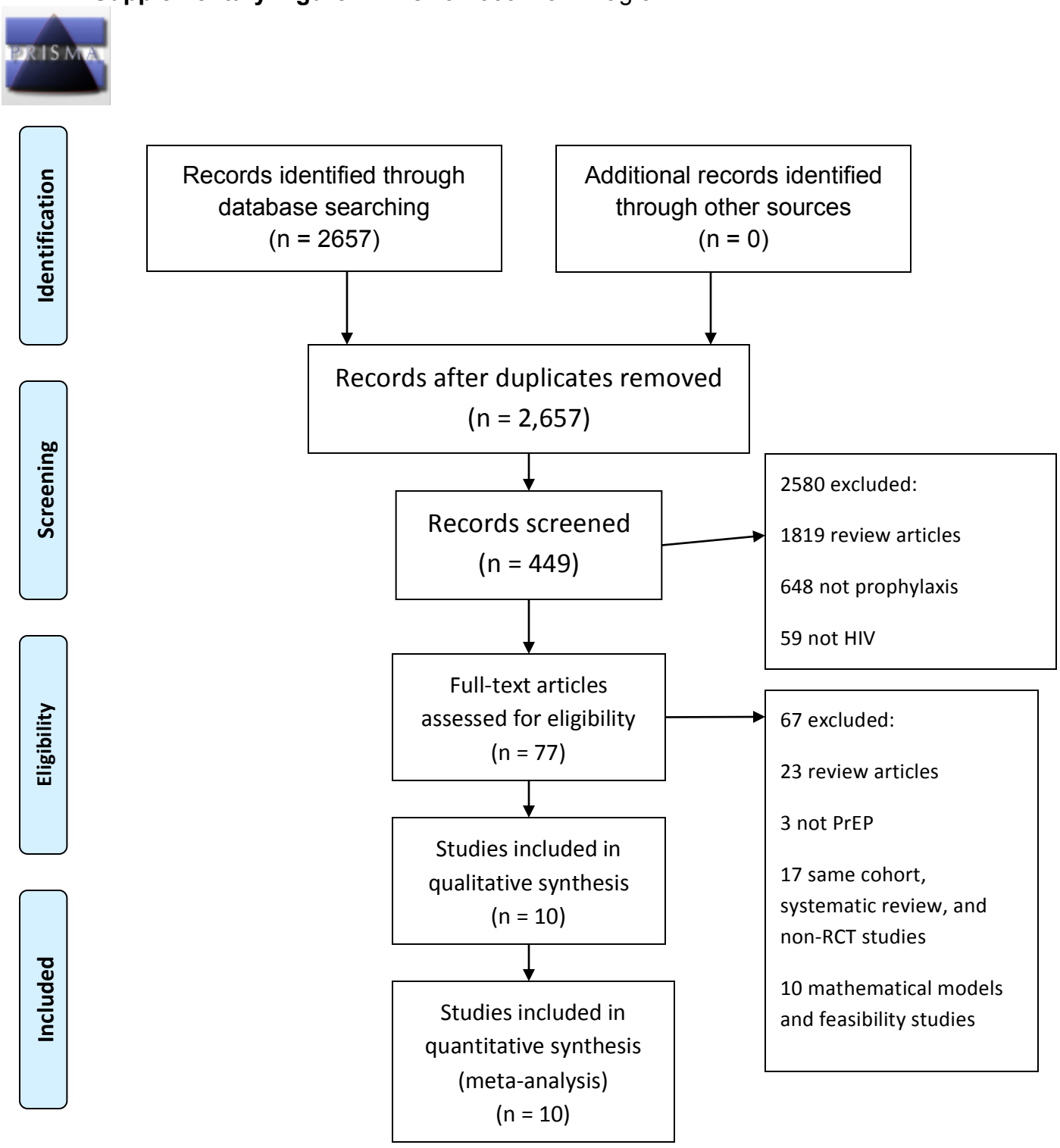
Supplementary Table 2: Cochrane Collaboration Tool for Assessing Risk of Bias

Study, Year	Sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Marrazzo, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Choopanya, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Grohskopf, 2013	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kibengo, 2013	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Mutua, 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Baeten, 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Thigpen, 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Van-Damme, 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Grant, 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Peterson, 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

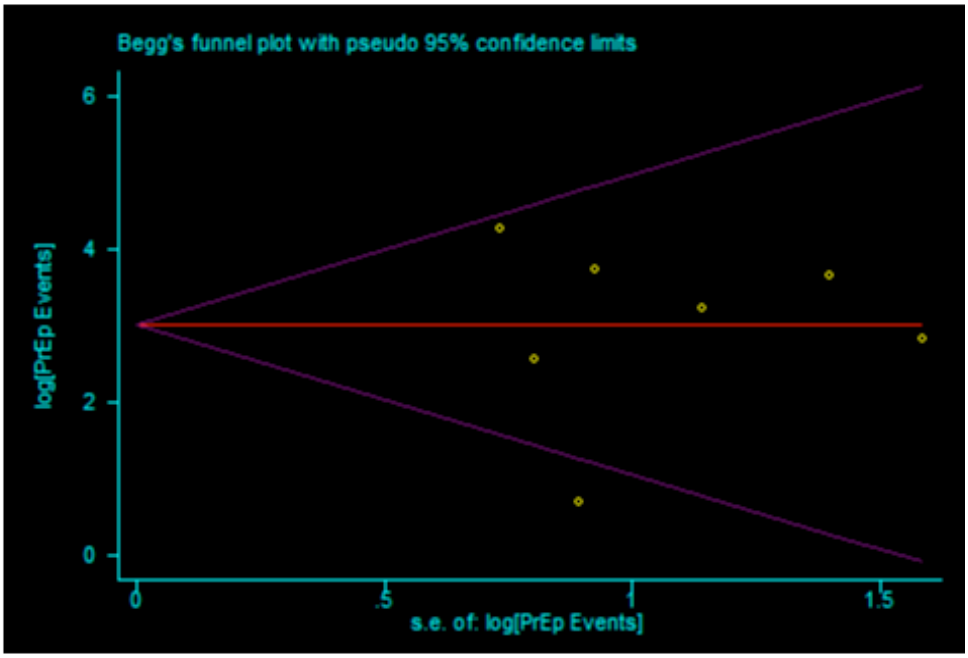
Supplementary Table 3: Meta-regression for Included Studies

Variable	Bias Coefficient	95% CI	P-value
Follow up (Months)	0.0006	From -0.019 to 0.02	0.94
Adherence	1.43	From -4.03 to 6.89	0.562
Age	-0.05	From -0.19 to 0.09	0.416
Male gender	0.09	From -0.61 to 0.81	0.758

Supplementary Figure 1. Prisma 2009 Flow Diagram



Supplementary Figure 2. Begg's funnel plot



Supplementary Figure 3. Egger's publication bias plot