Preexposure Prophylaxis for the Prevention of HIV Infection
Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Effective prevention strategies for HIV infection are an important public health priority. Preexposure prophylaxis (PrEP) involves use of antiretroviral therapy (ART) daily or before and after sex to decrease risk of acquiring HIV infection.

OBJECTIVE To synthesize the evidence on the benefits and harms of PrEP, instruments for predicting incident HIV infection, and PrEP adherence to inform the US Preventive Services Task Force.

DATA SOURCES Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and EMBASE through June 2018, with surveillance through January 2019.

STUDY SELECTION English-language placebo-controlled randomized clinical trials of oral PrEP with tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate monotherapy; studies on the diagnostic accuracy of instruments for predicting incident HIV infection; and studies on PrEP adherence.

DATA EXTRACTION AND SYNTHESIS Dual review of titles and abstracts, full-text articles, study quality, and data abstraction. Data were pooled using the Dersimonian and Laird random-effects model for effects of PrEP on HIV infection, mortality, and harms.

MAIN OUTCOMES AND MEASURES HIV acquisition, mortality, and harms; adherence to PrEP; and diagnostic test accuracy and discrimination.

RESULTS Fourteen RCTs (N = 18 837), 8 observational studies (N = 3884), and 7 studies of diagnostic accuracy (N = 32 279) were included. PrEP was associated with decreased risk of HIV infection vs placebo or no PrEP after 4 months to 4 years (11 trials; relative risk [RR], 0.46 [95% CI, 0.33-0.66]; I² = 67%; absolute risk reduction [ARD], −2.0% [95% CI, −2.8% to −1.2%]). Greater adherence was associated with greater efficacy (RR with adherence ≥70%, 0.27 [95% CI, 0.19-0.39]; I² = 0%) in 6 trials. PrEP was associated with an increased risk of renal adverse events (12 trials; RR, 1.43 [95% CI, 1.18-1.75]; I² = 0%; ARD, 0.56% [95% CI, 0.09%-1.04%]) and gastrointestinal adverse events (12 trials; RR, 1.63 [95% CI, 1.26-2.11]; I² = 43%; ARD, 1.95% [95% CI, 0.48%-3.43%]); most adverse events were mild and reversible. Instruments for predicting incident HIV infection had moderate discrimination (area under the receiver operating characteristic curve, 0.49-0.72) and require further validation. Adherence to PrEP in the United States in men who have sex with men varied widely (22%-90%).

CONCLUSIONS AND RELEVANCE In adults at increased risk of HIV infection, PrEP with oral tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP, although effectiveness decreased with suboptimal adherence.
Preexposure prophylaxis (PrEP) involves use of antiretroviral therapy regularly (eg, daily) or before and after possible HIV exposure events such as sex (“on-demand” or “event-driven”) to decrease risk of acquiring HIV infection. The purpose of this report was to synthesize the evidence on effects of PrEP on HIV acquisition risk, mortality, harms, and other clinical outcomes; effects of adherence on PrEP-associated outcomes; and accuracy of methods for identifying potential candidates for PrEP. It was used by the United States Preventive Services Task Force (USPSTF) to develop a new recommendation on PrEP for the prevention of HIV infection.

**Methods**

**Scope of the Review**
Detailed methods are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prevention-of-human-immunodeficiency-virus-hiv-infection-pre-exposure-prophylaxis. Figure 1 shows the analytic framework and key questions (KQs) that guided the review. The full report also includes contextual questions (not systematically reviewed) that addressed factors associated with PrEP adherence and rates of antiretroviral drug-resistant HIV in PrEP-treated individuals.

**Data Sources and Searches**
Ovid MEDLINE, the Cochrane Library, and EMBASE were searched for English-language articles published from inception through June 2018 (eMethods 1 in the Supplement). Searches were supplemented by review of reference lists of included studies. Since June 2018, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on January 25, 2019, and identified no eligible randomized trials.

**Study Selection**
Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. Randomized...
clinical trials (RCTs) of PrEP vs placebo or no PrEP in HIV-uninfected adults and adolescents (13-18 years) at higher risk for acquiring HIV were eligible for KQ1 and KQ5. Trials had to evaluate oral combination tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate monotherapy and report HIV infection, mortality, quality of life, or harms. Tenofovir disoproxil fumarate/emtricitabine is the only medication approved by the US Food and Drug Administration (FDA) and recommended for PrEP; tenofovir disoproxil fumarate monotherapy is an alternate regimen for people who inject drugs (PWID) and in persons at risk because of heterosexual behavior. Studies of the diagnostic accuracy of instruments to predict HIV acquisition in the United States or US-applicable settings were eligible for KQ2. United States–based RCTs and observational studies of PrEP implementation that reported adherence were eligible for KQ3 and KQ4.

Data Abstraction and Quality Rating
For each included study, 1 investigator abstracted information on populations, interventions or screening instruments, comparators, adherence, outcomes, study designs, and settings. A second investigator reviewed abstracted information for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement). Quality ratings for individual studies are provided in eTables 1-3 in the Supplement.

For all KQs, the overall strength of the body of evidence was assessed as high, moderate, low, or insufficient using methods developed for the USPSTF, based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias. The applicability of the findings to US primary care populations and settings was also assessed.

Data Synthesis
Meta-analysis was conducted to calculate pooled relative risks (RRs) for effects of PrEP vs placebo or no PrEP on HIV infection, mortality, and harms, using the DerSimonian and Laird random-effects model in Review Manager Version 5.3 (Cochrane Collaboration Nordic Cochrane Centre). Statistical heterogeneity was assessed using the $I^2$ statistic. When $I^2$ was greater than 30%, the analysis was also performed with the profile likelihood method using Stata/IC Version 13.1 (StataCorp). Results using the profile likelihood method were similar to those from the DerSimonian and Laird model and are not reported in this article. Sensitivity analyses and stratified analyses were conducted on study quality, PrEP regimen, HIV risk category, dosing schedule, study duration, and country. Stratified analyses were assessed for interactions using a test for heterogeneity across subgroups.

Sensitivity analyses were also conducted using data from the FDA medical review of PrEP7 on HIV incidence and fracture rates in place of data reported in journal articles when there were discrepancies. Results were very similar, and this article presents findings based on journal article data. Study-level adherence was assessed as a categorical variable in a stratified analysis ($\geq 70\%$, >40% to $<70\%$, or $\leq 40\%$) and as a continuous variable through meta-regression, and a plot of adherence against effectiveness (log RR) was constructed. For trials that used multiple adherence measurement methods, adherence data were selected using a prioritized list. For analyses with at least 10 trials, funnel plots were constructed and the Egger test conducted for small sample effects. All significance testing was 2-tailed; $P$ values of 0.05 or less were considered statistically significant.

Results
Across all KQs, 14 RCTs (in 37 articles11-47) (N = 18 837), 8 observational studies48-55 (N = 3884), and 7 studies of diagnostic accuracy of HIV risk prediction instruments56-62 (N = 32 279) were included (Figure 2). The main results for each key question are summarized below.

Benefits of PrEP
Key Question 1. What are the benefits of PrEP in individuals without preexisting HIV infection vs placebo or no PrEP on the prevention of HIV infection and quality of life?

Key Question 1a. How do the benefits of PrEP differ by population subgroups?

Key Question 1b. How do the benefits of PrEP differ by dosing strategy or regimen?

Twelve RCTs (reported in 33 publications11-44) evaluated PrEP vs placebo (11 trials12,14,17,18,21,27,31,33,39,40,42,43) or immediate vs delayed PrEP (1 trial31) (Table 1; eTables 4-6 in the Supplement). The trials enrolled between 72 and 4726 participants (total n = 18 244). The mean age in all trials was younger than 40 years. No trial enrolled pregnant women or people younger than 18 years. Duration of follow-up ranged from 4 months to 4 years.

All trials enrolled persons at increased risk for HIV infection. Six trials12,21,27,40,42,43 enrolled persons at increased risk because of heterosexual contact, 4 trials17,18,31,33 men who have sex with men or transgender women, 1 trial39 high-risk women and men who have sex with men, and 1 trial14 PWID. All trials of persons at increased risk because of heterosexual contact were conducted in Africa and the trial of PWID was conducted in Thailand; all trials conducted in the United States, Canada, and Europe focused on men who have sex with men.

Five trials12,14,17,18,27,43 evaluated tenofovir disoproxil fumarate monotherapy (300 mg), 8 trials12,17,21,27,33,39,40,42,43 tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg), and 1 trial41 tenofovir disoproxil fumarate (245 mg)/emtricitabine (200 mg). Eleven trials evaluated daily PrEP12,14,17,18,21,27,31,39,40,42,43 Dosing was intermittent or event-driven in 3 trials21,33,39 but only 1 reported results for event-driven (before and after sex) PrEP.33 In the other 2 trials, there were no HIV infections or results were combined with daily PrEP.21,39 In all trials, all patients received HIV risk reduction and adherence counseling. All trials provided free condoms, except for 1 trial39 that did not require it.

The adherence level, method for measuring adherence, and funding source of each trial are reported in Table 1. All trials were rated good quality except for 1 trial31 rated fair quality because of unclear allocation concealment methods and open-label design.

PrEP was associated with reduced risk of HIV infection vs placebo or no PrEP (11 trials [n = 18 712]; RR, 0.46 [95% CI, 0.33-0.66]), but statistical heterogeneity was present ($I^2 = 67\%$) (Figure 3).12,14,17,18,21,27,31,33,39,40,42,43 The absolute risk difference (ARD) was $-2.0\%$ (95% CI, −2.8% to −1.2%). Estimates were very similar.
(P = .79 for interaction) for PrEP with tenofovir disoproxil fumarate monotherapy (5 trials [n = 7546]; RR, 0.49 [95% CI, 0.28-0.84]; I² = 58%) or tenofovir disoproxil fumarate/emtricitabine (8 trials [n = 10,626]; RR, 0.44 [95% CI, 0.27-0.72]; I² = 74%). Funnel plot asymmetry was present (P = .03 by Egger test) (eFigure 1 in the Supplement).

A stratified analysis found a significant interaction (P < .001) between level of adherence (≤40%, >40 to <70%, or ≥70%) and effectiveness of PrEP; stratification by adherence eliminated statistical heterogeneity (Table 2, Figure 4). In 6 trials (n = 7328) with adherence 70% or greater, the RR was 0.27 (95% CI, 0.19-0.39; I² = 0%). There was also a strong association between effectiveness and adherence analyzed as a continuous variable (P < .001) (eFigure 2 in the Supplement), which accounted for all of the between-study heterogeneity. Findings were similar when analyses were restricted to trials that evaluated adherence based on plasma levels.

PrEP was effective across HIV risk categories (persons at risk because of heterosexual contact, men who have sex with men, or PWID; P = .43 for interaction) (Table 2). Four trials found similar PrEP effectiveness in subgroups defined by age, and 3 trials found similar effectiveness in male and female participants (eTable 7 in the Supplement). Few trials examined the interaction between presence of risk behaviors and effectiveness of PrEP, the risk behaviors examined in these trials varied (receptive anal intercourse, condomless sex, drug injection or needle sharing), and effectiveness of PrEP did not consistently vary according to presence of risk behaviors.

Estimates were similar when trials were stratified according to duration of follow-up, when the analysis was restricted to good-quality trials, or when trials were stratified according to whether they reported some industry support (usually donated study drugs) (Table 2). The estimate from 1 trial (n = 400) of event-driven PrEP (RR, 0.14 [95% CI, 0.03-0.63]) was similar to the pooled estimate from daily-dosing trials that reported high adherence (5 trials [n = 6928]; RR, 0.28 [95% CI, 0.20-0.41]). In this trial, men who have sex with men randomized to PrEP took a median of about 4 doses of PrEP per week (15 doses per month) based on pill counts. PrEP was more effective in trials conducted in the United States, Europe, or Canada (3 trials [n = 1323]; RR, 0.13 [95% CI, 0.05-0.32]; I² = 0%) than in trials conducted in Africa, Asia,
<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Duration of Follow-up</th>
<th>Interventions</th>
<th>HIV Risk Group; Risk-Based Inclusion Criteria</th>
<th>Patient Characteristics</th>
<th>Adherence, % (Method Used to Assess Adherence)</th>
<th>Quality</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>Thailand</td>
<td>4 y (mean)</td>
<td>A. Tenofovir disoproxil fumarate (300 mg) (n = 1204) B. Placebo (n = 1209)</td>
<td>PWID: Injection drug use in the previous 12 mo</td>
<td>A vs B: Age 20-29 y: 43% vs 43% Age 30-39 y: 38% vs 37% Age 40-49 y: 15% vs 13% Age 50-60 y: 5% vs 5% Men: 80% vs 80% Race: NR</td>
<td>67 (plasma) Good</td>
<td>CDC; Bangkok Metropolitan Administration</td>
<td></td>
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<tr>
<td>CDC Safety Study</td>
<td>United States</td>
<td>2 y</td>
<td>A. Tenofovir disoproxil fumarate (300 mg) (n = 201) B. Placebo (n = 199)</td>
<td>MSM: Biological male engaging in anal sex with another man in the previous 12 mo</td>
<td>A vs B: Mean age: 38 vs 37 y White: 76.9% vs 66.8% African American: 23% vs 37% Asian/Pacific Islander: 10% vs 4% Other race: 8% vs 25%</td>
<td>92 (pill count) Good</td>
<td>US Department of Health and Human Services; CDC</td>
<td></td>
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<tr>
<td>FEM PrEP</td>
<td>Kenya, South Africa, Tanzania</td>
<td>1 y</td>
<td>A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 1062) B. Placebo (n = 1058)</td>
<td>High-risk women: &gt;1 vaginal sex act in previous 2 wk or &gt;1 sex partner in previous mo</td>
<td>A vs B: Mean age: 24 vs 24 y Race: NR</td>
<td>37 (plasma) Good</td>
<td>USAID; Bill and Melinda Gates Foundation; Gilead Sciences (provided study drug)</td>
<td></td>
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<tr>
<td>IAVI Uganda Study</td>
<td>Uganda</td>
<td>4 mo</td>
<td>A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 24) B. Intermittent tenofovir disoproxil fumarate/emtricitabine (n = 24) C. Daily placebo (n = 12) D. Intermittent placebo (n = 12)</td>
<td>High-risk heterosexual men and women: Unprotected vaginal sex with ART-naive HIV-infected partner in the previous 3 mo</td>
<td>A vs B vs C vs D: Mean age: 33 vs 33 vs 33 vs 33 y Women: 50% vs 46% vs 67% vs 42% Race: NR</td>
<td>98 (MEMS) Good</td>
<td>IAVI; Gilead Sciences (provided study drug)</td>
<td></td>
</tr>
<tr>
<td>IAVI Kenya Study</td>
<td>Kenya</td>
<td>4 mo</td>
<td>A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 24) B. Intermittent tenofovir disoproxil fumarate/emtricitabine (n = 24) C. Daily placebo (n = 12) D. Intermittent placebo (n = 12)</td>
<td>MSM and high-risk women: Current or previous STI, multiple episodes of unprotected vaginal or anal sex, or engaging in transactional sex in the previous 3 mo</td>
<td>A vs B vs C vs D: Mean age: 26 vs 26 vs 27 vs 28 y Women: 12% vs 0% vs 8% vs 8% Race: NR</td>
<td>82 (MEMS) Good</td>
<td>IAVI; Gilead Sciences (provided study drug)</td>
<td></td>
</tr>
<tr>
<td>IPERGAY</td>
<td>France, Canada</td>
<td>9 mo (median)</td>
<td>A. On-demand tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 201)</td>
<td>MSM: Unprotected anal sex with ≥2 partners in previous 6 mo</td>
<td>A vs B: Mean age: 35 vs 34 y (IQR, 29–43) White: 94% vs 89% Other races: NR</td>
<td>86 (plasma) Good</td>
<td>ANRS; Canadian HIV Trials Network; Fonds de Dotation Pierre Berge pour la Prevention; Bill and Melinda Gates Foundation</td>
<td></td>
</tr>
<tr>
<td>iPrEx</td>
<td>Brazil, Ecuador, Peru, Thailand, South Africa, United States</td>
<td>1.2 y (median)</td>
<td>A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 1251) B. Placebo (n = 1248)</td>
<td>MSM: Anal sex with ≥4 male partners, a diagnosis of STI, history of transactional sex activity, condomless anal sex with an HIV-infected partner or of unknown infection status in previous 6 mo</td>
<td>A vs B: Age 18-24 y: 47% vs 53% Age 25-29 y: 22% vs 19% Age 30-33 y: 20% vs 18% Age ≥40 y: 11% vs 10% Born male: 100% vs 100% Black: 9% vs 8% White: 18% vs 17% Mixed race or other: 68% vs 70% Asian: 5% vs 5% Hispanic: 72% vs 73%</td>
<td>51 (plasma) Good</td>
<td>NIH; Bill and Melinda Gates Foundation</td>
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</table>

(continued)
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<thead>
<tr>
<th>Source*</th>
<th>Country</th>
<th>Duration of Follow-up</th>
<th>Interventionsb</th>
<th>HIV Risk Group; Risk-Based Inclusion Criteria</th>
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<th>Quality</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP Baeten et al,12 2012</td>
<td>Kenya, Uganda</td>
<td>2 y (median)</td>
<td>A. Tenofovir disoproxil fumarate (300 mg) + placebo tenofovir disoproxil fumarate/emtricitabine (n = 1571)</td>
<td>B. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) + placebo tenofovir disoproxil fumarate (n = 1565)</td>
<td>C. Placebo tenofovir disoproxil fumarate + placebo tenofovir disoproxil fumarate/emtricitabine (n = 1570)</td>
<td>High-risk heterosexual men and women: ART-naive HIV-infected partner</td>
<td>A vs B vs C</td>
<td>82 (plasma)</td>
</tr>
<tr>
<td>PROUD McCormack et al,11 2016</td>
<td>England</td>
<td>1 y</td>
<td>A. Immediate tenofovir disoproxil fumarate/emtricitabine (245/200 mg) (n = 275)</td>
<td>B. Tenofovir disoproxil fumarate/emtricitabine deferred for 1 y (n = 269)</td>
<td>MSM: Anal intercourse without a condom in the previous 90 d and likely to have anal intercourse without a condom in the next 90 d</td>
<td>A vs B</td>
<td>Mean age: 35 vs 35 y</td>
<td>White: 81% vs 83%</td>
</tr>
<tr>
<td>Study of TDF Peterson et al,40 2007</td>
<td>Cameroon, Ghana, Nigeria</td>
<td>6 mo (mean)</td>
<td>A. Tenofovir disoproxil fumarate (300 mg) (n = 469)</td>
<td>B. Placebo (n = 467)</td>
<td>High-risk women: Mean of ≥3 coital acts per wk and ≥4 sexual partners per mo</td>
<td>A vs B</td>
<td>Mean age: 24 vs 24 y</td>
<td>Race: NR</td>
</tr>
<tr>
<td>TDF2 Thigpen et al,42 2012</td>
<td>Botswana</td>
<td>1 y (median)</td>
<td>A. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) (n = 611)</td>
<td>B. Placebo (n = 608)</td>
<td></td>
<td>A vs B</td>
<td>Age 18-20 y: 2% vs 3%</td>
<td>Age 21-29 y: 90% vs 87%</td>
</tr>
<tr>
<td>VOICE Marrazzo et al,27 2015</td>
<td>South Africa, Uganda, Zimbabwe</td>
<td>3 y (maximum)</td>
<td>A. Tenofovir disoproxil fumarate (300 mg) + placebo (n = 1007)</td>
<td>B. Tenofovir disoproxil fumarate/emtricitabine (300/200 mg) + placebo (n = 1003)</td>
<td>C. Placebo only (n = 1009)</td>
<td>High-risk women: Sexually active in a high-prevalence area</td>
<td>A vs B vs C</td>
<td>Mean age: 26 vs 25 vs 25 y</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; FEM-PrEP, PrExposure Prophylaxis trial for HIV Prevention Among African Women; IAVI, International AIDS Vaccine Initiative; IPERGAY, Intervention Préventive de l’Exposition aux Risques avec et pour les GAYs, iPrEx, Pre-Exposure Prophylaxis Initiative; MEMS, medication event monitoring system; MSM, men who have sex with men; NIH, National Institutes of Health; NR, not reported; PrEP, pre-exposure prophylaxis; PROUD, Pre-exposure Option for Reducing HIV in the UK: immediate or Deferred; PWID, people who inject drugs; STI, sexually transmitted infection; TDF2, Tenofovir Disoproxil Fumarate 2 study;

USAID, United States Agency for International Development; VOICE, Vaginal and Oral Interventions to Control the Epidemic.


b Daily, oral dose unless specified.

c Sample of patient who reported that they were taking PrEP.
The area of each square represents the weight given to the study in the meta-analysis. The area of each diamond represents the sample size for each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate. The Mantel-Haenszel method was used to calculate the heterogeneity for each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate.

Diagnostic Accuracy of Risk Assessment Tools

Key Question 2. What is the diagnostic accuracy of provider or patient risk assessment tools in identifying individuals at increased risk of HIV acquisition who are candidates for PrEP?

Seven studies evaluated instruments developed and validated in US cohorts for predicting incident HIV infection66-68 (eTables 8-9 in the Supplement). Six studies evaluated men who have sex with men66-68,69,70 and 1 study evaluated PWID.65 Sample sizes (including development and validation cohorts) ranged from 300 to 9481 patients (total n = 32 311). Methodological shortcomings included application of risk instruments to previously collected data, evaluation of older (before 2000) cohorts, failure to validate accuracy in a separate (nondevelopment) cohort, and failure to predefine positive test thresholds.66-68

For men who have sex with men, studies evaluated the predictive utility of 4 different instruments (number of criteria ranged from 4 to 10). For 3 instruments (n = 20 064), discrimination was similar, with area under the receiver operating characteristic (AUROC) curves in the original validation cohorts ranging from 0.66 to 0.72.57-59 A fourth study (n = 9481)56 found a 10-item instrument associated with better goodness of fit than 2 of these instruments58,59 but did not report AUROC values and did not validate findings in a separate (nondevelopment) sample. The initial development and validation cohorts used to develop these instruments primarily consisted of white men who have sex with men. Two subsequent studies (n = 862) reported poorer discrimination in black men who have sex with men, with AUROC values ranging from 0.49 to 0.63.60,61 A 7-item instrument for predicting risk in PWID reported an AUROC value of 0.72 (CI not reported) in a cohort of 1904 primarily (93%) black participants.65 This instrument was not evaluated in a separate validation cohort.

No study evaluated a US-applicable instrument for predicting risk in HIV infection in persons at risk of HIV infection due to heterosexual contact. Instruments for predicting risk in women were developed using African cohorts.63-65

or internationally (8 trials [n = 16 849]; RR, 0.54 [95% CI, 0.37-0.79];  I² = 72%; P = .004 for interaction). All trials conducted in the United States, Europe, or Canada reported high adherence and enrolled men who have sex with men.

Associations of PrEP vs placebo or no PrEP with mortality did not meet the threshold for statistical significance (9 trials [n = 17 744]; RR, 0.81 [95% CI, 0.59-1.11];  I² = 0%).12,14,17,21,27,31,40,42,43 Individual trials reported few mortality events and risk estimates were imprecise (eFigure 3 in the Supplement). No trial reported effects of PrEP on quality of life.
PrEP Adherence

Key Question 3. What are rates of adherence to PrEP in US primary care–applicable settings?

Ten studies evaluated rates of adherence to PrEP in US primary care and primary care–applicable settings (eTable 10 in the Supplement).18,46-50,52-55 The studies enrolled between 20 and 1086 study participants (total n = 3177), and duration of PrEP use ranged from 6 months to 2 years. One study was rated good quality18 and the others were rated fair quality.

Three observational studies of US men who have sex with men (mean age, 34-36 years; n = 908) found adherence to PrEP of 66% to 90%, based on a tenofovir diphosphate level of 700 fmol/punch or greater on dried blood sampling (consistent with /H11350 4 doses/wk).52-54 Using the same measure, 2 observational studies of younger US men who have sex with men (mean age, 16-20 years; n = 272) found adherence to PrEP of approximately 50% at 12 weeks and 22% to 34% at 48 weeks.49,50 An RCT (n = 179) of primarily (97%) US men who have sex with men found adherence was higher with daily (48%) than with intermittent (31%) or event-driven (17%) PrEP during weeks in which sex was reported.46 No study evaluated PrEP adherence rates in US PWID or persons at increased risk of HIV infection due to heterosexual contact.

Key Question 4. What is the association between adherence to PrEP and effectiveness for preventing HIV acquisition?

Three RCTs (n = 5591) found PrEP associated with greater effectiveness compared with placebo for reducing risk of HIV infection among participants having higher adherence to daily PrEP based on daily pill counts or daily diaries, compared with participants having lower adherence (eTable 11 in the Supplement).12,14,16,17,29 Four of 5 RCTs (n = 6013) found that among participants randomized to PrEP, presence of tenofovir in plasma samples was associated with decreased likelihood of HIV infection compared with no detectable tenofovir.12,14,16,27,29,42,43 Five studies (n = 1138)33,49,50,52,54 found that all participants with seroconversion receiving PrEP had undetectable plasma levels of tenofovir or levels consistent with low adherence. The number of participants with seroconversion in each study was small (1 to 4 patients per study).

Harms of PrEP

Key Question 5. What are the harms of PrEP vs placebo or no PrEP when used for the prevention of HIV infection?

Table 2. Risk of HIV Infection in Randomized Clinical Trials of PrEP vs Placebo or No PrEP

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>RR (95% CI)</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>11,12,14,17,18,19,27,31,33,39,40,42,43</td>
<td>0.46 (0.33-0.66)</td>
</tr>
<tr>
<td>Restricted to good-quality trials</td>
<td>10,12,14,17,18,27,33,39,40,42,43</td>
<td>0.48 (0.33-0.71)</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .79 for interaction)</td>
<td></td>
<td></td>
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<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>5,12,14,18,27,40</td>
<td>0.49 (0.28-0.84)</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>8,12,17,27,31,33,39,40,43</td>
<td>0.44 (0.27-0.72)</td>
</tr>
<tr>
<td>Adherence, % (P &lt; .001 for interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>6,12,18,31,33,39,42</td>
<td>0.27 (0.19-0.39)</td>
</tr>
<tr>
<td>&gt;40 to &lt;70</td>
<td>14,17,40</td>
<td>0.51 (0.38-0.70)</td>
</tr>
<tr>
<td>≤40</td>
<td>27,43</td>
<td>0.93 (0.72-1.20)</td>
</tr>
<tr>
<td>HIV risk category (P = .43 for interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>5,12,27,40,42,43</td>
<td>0.54 (0.31-0.97)</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>17,18,31,33</td>
<td>0.23 (0.08-0.62)</td>
</tr>
<tr>
<td>People who inject drugs</td>
<td>14</td>
<td>0.52 (0.29-0.92)</td>
</tr>
<tr>
<td>Dosing schedule (P = .13 for interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>9,12,14,17,18,27,31,39,40,42,43</td>
<td>0.47 (0.32-0.71)</td>
</tr>
<tr>
<td>On-demand</td>
<td>13</td>
<td>0.14 (0.03-0.63)</td>
</tr>
<tr>
<td>Duration of follow-up, y (P = .35 for interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>3,39,40</td>
<td>0.21 (0.07-0.58)</td>
</tr>
<tr>
<td>≥1-2</td>
<td>17,31,42,43</td>
<td>0.48 (0.28-0.84)</td>
</tr>
<tr>
<td>≥2</td>
<td>12,14,18,27</td>
<td>0.47 (0.22-1.00)</td>
</tr>
<tr>
<td>Study-reported support (P = .38 for interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry</td>
<td>3,39,42,43</td>
<td>0.58 (0.27-1.22)</td>
</tr>
<tr>
<td>Government or not-for-profit funding only</td>
<td>12,14,17,18,27,31,33,40</td>
<td>0.39 (0.23-0.64)</td>
</tr>
<tr>
<td>Country setting (P = .004 for interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States or other high-income countries</td>
<td>3,18,31,33</td>
<td>0.13 (0.05-0.32)</td>
</tr>
<tr>
<td>Africa, Asia, or international trial</td>
<td>8,12,14,17,27,39,40,42,43</td>
<td>0.54 (0.37-0.79)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PrEP, preexposure prophylaxis; RR, relative risk.
There was no significant difference between PrEP vs placebo in risk of serious adverse events (12 trials [n = 18 282]; RR, 0.93 [95% CI, 0.77-1.12]; I^2 = 56%) (Table 3; eFigure 4 in the Supplement).12,17,31,42,43 All of the trials except 1 were blinded, which could attenuate sexual risk behaviors associated with use of PrEP. One open-label trial (n = 544), which enrolled men who have sex with men, found no statistically significant associations between PrEP vs no PrEP and risk of bacterial sexually transmitted infections (STIs), although estimates for syphilis (RR, 1.28 [95% CI, 0.76-2.16]) and chlamydia (RR, 1.32 [95% CI, 0.98-1.79]) may have been underpowered.31 There was no significant difference between PrEP vs placebo in risk of herpes simplex virus infection (3 trials [n = 4088]; RR, 0.85 [95% CI, 0.67-1.07]; I^2 = 19%)26,42,66 or hepatitis C virus infection (2 trials [n = 896]; RR, 0.73 [95% CI, 0.25-2.10]; I^2 = 0%).31,33

There were no significant differences between PrEP vs placebo or no PrEP in risk of gonorrhea, chlamydia, or syphilis (Table 3).12,17,31,42,43 All of the trials except 1 were blinded, which could attenuate sexual risk behaviors associated with use of PrEP. One open-label trial (n = 544), which enrolled men who have sex with men, found no statistically significant associations between PrEP vs no PrEP and risk of bacterial sexually transmitted infections (STIs), although estimates for syphilis (RR, 1.28 [95% CI, 0.76-2.16]) and chlamydia (RR, 1.32 [95% CI, 0.98-1.79]) may have been underpowered.31 There was no significant difference between PrEP vs placebo in risk of herpes simplex virus infection (3 trials [n = 4088]; RR, 0.85 [95% CI, 0.67-1.07]; I^2 = 19%)26,42,66 or hepatitis C virus infection (2 trials [n = 896]; RR, 0.73 [95% CI, 0.25-2.10]; I^2 = 0%).31,33

No trial of PrEP enrolled pregnant women. In women withdrawn from PrEP trials because of pregnancy, PrEP was not associated with increased risk of spontaneous abortion (RR, 1.09 [95% CI, 0.79-1.50]; I^2 = 0%) (Figure 9 in the Supplement).21,34,43 The Partners PrEP trial (n = 4706) found no significant differences between PrEP vs placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality, and the FEM-PrEP trial
Table 3. Adverse Events and Sexually Transmitted Infections in Randomized Clinical Trials of PrEP vs Placebo/No PrEP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Trials</th>
<th>RR (95% CI)</th>
<th>( I^2, % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>12</td>
<td>0.93 (0.77-1.12)</td>
<td>56</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .23 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>5</td>
<td>0.79 (0.56-1.12)</td>
<td>72</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>9</td>
<td>1.02 (0.81-1.30)</td>
<td>46</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>4</td>
<td>1.25 (0.99-1.59)</td>
<td>0</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .67 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>1</td>
<td>1.00 (0.34-2.92)</td>
<td>NA</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>4</td>
<td>1.27 (1.00-1.59)</td>
<td>0</td>
</tr>
<tr>
<td>Fracture</td>
<td>8</td>
<td>1.23 (0.97-1.56)</td>
<td>0</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .50 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>4</td>
<td>1.29 (0.98-1.70)</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>6</td>
<td>1.06 (0.66-1.72)</td>
<td>0</td>
</tr>
<tr>
<td>Renal adverse events</td>
<td>12</td>
<td>1.43 (1.18-1.75)</td>
<td>0</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .31 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>5</td>
<td>1.24 (0.87-1.76)</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>9</td>
<td>1.54 (1.21-1.96)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal adverse events</td>
<td>12</td>
<td>1.63 (1.26-2.11)</td>
<td>43</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .30 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>5</td>
<td>1.45 (1.13-1.85)</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>9</td>
<td>1.84 (1.26-2.70)</td>
<td>49</td>
</tr>
<tr>
<td>Any bacterial sexually transmitted infection</td>
<td>2</td>
<td>1.14 (0.97-1.34)</td>
<td>16</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .60 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>1</td>
<td>1.21 (0.86-1.72)</td>
<td>NA</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>2</td>
<td>1.07 (0.80-1.44)</td>
<td>58</td>
</tr>
<tr>
<td>HIV risk category (P = .38 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>1</td>
<td>1.05 (0.82-1.35)</td>
<td>NA</td>
</tr>
<tr>
<td>MSM</td>
<td>1</td>
<td>1.20 (1.01-1.42)</td>
<td>NA</td>
</tr>
<tr>
<td>Syphilis</td>
<td>4</td>
<td>1.08 (0.98-1.18)</td>
<td>0</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .86 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>2</td>
<td>1.13 (0.66-1.93)</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>4</td>
<td>1.07 (0.98-1.18)</td>
<td>0</td>
</tr>
<tr>
<td>HIV risk category (P = .90 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>2</td>
<td>1.05 (0.71-1.54)</td>
<td>0</td>
</tr>
<tr>
<td>MSM</td>
<td>2</td>
<td>1.08 (0.98-1.18)</td>
<td>0</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>5</td>
<td>1.07 (0.82-1.39)</td>
<td>49</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>1</td>
<td>0.57 (0.33-0.98)</td>
<td>NA</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>5</td>
<td>1.15 (0.97-1.37)</td>
<td>2</td>
</tr>
<tr>
<td>HIV risk category (P = .59 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>3</td>
<td>1.20 (0.76-1.92)</td>
<td>69</td>
</tr>
<tr>
<td>MSM</td>
<td>2</td>
<td>1.05 (0.85-1.30)</td>
<td>0</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>5</td>
<td>0.97 (0.80-1.18)</td>
<td>59</td>
</tr>
<tr>
<td>PrEP drug regimen (P = .004 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>1</td>
<td>0.68 (0.52-0.90)</td>
<td>NA</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate/emtricitabine</td>
<td>5</td>
<td>1.07 (0.94-1.22)</td>
<td>0</td>
</tr>
<tr>
<td>HIV risk category (P = .46 for interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>3</td>
<td>0.81 (0.47-1.41)</td>
<td>93</td>
</tr>
<tr>
<td>MSM</td>
<td>2</td>
<td>1.09 (0.62-1.92)</td>
<td>50</td>
</tr>
</tbody>
</table>
on trials with relatively brief follow-up. Although there was no association between PrEP and increased risk of bacterial STIs, most trials blinded patients to PrEP allocation, and sexual risk behaviors might differ in persons who know they are taking PrEP. A systematic review of an open-label RCT and nonrandomized studies found PrEP associated with an increased risk of rectal chlamydia (4 studies; odds ratio, 1.59 [95% CI, 1.19-2.13]) but found no association between PrEP and risk of chlamydia at any site. STIs overall, syphilis, or gonorrhea. Individuals who engage in riskier behaviors may be more adherent to PrEP, which could offset any adverse behavioral effects.

The findings of this review are generally consistent with those from other recent meta-analyses that found PrEP to be effective at reducing risk of HIV infection and found greater effectiveness in trials reporting higher adherence. The findings are strengthened by the inclusion of recent large new trials, including the only trial of event-driven PrEP and an open-label pragmatic trial.

Data on effects of PrEP in pregnancy were very limited. Trials excluded pregnant women and discontinued PrEP at the time pregnancy was confirmed. FDA labeling information and perinatal antiretroviral treatment guidelines permit use of tenofovir disoproxil fumarate/emtricitabine during pregnancy, although guidelines note that data on safety of PrEP during pregnancy and lactation are limited.

For predicting incident HIV infection, several instruments in men who have sex with men and 1 instrument in PWID were associated with moderate discrimination, but studies had methodological shortcomings. Discrimination was poorer in some studies of black men who have sex with men, and all instruments require further validation. Instruments for predicting risk of HIV infection in women were developed using African cohorts.

Research is needed to directly compare effects of daily vs alternative PrEP dosing strategies in studies adequately powered to assess effects on HIV infection; to verify the effectiveness of PrEP in high-income settings in persons at higher risk because of heterosexual contact and PWID; to determine the safety and effectiveness of PrEP during pregnancy and lactation and in transgender women and men; to understand effectiveness and long-term safety in adolescents; to understand effects of PrEP on quality of life; to understand effects of PrEP on behavioral risk compensation using open-label studies; to develop accurate instruments for identifying persons at higher risk for acquiring HIV infection; and to determine methods for increasing uptake and adherence to PrEP, to optimize effectiveness. Research on a number of alternative PrEP drugs and regimens is ongoing.
Table 4. Summary of Evidence

<table>
<thead>
<tr>
<th>KQ1: Benefits of PrEP vs Placebo or No PrEP</th>
<th>HIV infection</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 RCTs (n = 18 244)</td>
<td>HIV infection</td>
<td>9 RCTs (n = 17 756)</td>
</tr>
<tr>
<td>Consistency/Precision; Reporting Bias:</td>
<td>Consistent; imprecise</td>
<td>Consistent; imprecise</td>
</tr>
<tr>
<td>Overall Quality: Good</td>
<td>No reporting bias detected</td>
<td>No reporting bias detected</td>
</tr>
<tr>
<td>Body of Evidence Limitations: Good</td>
<td>See Body of Evidence Limitations column for KQ1, HIV infection</td>
<td>See Body of Evidence Limitations column for KQ1, HIV infection</td>
</tr>
<tr>
<td>EPC Assessment of Strength of Evidence for KQ: High</td>
<td>Studies of women and men at increased risk of heterosexual contact conducted in Africa; the only study of PWID was conducted in Asia; several studies of MSM were conducted in the United States, Europe, and Canada (all of these trials reported high adherence and enrolled MSM)</td>
<td></td>
</tr>
<tr>
<td>Applicability: Moderate</td>
<td>See Applicability column for KQ1, HIV infection</td>
<td></td>
</tr>
</tbody>
</table>

**KQ1a: Benefits of PrEP by Population Subgroups**

| HIV infection | 12 RCTs (n = 18 244) |
| STRATIFIED BY RISK CATEGORY (P = .43 for interaction) | HIV infection |
| MSM: 4 trials; RR, 0.23 (95% CI, 0.08-0.62); I² = 64% | 9 RCTs (n = 17 756) |
| PWID: 1 trial; RR, 0.52 (95% CI, 0.29-0.92) | Consistent; imprecise |
| Heterosexual contact: 5 trials; RR, 0.54 (95% CI, 0.31-0.97); I² = 82% | No reporting bias detected |
| No significant differences within-study subgroup analyses by age (4 trials) or sex (3 trials) | See Body of Evidence Limitations column for KQ1, HIV infection |
| EPC Assessment of Strength of Evidence for KQ: Moderate | Studies of women and men at increased risk of heterosexual contact conducted in Africa; the only study of PWID conducted in Asia; several studies of MSM conducted in the United States, Europe, and Canada |

**KQ1b: Benefits of PrEP by Dosing Strategy or Regimen**

| HIV infection | 12 RCTs of PrEP vs placebo or no PrEP (n = 18 172); 1 RCT of daily vs intermittent or on-demand PrEP (n = 535) |
| STRATIFIED BY TENOFOVIR DISOPROXIL FUumarate or TENOFOVIR DISOPROXIL FUumarate/EMTRICITABINE (P = .65 for interaction) | HIV infection |
| TENOFOVIR DISOPROXIL FUumarate: 5 trials; RR, 0.49 (95% CI, 0.28-0.84); I² = 74% | Consistent; imprecise |
| TENOFOVIR DISOPROXIL FUumarate/EMTRICITABINE: 8 trials; RR, 0.44 (95% CI, 0.27-0.72); I² = 74% | No reporting bias detected |
| Stratified by daily or on-demand dosing (P = .13 for interaction) | See Body of Evidence Limitations column for KQ1, HIV infection |
| Daily dosing: 9 trials; RR, 0.47 (95% CI, 0.32-0.71); I² = 75% | High for tenofovir disoproxil fumarate or tenofovir disoproxil fumarate/emtricitabine, moderate for daily dosing vs on-demand dosing |
| On-demand dosing: 1 trial; RR, 0.14 (95% CI, 0.03-0.63) | Five trials evaluated tenofovir disoproxil fumarate monotherapy, which is not approved for PrEP in the United States |
| One head-to-head trial found no significant difference between daily vs intermittent or on-demand PrEP but not powered to assess effects on HIV infection | One trial evaluated on-demand dosing of PrEP vs placebo in MSM; no studies on intermittent or on-demand dosing in women or PWID |

(continued)
Table 4. Summary of Evidence (continued)

<table>
<thead>
<tr>
<th>KQ2: Diagnostic Accuracy of Instruments for Identifying Individuals at Risk of Incident HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Studies; No. of Participants; Study Design</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7 studies of risk prediction or diagnostic accuracy (n = 32 311)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ3: Adherence to PrEP in US Primary Care–Applicable Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Studies; No. of Participants; Study Design</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3 RCTs and 7 observational studies (n = 3177)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ4: Association Between Adherence to PrEP and Effectiveness for Preventing HIV Acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Studies; No. of Participants; Study Design</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7 RCTs and 5 observational studies (n = 11 479)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ5: Harms of PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Studies; No. of Participants; Study Design</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serious adverse events 12 RCTs (n = 18 282)</td>
</tr>
<tr>
<td>Withdrawals resulting from adverse events 4 RCTs (n = 10 563)</td>
</tr>
<tr>
<td>Renal adverse events 12 RCTs (n = 18 170)</td>
</tr>
</tbody>
</table>

(continued)
Table 4. Summary of Evidence (continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies; No. of Participants; Study Design</th>
<th>Summary of Findings by Outcome</th>
<th>Consistency/Precision; Reporting Bias</th>
<th>Overall Quality</th>
<th>Body of Evidence Limitations</th>
<th>EPC Assessment of Strength of Evidence for KQ</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI adverse events</td>
<td>12 RCTs (n = 18,300)</td>
<td>RR, 1.63 (95% CI, 1.26-2.11); $I^2 = 43%$; ARD, 1.95% (95% CI, 0.48%-3.43%)</td>
<td>Some inconsistency; precise No reporting bias detected</td>
<td>Good</td>
<td>Composite outcome, with no significant difference for specific gastrointestinal adverse events</td>
<td>High</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Fracture</td>
<td>7 RCTs (n = 15,241)</td>
<td>RR, 1.23 (95% CI, 0.97-1.56); $I^2 = 0%$</td>
<td>Consistent; precise No reporting bias detected</td>
<td>Moderate</td>
<td>Limited details on fracture site; most fractures traumatic in studies that reported this information Results heavily weighted by 1 trial</td>
<td>Low</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Syphilis</td>
<td>4 RCTs (n = 10,775)</td>
<td>RR, 1.08 (95% CI, 0.98-1.18); $I^2 = 0%$</td>
<td>Consistent; precise No reporting bias detected, but NR in most trials</td>
<td>Good</td>
<td>Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP</td>
<td>Moderate</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>5 RCTs (n = 9296)</td>
<td>RR, 1.07 (95% CI, 0.82-1.39); $I^2 = 49%$</td>
<td>Some inconsistency; some imprecision No reporting bias detected, but NR in most trials</td>
<td>Good</td>
<td>Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP</td>
<td>Moderate</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>5 RCTs (n = 9296)</td>
<td>RR, 0.97 (95% CI, 0.80-1.18); $I^2 = 59%$</td>
<td>Consistent; precise No reporting bias detected, but NR in most trials</td>
<td>Good</td>
<td>Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP</td>
<td>Moderate</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Combined bacterial STIs</td>
<td>2 RCTs (n = 5291)</td>
<td>RR, 1.14 (95% CI, 0.97-1.34); $I^2 = 0%$</td>
<td>Consistent; some imprecision No reporting bias detected, but NR in most trials</td>
<td>Good</td>
<td>Most trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP</td>
<td>Moderate</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Herpes simplex virus infection</td>
<td>3 RCTs (n = 4103)</td>
<td>RR, 0.85 (95% CI, 0.67-1.07); $I^2 = 19%$</td>
<td>Some inconsistency; some imprecision No reporting bias detected, but NR in most trials</td>
<td>Good</td>
<td>Trials were blinded, which might affect behaviors differently than when patients know they are receiving PrEP</td>
<td>Moderate</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Hepatitis C virus infection</td>
<td>2 RCTs (n = 896)</td>
<td>RR, 0.73 (95% CI, 0.25-2.10); $I^2 = 0%$</td>
<td>Some inconsistency; imprecise No reporting bias detected, but NR in most trials</td>
<td>Good</td>
<td>One trial was blinded, which might affect behaviors differently than when patients know they are receiving PrEP</td>
<td>Low</td>
<td>See Applicability column for KQ1, HIV infection</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>3 RCTs (n = 485)$^b$</td>
<td>RR, 1.09 (95% CI, 0.79-1.50); $I^2 = 0%$</td>
<td>Consistent; some imprecision No reporting bias detected</td>
<td>Good</td>
<td>Analysis restricted to women who became pregnant in trials of PrEP and were taken off PrEP</td>
<td>Moderate</td>
<td>Analyses of women at high risk of HIV infection due to heterosexual contact who were taken off PrEP at time of pregnancy</td>
</tr>
</tbody>
</table>

Abbreviations: ARD, adjusted risk difference; ARR, adjusted relative risk; AUROC, area under the receiver operating characteristics curve; EPC, Evidence-based Practice Center; KQ, key question, MSM, men who have sex with men; NA, not applicable; NR, not reported; OR, odds ratio; PrEP, preexposure prophylaxis; PWID, people who inject drugs; RCT, randomized clinical trial; RR, relative risk; STI, sexually transmitted infection.  

$^a$ For KQ1 and KQ5, number of participants included in analysis.  

$^b$ In women who became pregnant while receiving PrEP.
Limitations

This review had some limitations. First, the DerSimonian and Laird random-effects model was used to pool studies, which may result in CIs that are too narrow, particularly when heterogeneity is present. However, analyses were repeated using the profile likelihood method, which resulted in similar findings. Second, these findings are based on analyses of study-level data, limiting the ability to evaluate subgroup effects. Third, non-English-language articles were excluded, but large non-English-language trials of PrEP were not identified. Fourth, in the pooled analysis of HIV infection, graphical and statistical tests indicated small sample effects, a potential marker for publication bias. However, no unpublished PrEP trials were identified in searches on a clinical trials registry (ClinicalTrials.gov) or reviews of reference lists. Fifth, trials of PrEP in persons at risk because of heterosexual contact were conducted in Africa and 1 trial of PrEP in PWID was conducted in Asia, which could limit applicability to the United States and other high-income settings.

Conclusions

In adults at increased risk of HIV infection, PrEP with oral tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine was associated with decreased risk of HIV infection compared with placebo or no PrEP, although effectiveness decreased with suboptimal adherence.

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Concept and design: Chou, Korthuis.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chou, Evans, Hoverman, Sun, Dana, Bougatsos, Grusing.

Critical revision of the manuscript for important intellectual content: Chou, Hoverman, Sun, Korthuis.

Statistical analysis: Chou, Hoverman, Dana.

Obtained funding: Chou.

Administrative, technical, or material support: Evans, Dana, Bougatsos, Grusing.

Supervision: Chou, Bougatsos.

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REFERENCES


